Guide to Pain Management in Low-Resource Settings

Edited by Andreas Kopf and Nilesh B. Patel

INTERNATIONAL ASSOCIATION FOR THE STUDY OF PAIN®

Guide to Pain Management in Low-Resource Settings

Educational material written for general distribution to health care providers by a multidisciplinary and multinational team of authors

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Foreword

The belief that pain treatment is a human right has been accepted by many for a long time, but in 2004 the statement that "the relief of pain should be a human right" was felt to be of sufficient importance for it to be published following the launch of the first Global Campaign Against Pain in Geneva in 2004 by the International Association of Pain (IASP), the European Federation of Chapters of the IASP (EFIC), and the World Health Organization (WHO). Unfortunately, however, a large number of those who suffer pain, and especially the people of developing countries, do not receive treatment for acute and, more especially, chronic pain.

There are various reasons for this problem, which include a lack of adequately trained health professionals, the unavailability of drugs, especially opioids, and a fear of using opioids because there is an erroneous belief that inevitably the use of these drugs will cause addiction. The first major step in improving services for pain patients is to provide an educated workforce in developing countries—not only doctors and nurses, but district officers and other health workers. A survey by IASP in 2007 revealed that among its members in developing countries, very few believed they had received an adequate education in the understanding and management of pain as undergraduates. In most regions of the world, less than half had been trained in pain management, even though it was a significant part of their daily work. It is not surprising, therefore, that 91% said that lack of education was the main barrier to good pain management in their part of the world.

It is clear that in many developing countries, relief of pain is not a priority, and that concern with infectious diseases such as malaria, tuberculosis, and above all HIV/AIDS takes precedence. In fact, 75% of those who responded to the IASP survey considered a lack of government priorities for pain management as the second most common barrier to good treatment. Almost as many reported that a fear of addiction to opioids among doctors, nurses, and health providers was a barrier to the availability and use of those drugs, although, in fact, such fear is primarily a consequence of poor education.

The production of this manual is timely because it will fill a major gap in the knowledge of those who deal with people in pain in developing countries. It covers the basic science of pain, and perhaps uniquely, the rationale for the use of natural medicines. It also provides background knowledge and advice on the management of the major painful disorders occurring in developing countries, including the two major scourges of the present time—cancer and HIV/AIDS.

This is a book that should be available to all who are responsible for providing treatment for pain, whether acute or chronic, and whether they work in cities, towns, or in a much more rural settings, because all will find it an invaluable aid to their practice.

Professor Sir Michael Bond
Glasgow, Scotland
August 2009

Introduction

Pain is widely undertreated, causing suffering and financial loss to individuals and to society. It is believed that health care of all patients should include assessment of pain and its impact on the patient, specific efforts by health care professionals to control pain, and the development of programs to generate experts in pain management. Additionally, clinical and basic science research is to be encouraged to provide better care in the future. The aim of these efforts is to ensure that pain control receives high priority in the health care system.

This book, *Guide to Pain Management in Low-Resource Settings,* is intended to encourage research on pain mechanisms and pain syndromes and help improve the management of patients with acute and chronic pain by bringing together basic scientists, physicians, and other health professionals of various disciplines and backgrounds who have an interest in pain.
The target audience is basic research and preclinical staff, surgical and internal medicine practitioners of all disciplines, anesthetists and anesthesiologists, all advanced nursing staff, and local health care workers in district and mission hospitals, as well as medical and nursing students.

In low-resource settings, many health care workers have little or no access to basic, practical information. Indeed, many have come to rely on observation, on advice from colleagues, and on building experience empirically through their own treatment successes and failures. The disparity of theoretical and practical availability of information is due to several factors, including unequal distribution of Internet access, and also a failure of international development policies and initiatives, which have tended to focus on innovative approaches for higher-level health professionals and researchers while ignoring, relatively speaking, other approaches that remain essential for the vast majority of primary and district health workers. The information poverty of health workers in low-resource settings is exacerbating what is clearly a public health emergency. Primary and district health workers should be at the center of efforts to address this crisis. The availability of health information may provide confidence in clinical decision-making, improving practical skills and attitudes to care.

Information on pain and pain management is crucial. All health care workers will see patients suffering from pain. Pain is the main reason for seeking medical help. Thus, any physician, nurse, or other clinical worker needs to have basic knowledge about the pathophysiology of pain and should be able to use at least simple first-line treatments. Unlike "special pain management," which should be reserved for specialist physicians with specific postgraduate training in complex pain syndromes, knowledge of "general pain management" is a must for all other health care workers to prepare them for the majority of patients in pain with common pain syndromes.

The editors intend that with the help of this *Guide* the reader will be know how to identify patients suffering from pain, understand the nature of pain and its influence on the patient's life, know the methods of analgesia that can provide effective pain management for most patients, know how to apply those methods and how to classify them in graduated schemes including nonpharmacological approaches, and know how to evaluate the efficiency of pain management. The main focus of the *Guide* is to address the following four pain syndromes: acute post-traumatic postoperative pain, cancer pain, neuropathic pain, and chronic noncancer pain.

The editors understand the barriers and future needs regarding good pain management. These barriers include lack of pain education and a lack of emphasis on pain management and pain research. In addition, when pain management does feature in government health priorities, there are fears of opioid addiction, the high cost of certain drugs, and in some cases, poor patient compliance. In developing countries, the available resources for health care understandably focus on the prevention and treatment of "killer" diseases. Yet most such disease conditions are accompanied by unrelieved pain, which is why pain control matters in the developing world, according to Prof. Sir Michael Bond. The WHO recommends that "since in most parts of the world, the majority of cancer patients present with

advanced disease … the only realistic treatment option is pain relief and palliative care." Due to the limited resources for health care, the WHO further proposes that in the future, palliative instead of curative approaches to treatment should be encouraged.

However, it is a sad reality that the medicines that are essential for relieving pain often are not available or accessible. There are numerous reports, some of them published in major medical and science journals, about the deficits of adequate pain management, predominantly in developing countries in all regions of the world. It is sincerely believed that with relatively minor input (referring not to efforts to change the situation but to the availability of essential drugs and techniques), the quality of analgesic treatment for cancer and HIV/AIDS patients in low-resource countries might be considerably improved, as documented by local initiatives around the world. The IASP has recently produced an atlas of pain training and pain facilities in developing countries. More information on this atlas can be found on the IASP website (www.iasp-pain.org).

For the pain specialist in developed countries, plenty of detailed information is available, but for the non-pain specialist and other health care providers, including nurses and clinical staff in many other regions of the world, who have to deal with patients in pain, there is a lack of a basic guide or manual on pain mechanisms, management, and treatment rationales. This is of particular concern in areas of the world where, outside the main urban areas, there is no access to information about pain etiology or management and no access to a pain specialist.

The IASP Developing Countries Task Force (now the Developing Countries Working Group) was founded to encourage ongoing medical education and clinical training in low-resource countries and is supporting local efforts to raise awareness of pain. The educational grant program, the "Initiative for Improving Pain Education," addresses the need for improved education about pain and its treatment in developing countries by providing educational support grants. These grants are intended to improve the scope and availability of essential education for pain clinicians of all disciplines, taking into account specific local needs. Following a joint proposal by the University of Nairobi (N. B. Patel) and the Charité University Medicine Berlin (A. Kopf), the IASP awarded one of the grants to a book project on pain management in low-resource countries. The result is this *Guide,* which is intended to provide concise and up-to-date-information in a novel curriculum structure for the medical practitioner in countries belonging to the developing world. It will also serve medical faculties by suggesting core curriculum topics on pain physiology and management. It is believed that the project will encourage medical colleges to integrate these educational objectives into their local student and nursing curriculums. It will provide the non-pain specialist with basic relevant information—in a form that is easily understood—about the physiology of pain and the different management and treatment approaches for different types and syndromes of pain.

Any practitioner who deals with pain problems must be aware of the entire range of pathophysiological and psychopathological problems that are commonly encountered in pain patients, and must therefore have access to a reasonable range of medical, physical, and psychological therapies to avoid imposing on the patients and society any additional financial and personal costs. The aim of these efforts is to ensure that pain control receives higher priority, especially in the treatment of cancer and HIV/AIDS patients, as well as for postoperative and injury-related acute pain. Therefore, this book will encourage the management of patients with acute and chronic pain, since it is well understood from the literature that even basic education has a considerable impact on the quality of analgesic therapy for the patient.

The editors appreciate the enthusiasm and efforts put in by the volunteer authors of this *Guide,* without whom this book would not have been possible. Many have experience in the problems faced by health care providers in the developing world. They have tried to project their thoughts into particular situations and settings: "Can I cope with what is expected of me, working as a doctor or nurse or health care provider in a developing country and facing a wide range of pain problems?" This question has presumably passed uneasily through the minds of many practitioners. The purpose is to provide the reader with various approaches to the management of some common pain management problems. It is by no means intended to be a definitive reference. Treatment algorithms presented are based on the review of available literature and experience in pain clinics, with a specific view on the potential local limitations in the developing world. Instead of a textbook approach with independent chapters written in a systematic manner, the *Guide* tries to follow a problem-orientated learning path. The chapters are intended to

be sufficiently broad and understandable to be of value to the nonspecialist. The structure, including questions and answers, pearls of wisdom, and illustrative case reports, as well as valuable literature suggestions for further reading, will, we hope, make the *Guide* a helpful companion and aid to pain management. All readers are invited to contribute to the improvement of further editions by sending their comments and suggestions to the editors.

The *Guide* does have some shortcomings. Although pain management has been a topic of increased interest for at least two decades, developing countries have few initiatives in this direction, and little is known about the needs, characteristics, and treatment modalities with regard to pain. Refresher courses, workshops, medical schools, conferences, and schools of anesthesia usually have not actively incorporated pain management in their training programs for students, residents, clinical officers, and nurses. Therefore, knowledge about the local characteristics of pain and treatment-related modalities is scarce, which has made it difficult for us to determine the relevance of some of the topics but will, we hope, not limit the usefulness of the *Guide.* The authors, with their wide international background, have tried to provide an ubiquitous view on pain management. It is the hope of the editors that the *Guide* will be useful to readers from a variety of regions of the world and from a variety of medical health care providers. Depending on feedback from the readers, the editors plan to produce a second volume with an emphasis on the general terms and requirements of good pain management, and possibly revised editions as well as editions in other common languages.

Andreas Kopf, Berlin, Germany
Nilesh Patel, Nairobi, Kenya
September 2009

The guide is dedicated to Professor Mohammed Omar Tawfik, Cairo, Egypt, whose professional life was dedicated to the teaching and dissemination of pain management.

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Basics

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Chapter 1
History, Definitions, and Contemporary Viewpoints

Wilfried Witte and Christoph Stein

The experience of pain is fundamental and has been part of the cultural development of all societies. In the history of pain, "supernatural" powers played an equally important role as natural factors. To view pain as the result of a "communication" between mankind and divine powers has been a fundamental assumption in many societies. The more societies are separated from Western medicine or modern medicine, the more prevalent is this view of pain. On the other hand, a purely medical theory based on natural phenomena independent of divine powers developed very early on. It happened to a greater extent in ancient China, while in ancient India medicine was heavily influenced by Hinduism and Buddhism. Pain was perceived in the heart—an assumption familiar to ancient Egyptians. The medical practitioners in pharaonic times believed that the composition of body fluids determined health and disease, and magic was indiscriminable from medicine.

Ancient Greek medicine borrowed heavily from its Asian and Egyptian predecessors. The introduction of ancient medical knowledge into medieval Europe was mainly mediated through Arabic medicine, which also added its own contributions. Latin was the language of scholars in medieval Europe, and ideology was guided by Judeo-Christian beliefs. Despite multiple adaptations, medical theory remained committed to ancient models for centuries. Pain had an important role. The Bible illustrates the need to withstand catastrophes and pain in the story of Job. Strength of faith is proved by Job's humility toward God. Humility is still an ideal in Christian thought today. In the New Testament, Jesus Christ finishes his life on earth as a martyr hanging and dying at the cross. His suffering marks the way to God. To bear suffering in life is necessary to be absolved from sin. The message of pain is to show mankind the insufficiency of life on earth and the brilliance of being in heaven. Thus, whatever science may say about pain, an approach based only on a physiological concept does not take into account the religious or spiritual meaning of pain.

The most important and radically mechanistic scientific theory of pain in early modern age derives from the French philosopher René Descartes (1596–1650). In his concept, the former assumption that pain was represented in the heart was relinquished. The brain took the place of the heart. In spite of (or because of) its one-sidedness, Descartes' theory opened the gate for neuroscience to explain the mechanisms of pain.

The question of how pain should be treated has led to different answers over time. If supernatural powers had to be pleased to get rid of pain, certain magical rituals had to be performed. If scientifically invented remedies were not used or not available, ingredients from plants or animals had to be used to ease the pain. Especially, the knowledge that opium poppies have analgesic effects was widespread in ancient societies such as Egypt. For a long time, opium was used in various preparations, but its chemical constituents were not known.

The isolation of the opium alkaloid morphine was first accomplished in 1803 by the German pharmacist Friedrich Wilhelm Sertürner (1783–1806). The industrial production of morphine began in Germany during the 1820s, and in the United States in the 1830s. During the late 18th to the mid-19th century, the natural sciences took over the lead in Western medicine. This period marked the beginning of the age of pathophysiological pain theories, and scientific knowledge about pain increased step by step.

The discovery of drugs and medical gases was a cornerstone of modern medicine because it allowed improvements in medical treatment. It was modern anesthesia in particular that promoted the development of surgery. General anesthesia using ether was introduced successfully in Boston on October 16, 1846, by the physician William Thomas Morton (1819–1868). The importance of this discovery, not only for surgery but for the scientific understanding of pain in general, is underscored by the inscription on his tombstone: "Inventor and Revealer of Inhalation Anesthesia: Before Whom, in All Time, Surgery was Agony; By Whom, Pain in Surgery was Averted and Annulled; Since Whom, Science has Control of Pain." This statement suggested that pain would vanish from mankind just by applying anesthesia. Surgery itself changed to procedures that were not necessarily connected with a high level of pain. Thus, the role of surgery changed. Surgeons had more time to perform operations, and patients were no longer forced to suffer pain at the hands of their surgeons.

Further innovations followed. One year later, in 1847, chloroform was used for the first time for anesthesia in gynecology by the Scottish physician James Young Simpson (1811–1879). In Vienna, the physician Carl Koller (1857–1944) discovered the anesthetic properties of cocaine in 1884. At about the same time, during the last two decades of the 19th century, the U.S. neurologist James Leonard Corning (1855–1923) and the German surgeon August Bier (1861–1949) carried out trials of spinal anesthesia with cocaine solutions. Modern anesthesia enabled longer and more complex surgical procedures with more successful long-term outcomes. This advance promoted the general consensus that the relief of somatic pain was good, but it was secondary to curative therapy: no pain treatment was possible without surgery! Thus, within the scope of anesthetic practice, pain management as a therapeutic goal did not exist at that time. Chronic pain was not a topic at all.

The first decades of morphine use may be seen as a period of high expectations and optimism regarding the ability to control pain. The first drawback to this optimism was the discovery made in the American Civil War (1861–1865), when cases of morphine dependence and abuse appeared. As a consequence, restrictions on the distribution of opiates were begun. The negative view of morphine use was enhanced by experiences in Asia, where an extensive trade in opium and morphine for nonmedical purposes was already established during the 19th century. Therefore, at the beginning of the 20th century, societal anxiety regarding the use of morphine became strong and developed into opiophobia (i.e., the fear of using opioids), which was a major step backwards for pain management in the following decades.

Wars stimulated pain research because soldiers returned home with complex pain syndromes, which posed insurmountable problems for the available therapeutic repertoire. Following his experience after 1915 during the First World War, the French surgeon René Leriche (1879–1955) began to concentrate on "pain surgery," mainly addressing the autonomic nervous system. Leriche applied methods of regional anesthesia (infiltration with procaine, sympathetic ganglionic blockade) as well as surgery, particularly periarterial sympathectomy. He not only rejected the idea of pain as a necessary evil but also criticized the reductionist scientific approach to experimental pain as a purely neuroscientific phenomenon. He viewed chronic pain as a disease in its own right ("douleur-maladie"), not just as a symptom of disease.

Regional anesthesia was the mainstay of pain therapy applied by the French surgeon Victor Pauchet (1869–1936). Already, before his experiences in the war, he had authored the first edition of his textbook *L'Anesthésie Régionale* in 1912. Through Louis Gaston Labat (1876–1934), a physician from Paris who later practiced in the United States, his wisdom became known in the New World and was an important stimulus for the dissemination of regional anesthesia in the United States between the two World Wars. In the 1920s, the notion that regional anesthesia could be used not only for surgery but also for chronic pain spread throughout the United States.

After the Second World War these ideas were taken up by John Joseph Bonica (1914–1994), who had emigrated with his parents from Sicily to the United States at the age of 11 years. As an army

surgeon entrusted with the responsibility of giving anesthesia, he realized that the care of wounded soldiers was inadequate. The patients were left alone with their pain after surgery. Bonica observed that pain frequently became chronic and that many of these patients fell prey to alcohol abuse or depressive disorders. Bonica's answer to this problem, which also affected other pain patients, was to establish pain clinics where physicians of different disciplines, psychologists, and other therapists worked together in teams to understand the complexity of chronic pain and treat it adequately. Anesthesiology remained Bonica's specialty. Only a few pain clinics existed in the United States when he published the first edition of his textbook *Pain Management* in 1953. This landmark may be regarded as the date of birth of a new medical discipline.

Nevertheless, it took many years before a broader audience became interested in pain therapy. In the year 1973, to make this topic more popular, Bonica founded the International Association for the Study of Pain (IASP). In the following years, national chapters of the IASP were founded around the globe. In 1979, IASP coined the important definition of pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage," which is still valid. This definition was important because for the first time it implied that pain is not always a consequence of tissue damage but may occur without it. Western science then began to realize that "somatic" factors (tissue damage) cannot be separated from "psychological" factors (learning, memory, the soul, and affective processes). Together with the recognition of social influences on pain perception, these factors form the core of the modern biopsychosocial concept of pain.

During the 20th century multiple pain theories were conceived. The most important theory—to which Bonica also subscribed—came from the Canadian psychologist Ronald Melzack (1929–) and the British physiologist Patrick D. Wall (1925–2001). Their theory was published in 1965 and is known as the "gate control theory." The term "gate" was supposed to describe spinal cord mechanisms regulating the transmission of pain impulses between the periphery and the brain. This theory was important because it no longer regarded the central nervous system as a simple passive medium for transmission of nerve signals. It implied that the nervous system was also "actively" altering transmission of nerve impulses. However, the "gate control theory" emphasized a strictly neurophysiological view of pain, ignoring psychological factors and cultural influences.

Medical ethnology examines cultural influences on perception and expression of pain. The most important early study was published in 1952 and was financed by the U.S. Public Health Service. On the basis of about 100 interviews with veterans of both World Wars and the Korean War, who were accommodated in a Veterans' Hospital in the Bronx, New York City, the investigators examined how different cultural backgrounds influence pain perception. The veterans were differentiated into those of Italian, Irish, or Jewish origin—besides the group of the "Old Americans," comprising U.S.-born Whites, mostly Protestant Christians. One result of this investigation was that the "Old Americans" presented the strongest stoicism in the experience of pain, while their attitude towards pain was characterized as "future-oriented anxiety." According to the interpretation of the investigators, this anxiety demonstrated an attempt to be conscious about one's own health. The more a Jew or Italian or Irish immigrant was assimilated into the American way of life, the more their behavior and attitudes were similar to those of the "Old Americans." However, pain was still seen merely as a symptom, and non-Western cultures were not a focus of interest.

It took about another three decades to change this situation. During the 1990s, studies demonstrated that different attitudes and beliefs in different ethnic groups around the world play a role in the variation of intensity, duration, and subjective perception of pain. As a consequence, health workers have to realize that patients with (chronic) pain value therapists who recognize their cultural and religious beliefs.

Another important aspect that attracted interest was the relief of pain in patients with advanced disease. It was the nurse, social worker, and later physician Cicely Saunders (1918–2005) who developed the "Total Pain" concept. Chronic pain in advanced disease totally changes everyday life and challenges the will to live. This problem is continuously present, so Saunders drew the conclusion that "constant pain needs constant control." According to this concept, pain cannot be separated from the personality and environment of a patient with advanced and fatal illness. The foundation of St. Christopher's Hospice in London, England, in 1967 by Saunders may be seen as the starting point of palliative medicine. It reflects a change of interest in

medicine from acute (infectious) diseases to cancer and other chronic diseases in the first half of the 20th century. The term "palliative care" (or palliative therapy) comes from the Latin word "pallium" (cover, coat) and is supposed to alleviate the last phase of life if curative therapy is no longer possible. Palliative care is, a priori, designed to concentrate on quality of life. It has roots in non-Christian societies, but it is mainly regarded to be in the tradition of medieval hospices. However, the historical background of the hospices was not the same in every European country, and neither was the meaning of the word "pallium"; sometimes it was used by healers to disguise their inability to treat patients curatively.

Palliative care became even more important when another totally unexpected pandemic occurred in the mid-1980s—HIV/AIDS. Particularly in Africa, this new "plague" rapidly developed into an enormous health problem that could no longer be ignored. Cancer and neuropathic pain play important roles in patients with HIV/AIDS. The development of palliative medicine in Africa began in Zimbabwe in 1979, followed by South Africa in 1982, Kenya in 1989, and Uganda in 1993. The institutions in Uganda became models in the 1990s, based on the initiative of the physician Anne Marriman (1935-), who spent a major part of her life in Asia and Africa. Uganda provided a favorable environment for her project "Hospice Africa Uganda" because at the time Uganda was the only African country whose government declared "palliative care for AIDS and cancer victims" a priority within its "National Health Plan." The rate of curative cancer treatment in Uganda is low, as in most economically disadvantaged countries. This situation makes problems associated with cancer and AIDS all the more urgent.

Broad acceptance of chronic pain management in the 20th century required the leadership of the World Health Organization (WHO), stimulated by Jan Stjernswärd from Sweden (1936–). In 1982, Stjernswärd invited a number of pain experts, including Bonica, to Milan, Italy, to develop measures for the integration of pain management into common knowledge and medical practice. Cancer was chosen as a starting point. At that time, the experts were concerned about the increasing gap between successful pain research, on the one hand, and decreasing availability of opioids to patients, especially cancer patients, on the other. A second meeting took place in Geneva in 1984. As a result, the brochure "Cancer Pain Relief" was published in 1986. In distributing this brochure, the WHO filled the gap by "forcing" health care systems to use opioids according to the now widely known three-step "analgesic ladder." The success of this initiative was, unfortunately, not the same in different regions of the world. While opioid availability and opioid consumption multiplied in the Anglo-American and Western European countries, other regions of the world observed only minor increases or even falling numbers of opioid prescriptions. It must be added, though, that in the Anglo-American and Western European sphere, facilitated access to opioids has promoted an uncritical extension of opioid use to noncancer pain patients as well. This use might be justified in cases of neuropathic or chronic inflammatory pain, but it should be regarded as a misapplication in most other noncancer pain syndromes. Opioids should not be used as a panacea (one remedy working for all), and current practice in some countries might threaten opioid availability in the future if health care authorities decide to intervene and restrict opioid use even more than today.

In conclusion, the understanding of pain as a major health care problem has come a long way. From the old days, when pain often was regarded as an unavoidable part of life, which humans could only partially influence because of its presumed supernatural etiology, a physiological concept has developed, where pain control is now possible. In the last few decades the "natural science" concept has been revised and extended by the acceptance of psychosocial and ethnocultural influencing factors. Although basic research has helped to uncover the complex mechanisms of pain and facilitated the development of new strategies to treat pain, the age-old opioids are still the mainstay of pain management for acute pain, cancer pain, and neuropathic pain. While the understanding and treatment of other chronic noncancer pain syndromes are still demanding, cancer pain, acute pain, and neuropathic pain may be relieved in a large number of patients with easy treatment algorithms and "simple" opioid and nonopioid analgesics. Therefore, the future of pain management in both high- and low-resource environments will depend on access to opioids and on the integration of palliative care as a priority in health care systems. *Pain Management in Low-Resource Settings* intends to contribute to this goal in settings where the poor financing of health care systems highlights the importance of pain management in palliative care.

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Chapter 2
Obstacles to Pain Management in Low-Resource Settings

Olaitan A Soyannwo

Why is effective pain management difficult to achieve in low-resource countries?

Low-income and middle-income economies of the world are sometimes referred to as developing countries, although there are wide differences in their economic and development status, politics, population, and culture. Poverty is, however, a common factor in the health situation of low-resource countries, and it is the main determinant of disease, since most of the population lives on less than US$1 a day (below the "breadline"). Malnutrition, infections, and parasitic diseases are prevalent, with high rates of morbidity and mortality, especially in rural areas and among pregnant women and children. Most countries therefore define and implement an "essential health package" (EHP), which is a minimum package of cost-effective public health and clinical interventions provided for dealing with major sources of disease burden.

These health priorities were addressed in the 2000 United Nations Millennium Development Goals (MDG), which emphasized the eradication of poverty and hunger, universal primary education, gender equality, reduction of child mortality, improvement of maternal health, combating HIV/AIDS, malaria, and other major diseases, environmental sustainability, and global partnership for development. Although communicable diseases are the emphasis, a transition in the epidemiology of diseases even in poor countries is now noticeable as noncommunicable diseases, injuries, and violence are as important as communicable diseases as causes of death and disability. Many of these conditions have accompanying pain (acute and chronic), which is inadequately addressed and treated. While there is consensus that stronger health systems are key to achieving improved health outcomes, there is less agreement on how to strengthen them. In countries where the average income is below the "breadline," there is little priority specifically for pain issues as most people concentrate on working to earn an income regardless of any pain problem.

Is pain management a problem in resource-poor countries?

Pain is the most common problem that makes patients visit a health care practitioner in low-resource countries. In a WHO study, persistent pain was a commonly reported health problem among primary care patients and was consistently associated with psychological illness. Both acute and chronic cancer and noncancer pains are undertreated, and analgesics may not even be available in rural hospitals.

How do patients handle their pain problems?

Usually, the first attempt at pain management in these patients is the use of home remedies, including herbal

and over-the-counter (OTC) medications. These can be simple analgesics, herbal preparations, or complementary drugs. Self-prescription and recommendations from nonmedical practitioners (friends, relatives, other patients, patent medicine vendors, and traditional medical practitioners) are common. Such recommendations may be effective for simple, uncomplicated pain, but when pain is severe or persistent, patients then go to the hospital as a last resort. In the hospital setting, most pain problems are treated by general medical practitioners, family physicians, or first-line specialists such as orthopedic surgeons, neurologists, and oncologists. Pain management specialists and dedicated pain clinics or acute pain teams are few and sometimes nonexistent in many resource-poor countries. Thus, although relief of pain is part of the fundamental right to the highest attainable standard of health, this aim is difficult to achieve in low-resource countries, where most of the population lives in rural areas. Frequently, health care is delivered by a network of small clinics—some without doctors or essential analgesics. Even when doctors are available, for example for surgery, patients expect pain as an inevitable part of surgical intervention, and despite the high incidence of reported pain, may still rate "pain relief" as satisfactory.

Why is it difficult to provide effective pain management?

Lack of knowledge

Inadequate knowledge among health care professionals in low-resource countries is one of the major obstacles to effective pain management. Comprehensive pain assessment and multimodal treatment approaches are poorly understood since pain is mostly taught as a symptom of disease rather than an experience with physical, psychosocial, and other dimensions. Lack of training and myths may lead to unreasonable fears of side effects of opioid analgesics and erroneous beliefs about the risk of addiction, even in cancer patients. Patients may also have a poor understanding of their own medical problems, and may expect pain, which they think has to be endured as an inevitable part of their illness.

Hence appropriate education is essential for all health professionals involved in pain management, and multidisciplinary teamwork is central to successful pain management. Pain education should be included in the curricula and examination of undergraduate and postgraduate health care students, and also incorporated into continuing education programs. Several organizations have produced comprehensive educational packages, protocols, and guidelines for clinical practice, including IASP (www.iasp-pain.org). However, these items must be adapted to be cost effective and culturally appropriate.

Poor attitudes among health care professionals

Often patients are denied appropriate analgesics when prescribed because the health professionals who are supposed to administer the drugs are too busy, are not interested, or refuse to believe the patient's complaint.

Inadequate resources

Due to staffing, equipment, and financial constraints, facilities for pain services are grossly inadequate or nonexistent in many developing countries. The inadequate resources preclude the organization of acute pain teams and chronic pain clinics, which are widely used in developed countries to provide effective pain control using evidence-based methods, education, advice on difficult pain problems, and research. In the developing world, improvements in acute pain management are most likely to result from effective training programs, use of multimodal analgesia, and access to reliable drug supplies.

Lack of opioid analgesics

Moderate to severe pain requires opioid analgesics for treatment as proposed by the WHO analgesic ladder, which has also been adopted by the World Federation Societies of Anaesthetists (WFSA). Unfortunately, in many low-resource countries, fears (opiophobia), concerns, and myths about opioid use focus more on tolerance, dependence, and addiction, which should normally not preclude appropriate medical use of opioids. In 1996, the International Narcotics Control Board (INCB) made recommendations which led to the publication of the WHO guideline manual "Achieving Balance in National Opioid Control Policy (2000)". The manual explains the rationale and imperative for the use of opioid analgesics.

Lack of government priority

National policies are the cornerstone for implementation of any health care program, and such policies are lacking in many low-resource countries. Effective pain management can only be achieved if the government includes pain relief in the national health plan. Policy

makers and regulators must ensure that national laws and regulations, while controlling opioid usage, do not restrict prescribing to the disadvantage of patients in need. The public health strategy approach, as pioneered for palliative care, is best for translating new knowledge and skills into evidence-based, cost-effective interventions that can reach everyone in the population.

Conclusion

Unrelieved pain causes a lot of suffering to the individuals affected, whether rich or poor. All efforts must, therefore, be made to promote effective pain management even for people living below the "breadline."

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www.medsch.wisc.edu/painpolicy/publicat/oowhoabi.htm
(INCB Guidelines)

International Association for the Study of Pain
IASP
Working together for pain relief

Guide to Pain Management in Low-Resource Settings

Chapter 3
Physiology of Pain

Nilesh B. Patel

Pain is not only an unpleasant sensation, but a complex sensory modality essential for survival. There are rare cases of people with no pain sensation. An often-cited case is that of F.C., who did not exhibit a normal pain response to tissue damage. She repeatedly bit the tip of her tongue, burned herself, did not turn over in bed or shift her weight while standing, and showed a lack of autonomic response to painful stimuli. She died at the age of 29.

The nervous system mechanism for detection of stimuli that have the potential to cause tissue damage is very important for triggering behavioral processes that protect against current or further tissue damage. This is done by reflex reaction and also by preemptive actions against stimuli that can lead to tissue damage such as strong mechanical forces, temperature extremes, oxygen deprivation, and exposure to certain chemicals.

This chapter will cover the neuronal receptors that respond to various painful stimuli, substances that stimulate nociceptors, the nerve pathways, and the modulation of the perception of pain. The term *nociception* (Latin *nocere,* "to hurt") refers to the sensory process that is triggered, and pain refers to the perception of a feeling or sensation which the person calls pain, and describes variably as irritating, sore, stinging, aching, throbbing, or unbearable. These two aspects, nociception and pain, are separate and, as will be described when discussing the modulation of pain, a person with tissue damage that should produce painful sensations may show no behavior indicating pain. Nociception can lead to pain, which can come and go, and a person can have pain sensation without obvious nociceptive activity. These aspects are covered in the IASP definition: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."

Physiology of pain

Nociceptors and the transduction of painful stimuli

The nervous system for nociception that alerts the brain to noxious sensory stimuli is separate from the nervous system that informs the brain of innocuous sensory stimuli.

Nociceptors are unspecialized, free, unmyelinated nerve endings that convert (transduce) a variety of stimuli into nerve impulses, which the brain interprets to produce the sensation of pain. The nerve cell bodies are located in the dorsal root ganglia, or for the trigeminal nerve in the trigeminal ganglia, and they send one nerve fiber branch to the periphery and another into the spinal cord or brainstem.

The classification of the nociceptor is based on the classification of the nerve fiber of which it is the terminal end. There are two types of nerve fibers: (1) small-diameter, unmyelinated nerves that conduct the nerve impulse slowly (2 m/sec = 7.2 km/h), termed C fibers,

and (2) larger diameter, lightly myelinated nerves that conduct nerve impulses faster (20 m/sec = 72 km/h) termed Aδ fibers. The C-fiber nociceptors respond polymodally to thermal, mechanical, and chemical stimuli; and the Aδ-fiber nociceptors are of two types and respond to mechanical and mechanothermal stimuli. It is well known that the sensation of pain is made up of two categories—an initial fast, sharp ("epicritic") pain and a later slow, dull, long lasting ("protopathic") pain. This pattern is explained by the difference in the speed of propagation of nerve impulses in the two nerve fiber types described above. The neuronal impulses in fast-conducting Aδ-fiber nociceptors produce the sensation of the sharp, fast pain, while the slower C-fiber nociceptors produce the sensation of the delayed, dull pain.

Peripheral activation of the nociceptors (transduction) is modulated by a number of chemical substances, which are produced or released when there is cellular damage (Table 1). These mediators influence the degree of nerve activity and, hence, the intensity of the pain sensation. Repeated stimulation typically causes sensitization of peripheral nerve fibers, causing lowering of pain thresholds and spontaneous pain, a mechanism that can be experienced as cutaneous hypersensitivity, e.g., in skin areas with sunburn.

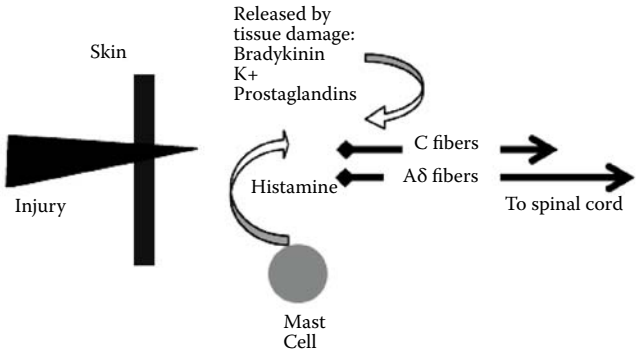

Fig. 1. Some chemicals released by tissue damage that stimulates nociceptors. In addition release of substance-P, along with histamine, produce vasodilation and swelling.

In addition, local release of chemicals such substance P causes vasodilation and swelling as well as release of histamine from the mast cells, further increasing vasodilation. This complex chemical signaling protects the injured area by producing behaviors that keep that area away from mechanical or other stimuli. Promotion of healing and protection against infection are aided by the increased blood flow and inflammation (the "protective function of pain").

Table 1
Selected chemical substances released with stimuli sufficient to cause tissue damage

Substance	Source
Potassium	Damaged cells
Serotonin	Platelets
Bradykinin	Plasma
Histamine	Mast cells
Prostaglandins	Damaged cells
Leukotrienes	Damaged cells
Substance P	Primary nerve afferents

Hypersensitivity may be diagnosed by taking history and by careful examination. Certain conditions may be discriminated:

a) Allodynia: Pain due to a stimulus that does not normally provoke pain, e.g., pain caused by a T-shirt in patients with postherpetic neuralgia.

b) Dysesthesia: An unpleasant abnormal sensation, whether spontaneous or evoked. (Note: a dysesthesia should always be unpleasant, while paresthesia should not be unpleasant; e.g., in patients with diabetic polyneuropathy or vitamin B_1 deficiency.)

c) Hyperalgesia: An increased response to a stimulus that is normally painful. (Note: hyperalgesia reflects increased pain on suprathreshold stimulation; e.g., in patients with neuropathies as a consequence of perturbation of the nociceptive system with peripheral and/or central sensitization.)

d) Hyperesthesia: Increased sensitivity to stimulation, excluding the special senses, e.g., increased cutaneous sensibility to thermal sensation without pain.

With the knowledge of pain pathways and sensitization mechanisms, therapeutic strategies to interact specifically with the pain generation mechanisms can be developed.

Central pain pathways

The spinothalamic pathway and the trigeminal pathway are the major nerve routes for the transmission of pain and normal temperature information from the body and face to the brain. Visceral organs have only C-fiber nociceptive nerves, and thus there is no reflex action due to visceral organ pain.

The spinothalamic pathway

The nerve fibers from the dorsal root ganglia enter the spinal cord through the dorsal root and send branches 1–2 segments up and down the spinal cord

(dorsolateral tract of Lissauer) before entering the spinal gray matter, where they make contacts with (innervate) the nerve cells in Rexed lamina I (marginal zone) and lamina II (substantia gelatinosa). The Aδ fibers innervate the cells in the marginal zone, and the C fibers innervate mainly the cells in the substantia gelatinosa layer of the spinal cord. These nerve cells, in turn, innervate the cells in the nucleus proprius, another area of the spinal cord gray matter (Rexed layers IV, V, and VI), which send nerve fibers across the spinal midline and ascend (in the anterolateral or ventrolateral part of the spinal white matter) through the medulla and pons and innervate nerve cells located in specific areas of the thalamus. This makes up the spinothalamic pathway for the transmission of information on pain and normal thermal stimuli (<45°C). Dysfunctions in the thalamic pathways may themselves be a source of pain, as is observed in patients after stroke with central pain ("thalamic pain") in the area of paralysis.

The trigeminal pathway

Noxious stimuli from the face area are transmitted in the nerve fibers originating from the nerve cells in the trigeminal ganglion as well as cranial nuclei VII, IX, and X. The nerve fibers enter the brainstem and descend to the medulla, where they innervate a subdivision of the trigeminal nuclear complex. From here the nerve fibers from these cells cross the neural midline and ascend to innervate the thalamic nerve cells on the contralateral side. Spontaneous firing of the trigeminal nerve ganglion may be the etiology of "trigeminal neuralgia" (although most of the time, local trigeminal nerve damage by mechanical lesion through a cerebellar artery is found to be the cause, as seen by the positive results of Janetta's trigeminal decompression surgery).

The area of the thalamus that receives the pain information from the spinal cord and trigeminal nuclei is also the area that receives information about normal sensory stimuli such as touch and pressure. From this area, nerve fibers are sent to the surface layer of the brain (cortical areas that deal with sensory information). Thus, by having both the nociceptive and the normal somatic sensory information converge on the same cortical area, information on the location and the intensity of the pain can be processed to become a "localized painful feeling." This cortical representation of the body—as described in Penfield's homunculus—may also be a source of pain. In certain situations, e.g., after limb amputations, cortical representation may change, causing painful sensations ("phantom pain") and nonpainful sensations (e.g., "telescoping phenomena").

Appreciating the complexity of the pain pathway can contribute to understanding the difficulty in assessing the origin of pain in a patient and in providing pain relief, especially in chronic pain.

Pathophysiology of pain

Pain sensations could arise due to:

1) Inflammation of the nerves, e.g., temporal neuritis.

2) Injury to the nerves and nerve endings with scar formation, e.g., surgical damage or disk prolapse.

3) Nerve invasion by cancer, e.g., brachial plexopathy.

4) Injury to the structures in the spinal cord, thalamus, or cortical areas that process pain information, which can lead to intractable pain; deafferentation, e.g., spinal trauma.

5) Abnormal activity in the nerve circuits that is perceived as pain, e.g., phantom pain with cortical reorganization.

Modulation of the perception of pain

It is well known that there is a difference between the objective reality of a painful stimulus and the subjective response to it. During World War II, Beecher, an anesthesiologist, and his colleagues carried out the first systematic study of this effect. They found that soldiers suffering from severe battle wounds often experienced little or no pain. This dissociation between injury and pain has also been noted in other circumstances such as sporting events and is attributed to the effect of the context within which the injury occurs. The existence of dissociation implies that there is a mechanism in the body that modulates pain perception. This endogenous mechanism of pain modulation is thought to provide the advantage of increased survival in all species (*Überlebensvorteil*).

Three important mechanisms have been described: segmental inhibition, the endogenous opioid system, and the descending inhibitory nerve system. Moreover, cognitive and other coping strategies may also play a major role in pain perception, as described in other chapters in this guide.

Segmental inhibition

In 1965, Melzack and Wall proposed the "gate theory of pain control," which has been modified subsequently

but which in essence remains valid. The theory proposes that the transmission of information across the point of contact (synapse) between the Aδ and C nerve fibers (which bring noxious information from the periphery) and the cells in the dorsal horn of the spinal cord can be diminished or blocked. Hence, the perception of the painfulness of the stimulus either is diminished or is not felt at all. The development of transcutaneous electrical nerve stimulation (TENS) was the clinical consequence of this phenomenon.

The transmission of the nerve impulse across the synapse can be described as follows: The activation of the large myelinated nerve fibers (Aβ fibers) is associated with the low-threshold mechanoreceptors such as touch, which stimulate an inhibitory nerve in the spinal cord that inhibits the synaptic transmission. This is a possible explanation of why rubbing an injured area reduces the pain sensation (Fig. 2).

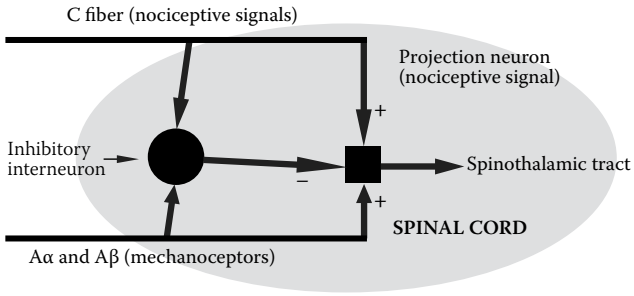

Fig. 2. The gate control theory of Pain (Melzack and Wall). + excitatory synapse; – inhibitory synapse

Endogenous opioid system

Besides the gating of transmission of noxious stimuli, another system modulates pain perception. Since 4000 BCE, it has been known that opium and its derivatives such as morphine, codeine, and heroin are powerful analgesics, and they remain the mainstay of pain relief therapy today. In the 1960s and 1970s, receptors for the opium derivatives were found, especially in the nerve cells of the periaqueductal gray matter and the ventral medulla, as well as in the spinal cord. This finding implied that chemicals must be produced by the nervous system that are the natural ligands of these receptors. Three groups of endogenous compounds (enkephalins, endorphins, and dynorphin) have been discovered that bind to the opioid receptors and are referred to as the endogenous opioid system. The presence of this system and the descending pain modulation system (adrenergic and serotoninergic) provides an explanation for the system of internal pain modulation and the subjective variability of pain.

Descending inhibitory nerve system

Nerve activity in descending nerves from certain brainstem areas (periaqueductal gray matter, rostral medulla) can control the ascent of nociceptive information to the brain. Serotonin and norepinephrine are the main transmitters of this pathway, which can therefore be modulated pharmacologically. Selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (e.g., amitriptyline) may therefore have analgesic properties (Fig. 3).

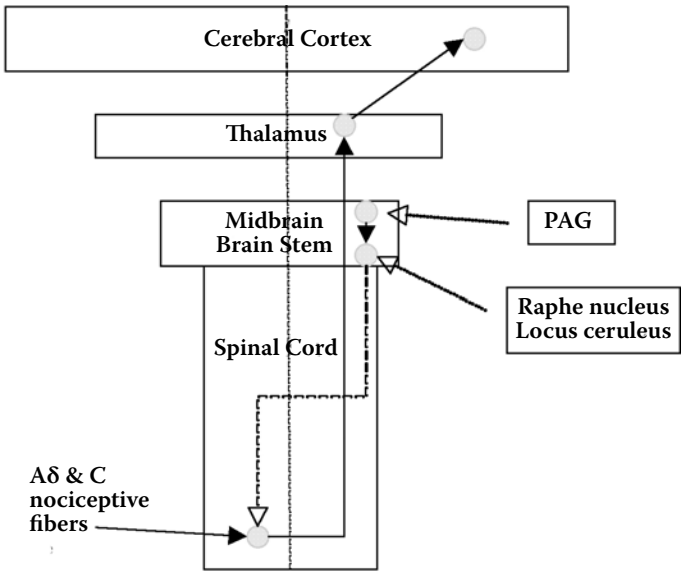

Fig. 3. Ascending (solid lines) and descending pain pathways. The raphe nucleus and locus ceruleus provide serotoninergic (5-HT) and adrenergic modulation. PAG = periaqueductal gray matter, part of the endogenous opioid system.

Referred pain

Visceral organs do not have any Aδ nerve innervation, but the C fibers carrying the pain information from the visceral organs converge on the same area of the spinal cord (substantia gelatinosa) where somatic nerve fibers from the periphery converge, and the brain localizes the pain sensation as if it were originating from that somatic peripheral area instead of the visceral organ. Thus, pain from internal organs is perceived at a location that is not the source of the pain; such pain is *referred pain*.

Spinal autonomic reflex

Often the pain information from the visceral organs activates nerves that cause contraction of the skeletal muscles and vasodilation of cutaneous blood vessels, producing reddening of that area of the body surface.

Conclusion

Chemical or mechanical **s**timuli that activate the nociceptors result in nerve signals that are perceived as pain by the brain. Research and understanding of the basic mechanism of nociception and pain perceptions provides a rationale for therapeutic interventions and potential new targets for drug development.

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Chapter 4
Psychological Factors in Chronic Pain

Harald C. Traue, Lucia Jerg-Bretzke, Michael Pfingsten, and Vladimir Hrabal

Everyone is familiar with the sensation of pain. It usually affects the body, but it is also influenced by psychological factors, and it always affects the human consciousness. This connection between the mind and body is illustrated by the many widely known metaphors and symbols. Unsolved problems and conflicts have us racking our brains over them, and the folk term for low back pain in German (Hexenschuss—witch's shot) entails the medieval psychosomatic belief that a proud man can be shot in the back by a witch's magical powers, producing the kind of agonizing pain that can cripple him. Many cultures believe in magical (often evil) powers that can cause pain. This belief in magical powers reflects the experience that the cause of pain cannot always be determined. Sometimes, the somatic structures of the body are completely normal and it is not possible to find a lesion or physiological or neuronal dysfunction that is a potential source of pain. The belief in magical powers is also rooted in the experience that psychological factors are just as important for coping with pain as is addressing the physical cause of the pain. Modern placebo research has confirmed such psychological factors in many different ways.

It should be mentioned, however, that certain lay theories such as the modern legend of the "worn-out disk" only describe the actual cause of these symptoms in very few cases. In more than 80% of all cases of back pain, there is no clear organic diagnosis. The diagnosis for these cases is usually "nonspecific" back pain. Concluding the reverse, that the lack of somatic causes indicates a psychological etiology, would be just as wrong.

The International Association for the Study of Pain (IASP) has defined pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." This definition is fairly lean, but it encompasses the complexity of pain processing, contradicts oversimplified pain definitions that pain is a purely nociceptive event, and also draws attention to the various psychological influences.

Pain is often accompanied by strong emotions. It is perceived not only as a sensation described with words such as burning, pressing, stabbing, or cutting, but also as an emotional experience (feeling) with words such as agonizing, cruel, terrible, and excruciating. The association between pain and the negative emotional connotation is evolutionary. The aversion of organisms to pain helps them to quickly and effectively learn to avoid dangerous situations and to develop behaviors that decrease the probability of pain and thus physical damage. The best learning takes place if we pay attention and if the learned content is associated with strong feelings. With regard to acute pain—and particularly when danger arises outside the body—this connection is extremely useful, because the learned avoidance behavior with regard to acute pain stimulation dramatically reduces health risks. When it comes to chronic pain,

however, avoiding activities and social contact affects the patient by leading to even less activity, social withdrawal, and an almost complete focus of attention on the pain. This tendency leads to a vicious circle of pain, lack of activity, fear, depression, and more pain.

Patients often have a somatic pain model

In Western medicine, pain is often seen as a neurophysiological reaction to the stimulation of nociceptors, the intensity of which—similar to heat or cold—depends on the degree of stimulation. The stronger the heat from the stove, the worse the pain is usually perceived to be. Such a simple, neuronal process, however, only applies to acute or experimental pain under highly controlled laboratory conditions that only last for a brief period of time. Due to the manner in which pain is portrayed in popular science, patients also tend to adhere to this naive lay theory. This leads to unfavorable patient assumptions, such as (1) pain always has somatic causes and you just have to keep looking for them, (2) pain without any pathological causes must be psychogenic, and (3) psychogenic means psychopathological.

Physicians only start considering psychogenic factors as a contributing factor if the causes of the pain cannot be sufficiently explained by somatic causes. In these cases, they would say, for example, that the pain is "psychologically superimposed." Consequently, patients worry that they will not be taken seriously and will insist even more that the physician look for somatic causes. This situation leads to a useless dichotomy of somatogenic vs. psychogenic pain. But pain always consists of both factors—the somatic and the psychological. This obsolete dichotomization must be addressed within the context of holistic pain therapy.

The interaction of biological, psychological, and social factors

A complete pain concept for chronic pain is complex and attempts to take as many factors as possible into consideration. Psychologically oriented pain therapists cannot have a naive attitude toward the pain and neglect somatic causes, because otherwise, patients with mental disorders (e.g., depression or anxiety) will not receive the somatic care they require; just because someone has a mental disorder does not mean he or she is immune from physical disorders and the pain associated with them. Conversely, patients with clear somatic symptoms often do not receive adequate psychological care: pain-related anxiety and depressive moods, unfavorable illness-related behavior, and psychopathological comorbidities may be neglected.

From a psychological perspective, it is assumed that chronic pain disorders are caused by somatic processes (physical pathology) or by significant stress levels. There could be a physical illness, but also a functional process such a physiological reaction to stress in the form of muscle tension, vegetative hyperactivity, and an increase in the sensitivity of the pain receptors. Only as the disorder progresses do the original trigger factors become less important, as the psychological chronification mechanisms gain prevalence. The effects of the pain symptom then may themselves become a cause for sustaining the symptoms.

Modern brain-imaging techniques have confirmed psychological assumptions on pain and provide the basis for an improved understanding of how psychological and somatic factors act together. As Chen summarized, there is not just one pain center associated with the pain, but a neuronal matrix made up of all areas that are activated by sensory, affective, and cognitive data processing, particularly the primary sensory cortex, the insula, the cingulate gyrus, the periaqueductal gray, and the frontal cortical area: "The neurophysiological and neuro-hemodynamic brain measures of experimental pain can now largely satisfy the psychophysiologist's dream, unimaginable only a few years ago, of modeling the body-brain, brain-mind, mind-matter duality in an interlinking 3-P triad: physics (stimulus energy); physiology (brain activity); and the psyche (perception). We may envision that the modular identification and delineation of the arousal-attention, emotion-motivation and perception-cognition neuronal network of pain processing in the brain will also lead to deeper understanding of the human mind."

One of the important results of this research is that in studies using fMRI (functional nuclear magnetic resonance imaging of the brain), negative feelings such as rejection and loss that are generally referred to as painful experiences also create neuronal stimulation patterns similar to those created by noxious stimulation. This finding is of great clinical significance, because socially outcast and traumatized persons not only may have post-traumatic stress disorder (PTSD), but also show high levels of pain that can persist even after the body had healed.

Psychological pain therapy

Psychological interventions play a well-established role in pain therapy. They are an integrative component of medical care and have also been successfully used for patients with somatic disorders. Together with psychotherapeutic techniques, they can be used as an alternative or an addition to medical and surgical procedures. Patients with chronic pain usually need psychological therapy, because psychosocial factors play a crucial role in the chronicity of pain and are also a decisive factor in terms of enabling the patient to return to work.

Below is a list of psychological interventions and their usual therapy targets. The targets refer both to individual and group therapy. The interventions may be used within the context of various therapies and require different levels of psychological expertise, as shown in Table 1.

Due to the strong focus on physical processes, certain processes such as biofeedback and physical and psychological activation are particularly well received by many patients. Patients with chronic pain often feel incapable of doing something about their pain themselves. Due to many failed therapies, they have become passive and feel hopeless and depressed. Therefore, one main goal of psychological pain therapies is to decrease the patient's subjective feeling of helplessness.

The patient's active involvement is not always helpful, particularly if the patient cannot actively manage and change what is going on. This can occur if freedom from pain is seen as the only therapy target. It is not uncommon that the resulting disappointment, with its far-reaching impact on all areas of life, becomes the patient's actual problem. One of the "protection factors" against depression is the patient's flexibility in adjusting personal goals: a lack of flexibility results in intense pain and depression.

Acceptance does not equal resignation, but allows for:

- Not giving up the fight against pain,
- A realistic confrontation of the pain, and
- Interest in positive everyday activities.

The most important psychological therapies are based on the principles of the theory of learning and have led to the following rules:

- Let the patient find out his or limits with regard to activities such as walking, sitting, or climbing stairs, with no significant pain increase.
- Plan together gradual, systematic, and regular increases and set realistic interim goals ("better to go slowly in the right direction than quickly in the wrong direction").
- Medications must be taken in accordance with a schedule and not just when needed.
- Gradually confront situations that create anxiety (e.g., lifting heavy objects, rotation movements, or sudden movements).
- Behavioral changes are not given as doctor's orders, but are taught through carefully worded information (education).
- Psychological therapy is combined with medical and physiotherapeutic procedures.

Interdisciplinary teams, with a biopsychosocial treatment concept, do not distinguish between somatic and the psychological factors, but treat both simultaneously within their individual specialties and through consultation with one another.

Behavioral therapy interventions

Psychological pain therapy methods attempt to change pain behavior and pain cognition. *Behavioral processes* are geared toward changing obvious behaviors such as taking medication and using the health care system, as well as other aspects relating to general professional, private, and leisure activities. They focus particularly on *passive avoidance behaviors*, a pathological behavior showing anxious avoidance of physical and social activity. One significant aspect of this therapy is to increase activity levels. This step is accompanied by extensive education initiatives that help reduce anxiety and increase motivation to successfully complete this phase.

The goal of therapy is to reduce passive pain behavior and to establish more active forms of behavior. The therapy begins with the development of a list of objectives that specify what the patient wants to achieve, e.g., to be able to go to the soccer stadium again. These objectives must be realistic, tangible, and positive; complex or more difficult objectives can be addressed successively, and unfavorable conditions must be carefully taken into consideration. It does not make sense to encourage a patient to return to work and to make this an objective if this is unlikely, due to the conditions on the job market. A better therapy objective might be to achieve better quality of life by getting involved in meaningful leisure activities. Expanding one's activities also makes social reintegration (with family, friends, and associates) more likely. The support patients receive in therapy makes it more likely that they will continue

Table 1
Psychological interventions and therapy targets

Intervention	Therapeutic Targets	Treatment Context	Need for Psychological Expertise*
Patient training	Educate, i.e., expand patient's subjective pain theory (integration of psychosocial aspects)	General medicine	+
Handling of medications	Reduce medication, use correct medication, and prevent misuse	General medicine	++
Relaxation training	Learn how to use relaxation to cope with pain and stress	Psychologist + physiotherapist	+
Resource optimization	Analyze and strengthen own resources for coping with pain	General medicine	+
Activity regulation	Optimize activity levels (balance between rest and activity): reduce fear-motivated avoidance and increase activity level	Physician + psychologist/psychiatrist	++
Pain and coping	Optimize pain-coping capabilities	Psychologist/psychiatrist	++
Involvement of caregivers	Involve patient's caregivers in reaching therapy targets	General medicine	+
Improvement of self-observation	Find a personal connection between the pain and internal or external events, which can help establish ways to control the pain. Analyze conditions that increase pain and stress	Psychologist/psychiatrist	+++
Stress management	Learn systematic problem-solving tools and how to cope with stress	Psychologist/psychiatrist	+++
Learning how to enjoy activities	Strengthen activities the patient enjoys and likes to do	General medicine/physiotherapist	+
Communication	Change inadequate pain communication and interaction	General medicine or psychologist	+
Developing perspectives for the future	Develop realistic perspectives for the future (professional, private) and initiate action plans	General medicine	+
Special Therapies			
Cognitive restructuring	Modify catastrophizing and depressive cognitions	Psychologist/psychiatrist	+++
Biofeedback	Learn how to activate specific motor and neuronal (vegetative and central nervous) functions and learn better self-regulation	Psychologist	++++
Functional restoration	Restore private and professional functionality; reduce subjective impairment perception and movement-related anxiety	Interdisciplinary: orthopedic physician + physiologist	++++

* Low (+) to high (++++).

these activities after the end of therapy. Often, however, therapists must not only encourage activities, but also plan phases of rest and relaxation to make sure patients do not overly exert themselves.

Cognitive-emotional modification strategies, on the other hand, predominantly focus on changing thought processes (convictions, attitudes, expectations, patterns, and "automatic" thoughts). They focus on teaching *coping strategies and mechanisms*. These are various techniques that teach patients a new, more appropriate set of cognitive (and behavioral) skills to help them cope with pain and limitations. Patients are taught, for example, how to identify thoughts that trigger and sustain pain, how to perceive situational characteristics, and how to develop alternative coping strategies. If patients are taught appropriate coping techniques, they are better able to control a situation; new confidence in their abilities leads to a decrease in feelings of helplessness, and patients become more proactive. One of the goals of therapy is for patients to learn to monitor the function of expressing symptoms (something patients are usually not aware of) to be able to better manage and manipulate their social environment. The therapy should teach appropriate social skills, for example, about how to assert one's own interests to prevent the pain behavior from taking on this (so-called "instrumental") function.

Functional problem analysis is another important tool of behavior therapy. During the course of this analysis, patients and their therapists systematically collect information on how internal or external events are connected to the pain experience and pain behavior. At the same time, detailed information is collected on the effects of the behavior and the functions the behavior might have (e.g., in the professional environment or in personal relationships). By analyzing these situations, it is possible to develop an overview of how the pain experience is incorporated into situational, cognitive-emotional, and behavioral aspects and how it is maintained. This analysis can then be used to make further assumptions about the patient's pain triggers and maintenance conditions, followed by goals and initiatives that could break the pain cycle. Particularly important for the analysis of these conditions is the patient's self-observation with the help of pain diaries. The analysis can also be the basis for the patient's own education, especially if the patient's description specifies overall assumptions regarding the pain, its prognosis, and its treatment.

Educating the pain patient

Fear of pain and anxiety about having a "serious" disease are important factors in the chronification process. Uncertainty and the lack of explanations are significant factors contributing to the patient's worries. Fearful assumptions regarding the presence of a serious illness have negative behavioral consequences and foster passive pain behavior. To reduce this uncertainty, patients should be provided with information and knowledge using written or graphic materials as well as videos. It is especially important that the training should not criticize the patient's often very simplistic somatic pain concept, but rather expand on the patient's subjective theories about the disorder, thus opening up new ways of how the patient can be actively involved. Based on easy-to-understand information on pain physiology and psychology, psychosomatic medicine, and stress management, patients should be able to understand that pain is not only a purely somatic phenomenon, but is also influenced by psychological aspects (perception, attention, thoughts, and feelings). Informational materials are an important addition to therapist-linked activity, and patient education is an important therapeutic element that can form the basis for other interventions. Successful, informative training provides patients with the foundation they need to jointly develop and select therapy goals.

Relaxation techniques

Relaxation techniques are the most commonly used techniques in psychological pain therapy and constitute a cornerstone of cognitive-behavioral therapy. They are effective because they teach patients to intentionally produce a relaxation response, which is a psychophysiological process that reduces stress and pain. Well-done relaxation exercises can counteract short-term physiological responses (at the neuronal level) and prevent a positive feedback loop between pain and stress reactions, for example, by intentionally creating a positive affective state. As patients progressively learn these techniques, they are better able to recognize internal tension, which also makes them more aware of their personal stress situations and triggers (at the cognitive level). Some techniques (e.g., progressive muscle relaxation) often lead to better body perception in terms of tight muscles, which can help identify stressful situations.

The most commonly known relaxation techniques are progressive muscle relaxation as per Jacobson (PMR), autogenic training (AT), and other imagination, breathing, and meditation techniques. All these techniques must be practiced for quite some time before they can be mastered. Sustainable success can only be achieved through prolonged effort. Relaxation techniques are less successful in acute pain situations, which is why they are more usually used to treat chronic pain.

Biofeedback

Biofeedback therapy involves physiological learning by measuring physiological pain components such as muscle activity, vascular responses, or arousal of the autonomic nervous system and providing visual or acoustic feedback to the patient. Biofeedback therapy is helpful for migraines, tension headaches, and back pain. Several different methods are used for migraines, such as hand-warming techniques and vascular constriction training (targeting the temporalis artery).

In the hand-warming or thermal biofeedback technique, the patient receives information on the blood supply to one finger, usually by measuring the skin temperature with a temperature sensor. The patient is asked to increase the blood supply to the hand (and thereby reduce vasodilatation in the arteries of the head). In autogenic feedback training, the hand warming is supported by the development of formula-type intentions from autogenic training (heat exercises). The processes are demonstrated and used only during pain-free periods. First, the patient practices with feedback and heat imagery. Then, the conditions of the exercise are made harder, and the patient, supported by the temperature feedback, is asked to remain relaxed while imagining a stressful situation. And finally, the patient is asked to increase the temperature of the hand without any direct feedback, and is told subsequently if he or she was successful.

In electromyography (EMG) biofeedback for tension headaches or back pain, the feedback usually consists of the level of tension in the forehead, neck muscles or lumbar muscles and is used to teach patients how to reduce tension. Patients with pain in the locomotor apparatus might also, however, practice certain movement patterns. These patterns are then practiced not only in a reclined position or while resting, but also in other body positions and during dynamic physical activity. It is important that the muscle groups are selected on the basis of physiological abnormalities—on the basis of muscle activity on the surface EMG or physical diagnostic parameters such as active myogeloses (localized muscle tension that is painful to the touch). One specific application is a portable biofeedback device that can be used under normal day-to-day conditions.

Multimodal processes

Multimodal pain psychotherapy is based on two assumptions:

1) Chronic pain does not have individually identifiable causes, but is the result of various causes and influential factors.

2) A combination of various therapeutic interventions has proven successful in the treatment of chronic pain (usually independent of the specific pain disorder).

In a modern pain therapy, therapeutic processes are usually not isolated, but are used within the context of an umbrella concept. The process is centered on a reduction of the (subjectively perceived) handicap by changing the patient's general situational conditions and cognitive processes. These kinds of programs can be applied according to the shotgun principle, e.g., all modules are used with the view that we will definitely hit upon the most important areas, or the therapist can use the diagnosis to put together a specific modular treatment plan. The latter method should be used if an individual diagnosis is possible. In a group setting, the standardized process works better due to the expected differences between the patients.

Functional restoration programs

These programs are characterized by their clear focus on sports medicine and underlying behavioral therapy principles. Pain reduction as a treatment goal plays a minor role. Due to learning theory considerations pertaining to the "enhancement character" of pain behavior, the pain itself is basically pushed out of the therapeutic focus. These programs try to help patients function again in their private and professional lives (functional restoration). The primary goal of therapy is to reduce the subjective adverse effect and the consequent fear and anxiety.

The treatment integrates sport, work therapy, physical exercises, and psychotherapeutic interventions into one standardized overall concept. The physical therapy components usually include an increase in

overall fitness level, improvement in cardiovascular and pulmonary capacity, coordination and body perception, and an improved capacity to handle stress. The psychotherapeutic interventions try to change adverse emotional effects (antidepressive therapy). The patient's behavior is based on rest and relaxation, along with changing cognitively represented attitudes or anxieties with regard to activity and the ability to work.

The focus of this psychological (cognitive-behavioral) therapy is similar to that of the psychological methods described above. The therapy is highly somatically oriented, but the psychological effects of the training are just as important as the changes achieved in terms of muscle strength, endurance, and coordination. Intense physical activity is included in order to:

1) Decrease movement-related anxiety and functional motor blockages.

2) Sever the learned connection between pain and activity.

3) Provide the necessary training to cope with stress.

4) Provide fun and enjoyment, which is usually experienced during the playful parts of therapy and can lead to new emotional experiences.

Insights gleaned from the theory of learning show that pain must lose its discriminating function for patients to be able to manage their pain behavior. Therefore, the entire physical training cannot be geared toward the pain it causes, or be limited by it, but must instead be geared toward personalized preset goals. Goal plans strengthen the patient's experience of manageability and self-efficacy. Failures at the beginning of therapy (e.g., if goals are not reached) could significantly reduce the patient's motivation, initial goals should be very simple (weight, number of repetitions). Patients' beliefs about their illness, particularly with regard to movement-related fears, must be given particular attention during therapy. These fears must be specifically recorded and decreased in a gradual training process that mimics the behavior as closely as possible.

Physical training machinery can be used during the training (the patient feels safe due to the guided, limited movements), but they constitute "artificial" conditions and thus hinder the necessary transfer to daily life. Consequently, routine everyday activities should be incorporated into the training as early as possible. Since there is a close connection between back pain and the workplace, the therapy must be enhanced by socio-therapeutic interventions (adjustment of the individual's capabilities to his or her profile of professional requirements [behavior prevention]) and a change in the variables of the professional environmental (e.g., transfer within the workplace or retraining [conditional prevention]).

Effectiveness of psychologically based therapies

The effectiveness of psychological pain therapy for chronic pain patients is sufficiently documented. Several meta-analytical studies have shown that about two out of three chronic patients were able to return to work after having undergone cognitive-behavioral pain therapy. Cognitive-behavioral therapy techniques, compared to exclusively medication-based therapy, are effective in terms of a reduction of the pain experience, an improvement in the ability to cope with pain, a reduction of pain behavior, and an increase in functionality; most effects can be maintained over time.

Behavioral therapy is not just one homogenous therapy, but consists of several intervention methods, each of which is geared toward a specific modification goal. However, this multidimensional advantage is also a disadvantage, because it is often not quite clear what kind of content is needed. The effect itself has been proven without a doubt, but it is much less clear why and in which combination the interventions are effective.

Pearls of wisdom

- Psychogenic processes play an important role in the complex processing of pain information. The pain, therefore, affects not only the body, but the human being as a whole. It becomes more severe if the patient does not know the causes or the significance of the pain, which, in turn, leads to anxiety and increased pain levels.
- In terms of chronic disorders, various factors in their individual development have an additive effect. Therefore, an explanatory model can help determine the best therapeutic approach, which equally includes biological (somatic), psychological, and sociological components. This model focuses not on details that are no longer identifiable, but on the interactive whole.
- The patient himself is only a fixed, actively functioning component of the process, if he is willing to actively participate in the necessary behavioral

changes and to generally take on more responsibility for himself, his disease, and the course of his disease. The results of many years of psychological pain research provide important insights for this process.

- This is not about replacing medical therapy with psychological therapy, but about using the insights of different specialties in an integrated manner to treat this difficult group of patients in the best possible way.
- On the other hand, chronic patients are impressed by reports on medical interventions such as surgeries, injections, or medications, which raise high expectations for a quick removal of the pain without their own active involvement as a patients. Repeatedly, high hopes of curing pain are raised by the medical system, and usually dashed in careful long-term studies.
- Neither opiates nor the development of specific medications or surgery for certain types of pain have led to the expected solutions to end chronic pain.

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Websites

IASP: www.iasp-pain.org

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Chapter 5
Ethnocultural and Sex Influences in Pain

Angela Mailis-Gagnon

Case reports

A 40-year-old male patient comes to see you. He is Chinese and has been in a Western country for 2 years. His English is barely functional. While you try to obtain information for the neck pain that brought him to you, he keeps looking to the ground and avoids eye contact. Is he depressed or does he simply disrespect you?

A 25-year-old woman with a hijab and traditional Moslem attire is brought in by her husband in regard to diffuse body pain complaints. She looks uncomfortable when she realizes that the clinic doctor who will see her is a male. Given the fact that this doctor is the only one available at that time, how is he going to handle the problem?

A 75-year-old farmer with elementary school education sees you for severe knee arthritis. He cannot tolerate nonsteroidal anti-inflammatory medications and refuses knee surgery. His pain responds very well to small doses of controlled-release morphine. However, he becomes very nauseated and throws up every time. He becomes visibly upset when you offer him Gravol suppositories after you explain to him how to use them. Why do you think he became angry, and how are you going to address this problem?

These are common clinical problems seen by primary care physicians as well as pain clinics and are examples of how cultural and ethnic background affects pain perception, expression, and interactions with health care providers. Maryann Bates [1], a professor at the School of Education and Human Development at the State University of New York, studied pain patients of different ethnic backgrounds. Bates proposed that culture reflects *the patterned ways that humans learn to think about and act in their world*. Culture involves styles of thought and behavior that are learned and shared within the social structure of our personal world. In this context, culture is different than ethnicity. The latter refers specifically to the *sense of belonging in a particular social group within a larger cultural environment*. The members of an ethnic group may share common traits such as religion, language, ancestry, and others.

Why is it important to understand ethnicity and culture when it comes to pain diagnosis and management?

Culture and ethnicity affect both perception and expression of pain and have been the focus of research since the 1950s. Research with adult twins supports the view that it is the cultural patterns of behavior and not our genes that determine how we react to pain. Examples of how culture and ethnicity affect pain perception and expression are numerous, both in the laboratory and in clinical settings.

In the laboratory, an earlier classic study showed that persons of Mediterranean origin described a form of radiant heat as "painful," while Northern European

subjects called it simply "warm." When subjects of different ethnic backgrounds were given electric shocks, women of Italian descent tolerated less shocks than women of "old" American or Jewish origin. In another experimental study, when Jewish and Protestant women were told that their own religious group had not performed well compared with others in an experiment with electric shocks, only Jewish women were able to tolerate a higher level of shock. The Jewish women in the first place had tolerated lower levels of shocks to start with. Since their cultural background was such that they easily complained of pain, they had "more room to move" in terms of additional shock stimulus.

On the other hand, in a clinical study of six ethnic groups of pain patients (including "old" American, Hispanic, Irish, Italian, French Canadian, and Polish pain patients), the Hispanics specifically reported the highest pain levels. These patients were characterized by an "external locus of control" (the belief that life events are outside the person's control and in the hands of fate, chance, or other people). In yet another clinical study, patients in a pain center in New England, USA, were compared with those in an outpatient medical center in Puerto Rico. The Puerto Ricans (Hispanics or Latinos) were found to experience higher pain levels in general (in accordance with the other study mentioned above). Such a finding indeed supports the long-held belief that Latino cultures are more reactive to pain. However, when the researchers studied Puerto Ricans who had immigrated to New England, USA, many years before, their reactions were more like those of the New England group than their original Puerto Rican group. This finding shows that pain responses of different ethnic groups can change, as they are shaped and reshaped by the culture in which the groups live or move into. In studies among patients with cancer, Hispanics reported much worse pain and quality of life outcomes than Caucasians or African Americans. On the other hand, Hispanic cancer patients use religious faith as a powerful resource in coping with pain. African Americans complain of more pain than Caucasians during scoliosis surgery, while Mexican-Americans report more chest and upper back pain than non-Hispanic whites during a myocardial infarction. Another real-life example of how culture shapes people's reactions to painful events is the fact that only 10% of adult dental patients in China routinely receive local anesthetic injections from their dentist for tooth drilling compared with 99% of adult patients in North America. All these studies and the ones below are summarized by Mailis Gagnon and Israelson in their popular science book, *Beyond Pain* [3].

Can cultural influences increase *and* decrease pain perception?

To look at the complete opposite side, what about cultural influences that can decrease instead of increase pain perception? In certain parts of the world such as India, the Middle and Far East, Africa, some countries of Europe, and among North American First Nations, ability to endure pain is considered a proof of special access or relationship to the gods, a proof of faith, or readiness to "become an adult" during "initiations" or "rituals." Such rituals have puzzled and amazed Western scientists for many years. An example of such a ritual is the phenomenon of "hook-hanging," which is practiced primarily by certain devotees to Skanda, the god of Kataragama in Sri Lanka. Dr. Doreen Browne, a British anesthetist, visited Sri Lanka in 1983 and described her observations. The flesh of the back of the devotees was pierced by several hooks, and the subjects were hung and swung from scaffolds pulled by animals, visiting villages to bless the children and the crops. The subjects seemed to stare far away and at no time did they seem to feel pain; as a matter of fact, they were in a "state of exaltation." The training of these devotees starts in childhood and they seem to gradually develop the ability to switch to a different state of mind that could block pain. Indeed, a German psychiatrist, Dr. Larbig, showed with electroencephalographic (EEG) studies that the devotees' brainwaves change throughout all the stages of the process. It is well known that our brains emit different wave frequencies during activities or sleep. Alpha waves are emitted during our regular conscious activities, and they are fairly fast at 8–13 cycles every second. Another kind of brain waves called theta waves are slower at 4–7 cycles per second and occur during light sleep or when the individual detaches from reality to become absorbed in deep thoughts. The hook-hanging devotees actually displayed theta waves throughout all the stages of the process (i.e., during insertion of the hooks, swinging, and removal of the hooks).

Dr. Larbig was also fascinated by the amazing things that fakirs do and investigated a 48-year-old Mongolian fakir. This man could stick daggers in his neck, pierce his tongue with a sword, or prick his arms with long needles without any indication of pain or

damage to his flesh. The scientists recorded the fakir's behavior step by step throughout one of his shows and took blood from the veins in his arm and cerebrospinal fluid from his spine through a "spinal tap" (a special procedure which is performed by inserting a needle at the back of the spine, on the surface of the spinal cord). They also recorded the fakir's brain waves with an EEG machine. Throughout his performance, the fakir was observed to stare ahead to some fixed imaginary point and not blink for up to 5 minutes (normal people flicker their eyes several times every minute). As a matter of fact, the fakir was "somewhere else" in space and time, not aware of his surroundings. However, when he finished his performance, he would return quickly to a normal state of consciousness. Blood testing showed that at the end of the act the fakir's epinephrine (adrenaline) levels were high (similar to the adrenaline "rush" thrill-seekers experience). However, his endogenous opioids (the body's own pain killers) were not affected. EEG recordings showed that the fakir was switching his brain waves from the alpha rhythm to slower theta waves. Amazingly, while the fakir did not feel any pain during his act, he complained bitterly (when he had returned to his normal state of mind) to the nurse who pricked his arm to take blood for testing after his show!

Another extreme example of cultural influences in reducing perception and expression of pain is the procedure of "trepanation" (trephination or burr hole drilling) in East Africa. During the procedure, done up to the early 21st century for a number of reasons, the patients do not receive any form of analgesia or anesthesia. The *doktari* or *daktari* (tribal doctor) cuts the muscles of the head to uncover the bony skull in order to drill a hole and expose the dura. Trepanation (evidence of which has been found even in Neolithic times) was done for both medical reasons, for example intracranial pathology, and mystical reasons. During the procedure the patient sits calmly, fully awake, without signs of distress, and holds a pan to collect the dripping blood! I am not aware of any scientific studies that have looked into this phenomenon, so gruesome for Westerners, but I would not be surprised if the "subjects" were using some method to change their state of mind and block pain (one is the change in brain waves I described above, another one is hypnosis).

Today, scientists have a better understanding of some of the altered states of mind. For example, hypnosis is considered an "altered state of consciousness" and has been well investigated with studies of functional imaging (a method by which scientists can record the activity of brain cells in people's brains when they are performing certain mental activities or when the feel certain sensations). Hypnosis makes the person more prone to suggestions, modifies both perception and memory, and may produce changes in functions that are not normally under conscious control, such as sweating or the tone of blood vessels. Again, these studies are summarized in the popular science book, *Beyond Pain* [3].

How do we explain the differences in pain perception and expression between ethnic groups?

Ethnic groups may have different genetic make-ups and show distinct physiological and morphological characteristics (for example in the way certain drugs are metabolized, or in muscle enzymes after exercise). However, the physical differences between people of different cultures are less important than set beliefs and behaviors that influence the thoughts and actions of the members of a given cultural/ethnic group.

In regard to health care, patients have certain beliefs or explanations for their symptoms. Such beliefs result from interaction of cultural background, socioeconomic status, level of education, and gender. It is these beliefs that affect patients' ideas about what is wrong with them and what they should expect from health care providers. Furthermore, the way patients report pain is shaped to a certain degree by what is supposed to be the norm in their own culture. For example, some ethnocultural groups use certain expressions accepted in their own culture to describe painful physical symptoms, when in reality they describe their emotional distress and suffering. Research has shown that the description of physical pain (in reality reflecting "emotional pain") is more often seen in the course of stressful events such as immigration to a new country, separation from one's family, changes in one's traditional gender roles, financial difficulties, and depression. Health providers must then be able to recognize that different cultures have different beliefs and attitudes toward: (a) authority, such as the physician or persons in position of power; (b) physical contact, as during physical examination; (c) communication style in regard to the verbal or body language with which people communicate their feelings; (d) men or women health providers; and (e) expressing sexual or other issues.

What are the consequences of understanding cultural differences?

Racial and ethnic minorities are shown to be at risk for poor pain assessment and inferior management in acute, chronic, and cancer-related pain. These differences in treatment may arise from the health care system itself (the ability to reach and receive services) or from the interaction between patients and health care providers, as beliefs, expectations, and biases (prejudices) from both parties may interfere with care.

Patients may be treated by health care providers who come from a different race or ethnic background. The differences between patients and providers may be "visible," like age, gender, social class, ethnicity, race, or language, or "invisible," such as characteristics below the tip of the "cultural iceberg" such as attitudes, beliefs, values, or preferences [2]. Dangerous consequences arising from ethnic differences between patients and medical professionals have been shown in different studies demonstrating that patients of certain ethnic backgrounds (Mexican American or Asian, African, and Hispanic) are less likely than Caucasians to receive adequate analgesia in the emergency room or be prescribed certain amounts of powerful pain-killing drugs such as opioids. However, worldwide differences in administration of opioids in non-white nations are not solely due to health provider/patient interaction, but may relate to system politics. An example is the U.S. campaign against drug trafficking, which affects negatively the access of cancer patients to opioids in Mexico.

It is indeed challenging to try to understand both the differences and the similarities that exist in people with diverse ethnocultural backgrounds, but such knowledge is necessary to improve diagnosis and management of painful disorders.

What is the effect of gender on pain perception and expression and health care utilization?

There are many differences in pain perception and expression between females and males. Altogether, the differences between genders can be attributed to a combination of biological, psychological, and sociocultural factors, such as the family, the workplace, or the group's cultural background in general (summarized by Mailis Gagnon et al. [4]).

Female gender is associated with greater utilization of health care services and higher prevalence of certain pain conditions, while it serves as an especially significant predictor of pain perceptions and coping strategies. Research studies show that women use higher health care services per capita as compared to men for all types of morbidity and are more likely to report pain and other symptoms and to express higher distress than men. Furthermore, women in a deprived socioeconomic situation run a higher risk for pain. So, how do we explain these phenomena?

From the biological point of view, females are more vulnerable to experimentally induced pain, showing lower thresholds, higher pain discrimination, and less tolerance of pain stimuli than males. Numerous studies have shown that female hormones, and their fluctuations across life stages or during the month, play a substantial role in pain perception. Additionally, certain genetic factors unique to women may affect sensitivity to pain and/or metabolism of certain substances.

Psychologically, women also differ from men when it comes to coping strategies and expressions of pain. For example, in one study, women with arthritis reported 40% more pain and more severe pain than men, but were able to employ more active coping strategies such as speaking about the pain, displaying more nonverbal pain indicators such as facial grimacing, gestures like holding or rubbing the painful area or shifting in their chair, seeking spiritual help, and asking more about the pain. One of the explanations for differences in the ability to cope with the problem at hand relates to the greater role women have in taking care of the family. It is believed that this greater role makes women ask questions or seek help in an effort to maintain themselves or their family in a good condition.

Ethnocultural and environmental factors also account partially for differences in perceiving and reporting pain or other symptoms. For example, a few studies have shown higher pain perception and expression in South (Central) Asian groups (including patients from India and Pakistan), as follows:

a) A study of thermal pain responses in white British and South (Central) Asian healthy males showed no physiological differences when subjects were tested for warm and cold perception (this means the level at which a stimulus was felt as warm or cold). However, the South Asians showed lower pain thresholds to heat and were in general more sensitive to pain. The study's authors concluded that ethnicity plays an important

role, even if the investigators were not exactly sure what behavioral, genetic, or other determinants of ethnicity were involved.

b) In the Women's Health Surveillance Report from Statistics Canada, which surveyed approximately 100,000 households, the proportion of South (Central) Asians who reported chronic pain was much greater than any other ethnic group in the Canadian population over 65 years old (with 38.2% of the males and 55.7% of the South Asian females reporting chronic pain).

c) In a large cross-sectional study from a Canadian pain clinic [4], women significantly outnumbered men but presented with lower levels of physical pathology in almost all (Canadian-born or foreign-born) groups. Noticeably, nearly one in two South Asian women was classified to have high pain disability in the absence of physical pathology, the highest percentage of all female subgroups. The researchers felt that maybe these patients were sent by their doctors to the pain clinic with physical complaints, while in reality they were suffering from emotional distress. This may indeed make sense because South Central Asians constitute the most recent wave of immigrants to Canada, and therefore stress of immigration may be substantial.

Pearls of wisdom

- Ethnocultural research is in its infancy. Williams [5] stressed that racial and ethnic identifiers (such as language spoken at home, country of birth, race, etc.) are necessary to document pain disparities in clinical situations; plan and implement prospective studies to detect disparities; develop and evaluate pain assessment tools that reflect cultural, ethnic, and linguistic differences; clarify the role of both patients and physicians' ethnicity in pain management; examine racial and ethnic differences in pain perception, beliefs, attitudes, and behaviors that may underlie differences in pain experiences and clinical pain conditions; develop culturally sensitive models for assessing and treating pain and methods to disseminate such information; and document progress toward eliminating disparities in pain management and evaluate pain management outcomes.
- A word of caution: Ethnocultural research is not without difficulties. For example, simply grouping American people into blacks, Hispanics. and "old Americans" (white Anglo-Saxons whose families have lived in the United States for several generations), fails to appreciate the massive social, cultural, and economic differences between dependents of people brought to America 2–3 centuries ago and the millions of recent immigrants from different parts of the world, who may have adopted the culture of the group into which they moved to variable degrees or are of mixed background through intermarriage.
- Therefore, future studies will have to take numerous factors in account in order to reflect the complex reality of culture and ethnicity and their influence not only in pain perception and expression, but also in health care utilization and treatment outcomes.

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Chapter 6
Pharmacology of Analgesics (Excluding Opioids)

Kay Brune

The classes of analgesic drugs mentioned below are available worldwide and are constantly replaced by new compounds that are often too costly to be sold in all countries. However, pain therapy need not suffer from this limitation because the essential drugs including cyclooxygenase inhibitors, antiepileptic drugs, opiates and opioids, and ketamine are available in almost all countries, and the value of the novel compounds remains unclear.

Case report 1: Choosing the right analgesic

Recently, a good friend of mine drove home on his bicycle. He was hit by a car and fell to the ground. Thereafter, he suffered from chest pain and asked his doctor for help. He received 10 mg morphine s.c. He called me in the middle of the night and told me that the pain was still devastating, but in addition he felt awful, was nauseated and had vomited. I suggested taking 75 mg diclofenac resinate. He called the next morning telling me that he had fallen asleep shortly after having taken diclofenac.

This example demonstrates that so-called "strong analgesics," such as morphine and other opioids, are not always effective. In acute musculoskeletal or traumatic pain, cyclooxygenase (COX) inhibitors may be preferable. A drug like diclofenac (an aspirin-like drug) often does a better job. A detailed commentary on this case report follows later.

How does diclofenac, a member of the class of COX inhibitors, work?

COX inhibitors inhibit peripheral and central hyperalgesia. Like all commonly used analgesic compounds, including morphine (an opioid), pregabalin (an antiepileptic), ziconotide (an N-type calcium channel blocker), and ketamine (a blocker of the NMDA-receptor-attached sodium channel), COX inhibitors exert a major effect in the dorsal horn of the spinal cord (and therefore it is incorrect to call them "peripheral analgesics"). Compared to the above drug classes, COX inhibitors have a distinctly different mode of action. A peripheral trauma will initiate peripheral hyperalgesia, which results from a prostaglandin-induced increase in nociceptor sensitivity. Also, central hyperalgesia is initiated from the blockade of the activity of interneurons due to the production of prostaglandin E_2 (PGE_2). Following a peripheral trauma, the enzyme COX-2 is expressed in the dorsal horn cells by means of hormonal cytokines and neuronal messages. PGE_2 activates protein kinase A (pKA). The activation results in phosphorylation of the glycine-receptor-associated chloride channel. This, in turn, reduces the probability of chloride channel opening. The blockade of the chloride channel reduces the hyperpolarization of the second neuron and therefore makes it more excitable to glutamate-transmitted stimuli. In other words, trauma, inflammation, and tissue damage activate the production of COX-2 enzyme in the dorsal horn cells of the spinal cord, which reduces the hyperpolarization of the second

neuron and thus facilitates transmission of nociception-related inputs to the central nervous system, resulting in pain sensation. Inhibition of prostaglandin production by the induced COX-2 reduces (normalizes) excitability of the second neuron for glutamate-mediated transmission and thus exerts an antihyperalgesic effect.

Similarly, in the periphery, at the site of trauma or inflammation COX-2 is induced as well. It produces prostaglandin E_2 and increases the sensitivity of TRPV1 receptors, allowing for the activation of multimodal receptors (nociceptors) by temperature, pressure, and proteins. Again, blockade of prostaglandin production reduces peripheral hyperalgesia.

Going back to the case report, the acute trauma caused peripheral and central hyperalgesia within half an hour. This pain can be reduced effectively by inhibitors of COXs. The widespread use of COX inhibitors shows the importance of this class of analgesic compounds. In contrast to what was believed in the past, this group of drugs comprises old and new substances, including acetaminophen/paracetamol (formerly believed to have a unique mode of action), aspirin, dipyrone, ibuprofen, indomethacin, and piroxicam. In other words, this group comprises relatively weak compounds as well as highly effective ones. They differ in their pharmacokinetic behavior and some of their unwanted drug effects that are not related to their mode of action. Acetaminophen overdose, for example, leads to serious liver failure, which is almost never seen with ibuprofen.

How do the various COX inhibitors available differ pharmacokinetically?

This group of drugs exerts analgesia via inhibition of prostaglandin production. The differences, however, result from their pharmacokinetic characteristics (Table 1).

- Some (nonacidic) agents such as acetaminophen, dipyrone, and metamizol are distributed homogeneously throughout the body. They are analgesic but not anti-inflammatory.
- Other (acidic) agents achieve high concentrations in inflamed tissue, but also in the kidney, stomach wall, bloodstream, and liver. They have an analgesic and anti-inflammatory effect, but gastrointestinal (GI) and kidney toxicity is pronounced (for all except acetaminophen and dipyrone).
- Selective COX inhibitors demonstrate less GI toxicity, no interference with blood coagulation, and less aspirin-induced asthma. Examples are acetaminophen, celecoxib, and etoricoxib.
- Some of these compounds are absorbed quickly and others slowly. This difference is important if acute pain relief is required.
- Some compounds are eliminated quickly, others slowly. Those that are eliminated quickly have a short duration of action, and these are often less toxic at low doses. Slow elimination goes along with prolonged analgesic action but may lead to unwanted side effects, including water and fluid retention, increased blood pressure, and worsening of cardiac insufficiency.

So, why did I recommend diclofenac to my friend in case report 1?

The reasons I recommended diclofenac to my friend were:

1) Fast absorption

2) Very potent inhibition of COX, with greater inhibition of COX-2 than COX-1

The fast onset of absorption of diclofenac resinate is preferable to the "normal" diclofenac preparations in which the active ingredient is often given in an acid-resistant coating. This may lead to delayed absorption, and consequently, lack of fast pain relief. On the other hand, diclofenac, once absorbed, is eliminated quickly by metabolism. Consequently, to have a prolonged effect, slow absorption is necessary.

Case report 2: Choosing the right combination

A man, aged 71, complained about excruciating pain in his spine. The reason was metastasis of a prostate carcinoma, the growth of which was not completely controlled. Every evening the patient took liquid tramadol in a dose of 100 mg, which did not reduce his pain sufficiently. In his desperation he added 3 g (6 tablets) of aspirin, and despite GI discomfort, he found rest. The treating physician changed this combination and prescribed morphine (sustained-release) and naproxen together with a proton pump inhibitor (PPI). The patient was satisfied with this therapy.

Why was morphine plus naproxen the better choice?

Tumor metastases are surrounded by an inflammatory tissue capsule containing many activated nociceptors. This layer of inflammatory cells produces many prostaglandins, which lead to peripheral and central hyperalgesia. By

Table 1
Physicochemical and pharmacological data of acidic, nonselective COX inhibitors

Pharmacokinetic/Chemical Subclass	PK_A	Binding to Plasma Protein	Oral Bioavailability	t_{max}	t_{50}	Single Dose (Max. Daily Dose) for Adults
Short Elimination Half-Life						
Aspirin* (acetylsalicylic acid)	3.5 (3.0)	50–70% (~80%)	50%, dose dependent (1–5 h, dose dependent)	15 min (15–60 min)	15 min	0.05–1 g (6 g) (not in use)
Ibuprofen	4.4	99%	100%	0.5–2 h	2 h	200–800 mg (2.4 g)
Flurbiprofen	4.2	>99%	~ 90%	1.5–3 h	2.5–4 (8) h	50–100 mg (200 mg)
Ketoprofen	5.3	99%	90%	1–2 h	2–4 h	25–100 mg (200 mg)
Diclofenac	3.9	99.7%	50%, dose dependent	1–12 h, very variable	1–2 h	25–75 mg (150 mg)
Long Elimination Half-Life						
Naproxen	4.2	99%	90–100%	2–4 h	12–15 h	250–500 mg (1.25 g)
6–Methoxy-2–naphthylacetic acid (active metabolite of nabumetone)	4.2	99%	20–50%	3–6 h	20–24 h	0.5–1 g (1.5 g)
Piroxicam	5.9	99%	100%	3–5 h	14–160 h	20–40 mg; initial dose: 40 mg
Meloxicam	4.08	99.5%	89%	7–8 h	20 h	7.5–15 mg

* Aspirin releases salicylic acid (SA) before, during, and after absorption. Values in brackets refer to the active (weak) COX-1/COX-2 inhibitor SA.

combining COX-2 inhibition with opiates (opioids), a maximum of effect was achieved. Naproxen was chosen because it is eliminated slowly and—in the right dose—is sufficient for a full night of pain relief.

Case report 3: Choosing analgesics other than opioids or COX inhibitors

A woman, aged 78, fell down the stairs of her house and suffered a complete compression of the spinal cord between C4 and C5. She became tetraplegic instantly. Emergency neurosurgery was impossible in her vicinity. Furthermore, she had taken an aspirin-containing analgesic mixture the day before. This meant inhibition of blood coagulation for up to 5 days and consequently serious risks for neurosurgery. She remained tetraplegic for 2 years and then developed untreatable burning pain in the legs. Her standard medication of dipyrone was not effective. Low doses of morphine were dissatisfying, but adding gabapentin to low-dose morphine reduced the pain considerably. However, it caused the woman to be sleepy and dizzy all the time to an extent that did not permit to her to watch TV as she liked to do.

How does gabapentin work against pain?

Neuropathic pain results from damage to afferent neurons and changes in pain transmission in the dorsal horn of the spinal cord and above. It comprises a growing therapeutic problem. In post-traumatic, postherpetic (chronic) pain, antiepileptics can be a drugs can or morphine. The dose of both typesthus be kept relatively low. The addition of COX inhibitors does not further increase the effectiveness of these drugs. Still, since most neuronal cells in our body comprise voltage-gated sodium channels, the therapeutic use of blockers of these channels goes along with many central nervous system (CNS) side effects such as dizziness, sleepiness, lack of attention, and lack of alertness. These compounds must therefore be dosed cautiously in order to produce therapeutic effects without unacceptable CNS depression.

Are there options to block calcium channels more effectively?

Neuronal cells have specific calcium channels (N-type calcium channels) that play a role in the communication between cells. The release of glutamate in nociception from the first neuron for the activation of the second

neuron is also regulated by N-type calcium channels. The blockade of these channels blocks the inflow of calcium into glutamate cells, thus reducing glutamate release and activation of NMDA receptors. However, as these N-type channels are present in most neuronal cells, a general blockade would be incompatible with life. But recently ziconotide, a toxin from a sea snail, has been found to block these channels when administered directly into the spinal column, with tolerable side effects. Unfortunately, intrathecal administration of drugs is quite a sophisticated and expensive option for pain control, and presently it is done only at a few highly specialized pain centers for exceptional cases.

What other—more practical—options are available, when antiepileptic drugs fail to help?

Another option for treating pain in the clinical setting is the use of ketamine, which blocks use-dependent sodium channels of the glutamate NMDA receptor. Such receptors are not limited to the pain pathway, but are ubiquitously involved in neuronal communication. Consequently, the blockade of this sodium channel cannot be limited to pain pathways, but a certain degree of selectivity is achieved by the use dependence. In other words, painful stimuli lead to a higher probability of opening of this channel, which can be accessed only in the open position by ketamine, which can then block it. Still, the relatively low specificity of ketamine's action causes many unwanted drug effects, ranging from "bad trips" (dysphoria) to lack of coherent thinking and attention. Consequently, the use of ketamine is restricted to the clinical setting, in particular analgesic sedation. Nevertheless, low-dose ketamine (<0.2 mg/kg/h S-ketamine or <0.4 mg/kg/h ketamine) maybe helpful as a "rescue medication" in uncontrolled pain, e.g., due to nerve plexus infiltration in cancer. Unfortunately, as oral bioavailability is unpredictable, only the intravenous route can be used.

Pearls of wisdom

- The drugs discussed in this chapter allow for successful treatment of most pain conditions, but not all.
- It should be kept in mind that the most important prototypes of the nonopioid analgesics are the COX inhibitors, which comprise the most widely used drugs worldwide because they are also given against fever, inflammation, and many states of discomfort, including migraine. Due to their mode of action, their effect plateaus. In other words, the normalization of hyperalgesia ends when prostaglandin E_2 production is completely suppressed. Increasing the dose will not increase the effect any further.
- Constant inhibition of COXs in the vascular wall (selectively or nonselectively) leads to a constant blockade of the production of the vasoprotective factor prostacyclin (PGI_2). This appears to be the main reason for the increased incidence of cardiovascular events (heart attack, stroke, atherosclerosis), seen with the use of COX inhibitors, including acetaminophen (paracetamol).

Table 2
Physicochemical and pharmacological data of nonselective COX-2 inhibitors

Pharmacokinetic/ Chemical Subclass	COX-1/ COX-2 Ratio	Binding to Plasma Protein	VD	Oral Bio-availability	t_{max}	t_{50}	Primary Metabolism (Cytochrome P-450 Enzymes)	Single Dose (Max. Daily Dose) for Adults
Acetaminophen (paracetamol)		~ 20%	~70 L	~ 90%	1 h	1–3 h	Oxidation (direct sulfation)	1 g (4 g)
Celecoxib	30	91%	400 L	20–60%	2–4 h	6–12 h	Oxidation (CYP2C9, CYP3A4)	100–200 mg (400 mg) for osteoarthrosis and rheumatoid arthritis
Etoricoxib	344	92%	120 L	100%	1 h	20–26 h	Oxidation to 6'-hydroxymethyl-etoricoxib (major role: CYP3A4; ancillary role: CYP2C9, CYP2D6, CYP1A2)	60 mg (60 mg) for osteoarthrosis, 90 mg (90 mg) for rheumatoid arthritis, 120 mg (120 mg for acute gouty arthritis

- Still, comparing the unwanted drug side effects of all analgesic compounds, including opiates, one would come to the conclusion that they all have their problems. They should be used in serious pain, but not as a means to decrease daily discomfort; only then is their use meaningful and justifiable.

Table 3
Major side effects, drug interactions, and contradictions of COX inhibitors

Drug	Adverse Drug Reactions*	Drug Interactions	Contradictions (Absolute and Relative)
Nonselective, Acidic Drugs			
Aspirin	Inhibition of platelet aggregation for days, aspirin-induced asthma, ulcerations, bleeds	Vitamin K antagonists	Hypersensitivity to the active substance or to any of the excipients, impaired blood coagulation, pregnancy and all contradictions listed below
Diclofenac Ibuprofen Indomethacin Ketoprofen Ketorolac Naproxen Meloxicam	GI ulcerations, dyspepsia, increased BP, water retention, allergic (asthmatic) reactions, vertigo, tinnitus	ACE inhibitors, glucocorticoids, diuretics, lithium, SSRIs, ibuprofen: reduction of low-dose aspirin cardioprotection	Asthma, acute rhinitis, nasal polyps, angioedema, urticaria or other allergic-type reactions after taking ASA or NSAIDs; active peptic ulceration or GI bleeds; inflammatory bowel disease; established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease; renal failure
Selective (Preferential) COX-2 Inhibitors			
Acetaminophen (paracetamol)	Liver damage	Not prominent	Liver damage, alcohol abuse
Celecoxib	Allergic reactions (sulfonamide)	Blocks CYP2D6; interactions with SSRIs and beta-blockers	Existing pronounced atherosclerosis, renal failure
Etoricoxib	Water retention, increased blood pressure	Reduces estrogen metabolism	As with celecoxib, plus insufficient control of blood pressure; cardiac insufficiency
* More pronounced in highly potent and/or slowly eliminated drugs (all except ibuprofen)			

Table 4
Pharmacokinetic data on non-COX, nonopioid analgesics

Type (Drug)	t_{50}	Common Dosing	Adverse Reactions
Antiepileptics			
Carbamazepine	~2 days	~0.5 g b.i.d.[1]	Diplopia, ataxia (aplastic anemia)
Gabapentin	~6 hours	~1 g b.i.d.	Somnolence, dizziness, ataxia, headache, tremor
Pregabalin	~5 hours	~200 mg t.i.d.	
Blockers of NMDA-receptor Na^+-channels			
Ketamine (racemic)	Fast,[2] ~50 mg/d	0.5 mg/kg/h	Hypersalivation, hypertension, tachycardia, bad dreams
S^+-Ketamine	As racemic, comp. S^+-ketamine, twice as active		
N-Type Ca-Channel Blockers[3]			
Ziconotide	Permanent intrathecal administration		CNS disturbances from nausea to coma depending on the dose and distribution of the toxin, granuloma-formation

[1] No hard evidence for analgesic effects aside of trigeminal neuralgia; no dose recommendations for neuropathic pain available.
[2] Ketamine is highly lipophilic and sequesters into fat tissue (t_{50}, distribution ~ 20 min); continuous infusion requires attention (to avoid overdosing).
[3] Only in desperate patients if intrathecal administration is possible.

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Chapter 7
Opioids in Pain Medicine

Michael Schäfer

Classification of opioids

Treatment of pain very quickly reaches its limits. Anyone who has suffered from a severe injury, a renal or gall bladder colic, a childbirth, a surgical intervention, or an infiltrating cancer has had this terrible experience and may have experienced the soothing feeling of gradual pain relief, once an opioid has been administered. In contrast to many other pain killers, opioids are still the most potent analgesic drugs that are able to control severe pain states. This quality of opioids was known during early history, and opium, the dried milky juice of the poppy flower, *Papaver somniferum,* was harvested not only for its euphoric effect but also for its very powerful analgesic effect. Originally grown in different countries of Arabia, the plant was introduced by traders to other places such as India, China, and Europe at the beginning of the 14th century.

At that time, the use of opium for the treatment of pain had several limitations: it was an assortment of at least 20 different opium alkaloids (i.e., substances isolated from the plant), with very divergent modes of action. Overdosing occurred quite often, with many unwanted side effects including respiratory depression, and, because of irregular use, the euphoric effects quickly resulted in addiction.

With the isolation of a single alkaloid, morphine, from poppy flower juice by the German pharmacist Friedrich Wilhelm Sertürner (1806) and the introduction of the glass syringe by the French orthopedic surgeon Charles Pravaz (1844), much easier handling of this unique opioid substance became possible with fewer side effects.

Today we distinguish naturally occurring opioids such as morphine, codeine, and noscapine from semisynthetic opioids such as hydromorphone, oxycodone, diacetylmorphine (heroin) and from fully synthetic opioids such as nalbuphine, methadone, pentazocine, fentanyl, alfentanil, sufentanil, and remifentanil. All these substances are classified as opioids, including the endogenous opioid peptides such as endorphin, enkephalin, and dynorphin which are short peptides secreted from the central nervous system under moments of severe pain or stress, or both.

Opioid receptors and mechanism of action

Opioids exert their effects through binding to opioid receptors which are complex proteins embedded within the cell membrane of neurons. These receptors for opioids were first discovered within specific, pain related brain areas such as the thalamus, the midbrain region, the spinal cord and the primary sensory neurons. Accordingly, opioids produce potent analgesia when given systemically (e.g., via oral, intravenous, subcutaneous, transcutaneous, or intramuscular routes), spinally (e.g., via intrathecal or epidural

Table 1
List of different opioids that activate opioid receptors within the central nervous system

Opioid Alkaloids	Semisynthetic Opioids	Synthetic Opioids	Opioid Peptides
Morphine	Hydromorphone	Nalbuphine	Endorphin
Codeine	Oxycodone	Levorphanol	Enkephalin
Thebaine	Diacetylmorphine (heroin)	Butorphanol	Dynorphin
Noscapine	Etorphine	Pentazocine	
Papaverine	Naloxone (antagonist)	Methadone	
	Naltrexone (antagonist)	Tramadol	
		Meperidine	
		Fentanyl	
		Alfentanil	
		Sufentanil	
		Remifentanil	

routes), and peripherally (e.g., via intra-articular or topical routes).

Today, three different opioid receptors, the μ-, δ-, and κ-opioid receptor, are known. However, the most relevant is the μ-opioid receptor, since almost all clinically used opioids elicit their effects mainly through its activation. The three-dimensional structure of opioid receptors within the cell membrane forms a pocket at which opioids bind and subsequently activate intracellular signaling events that lead to a reduction in the excitability of neurons and, thus, pain inhibition. According to their ability to initiate such events, opioids are distinguished as full opioid agonists (e.g., fentanyl, sufentanil) that are highly potent and require little receptor occupancy for maximal response, partial opioid agonists (e.g., buprenorphine) that require greater receptor occupancy even for a low response, and antagonists (e.g., naloxone, naltrexone) that do not elicit any response. Mixed agonists/antagonists (e.g., pentazocine, nalbuphine, butorphanol) combine two actions: they bind to the κ-receptor as agonists and to the μ-receptor as antagonists.

Opioid-related side effects

The first time opioids are taken, patients frequently report acute side effects such as sedation, dizziness, nausea, and vomiting. However, after a few days these symptoms subside and do not further interfere with the regular use of opioids. Patients should be slowly titrated to the most effective opioid dose to reduce the severity of the side effects. In addition, symptomatic treatments such as antiemetics help to overcome the immediate unpleasantness. Also, respiratory depression may be a problem at the beginning, particularly when large doses are given without adequate assessment of pain intensity. Dose titration and regular assessments of pain intensity and breathing rate are recommended. During prolonged and regular opioid application, respiratory depression is usually not a problem. Cognitive impairment is an important issue at the beginning, particularly while driving a car or operating dangerous machinery such as power saws. However, patients on regular opioid treatment usually do not have these problems, but all patients have to be informed about the occurrence and possible treatment of these side effects to prevent arbitrary discontinuation of medication. Constipation is a typical opioid side effect that does not subside, but persists over the entire course of treatment. It can lead to serious clinical problems such as ileus, and should be regularly treated with laxatives or oral opioid antagonists (see below).

Sedation

Opioid-induced reduction of central nervous system activity ranges from light sedation to a deep coma depending on the opioid used, the dose, route of application, and duration of medication. In clinically relevant doses, opioids do not have a pure narcotic effect, but they also lead to a considerable reduction in the maximal alveolar concentration (MAC) of volatile anesthetics used to induce unconsciousness during surgical procedures.

Muscle rigidity

Depending on the speed of application and dose, opioids can cause muscle rigidity particularly in the trunk,

abdomen, and larynx. This problem is first recognized by the impairment of adequate ventilation followed by hypoxia and hypercarbia. The mechanism is not well understood. Life-threatening difficulty in assisted ventilation can be treated with muscle relaxants (e.g., succinylcholine 50–100 mg i.v., i.m.).

Respiratory depression

Respiratory depression is a common phenomenon of all μ-opioid agonists in clinical use. These drugs reduce the breathing rate, delay exhalation, and promote an irregular breathing rhythm. Opioids reduce the responsiveness to increasing CO_2 by elevating the end-tidal pCO_2 threshold and attenuating the hypoxic ventilation response. The fundamental drive for respiration is located in respiratory centers of the brainstem that consist of different groups of neuronal networks with a high density of μ-opioid receptors. Life-threatening respiratory arrest can be reversed by titration with the i.v. opioid antagonist naloxone (e.g., 0.4–0.8–1.2 mg).

Antitussive effects

In addition to respiratory depression, opioids suppress the coughing reflex, which is therapeutically produced by antitussive drugs like codeine, noscapine, and dextromethorphan (e.g., codeine 5–10–30 mg orally). The main antitussive effect of opioids is regulated by opioid receptors within the medulla.

Gastrointestinal effects

Opioid side effects on the gastrointestinal system are well known. In general, opioids evoke nausea and vomiting, reduce gastrointestinal motility, increase circular contractions, decrease gastrointestinal mucus secretion, and increase fluid absorption, which eventually results in constipation. In addition, they cause smooth muscle spasms of the gallbladder, biliary tract, and urinary bladder, resulting in increased pressure and bile retention or urinary retention. These gastrointestinal effects of opioids are mainly due to the involvement of peripheral opioid receptors in the mesenteric and submucous plexus, and are due to a lesser extent to central opioid receptors. Therefore, titration with methylnaltrexone (100–150–300 mg orally), which does not penetrate into the central nervous system, successfully attenuates opioid-induced constipation. More common practice, however, is the coadministration of laxatives such as lactulose (3 × 10 mg to 3 × 40 mg/day orally), which is mandatory during chronic opioid use.

Pruritus

Opioid-induced pruritus (itch) commonly occurs following systemic administration and even more commonly following intrathecal/epidural opioid administration. Although pruritus may be due to a generalized histamine release following the application of morphine, it is also evoked by fentanyl, a poor histamine liberator. The main mechanism is thought to be centrally mediated in that inhibition of pain may unmask underlying activity of pruritoreceptive neurons. Opioid-induced pruritus can be successfully attenuated by naltrexone (6 mg orally) or with less impact on the analgesic effect by mixed agonists such as nalbuphine (e.g., 4 mg i.v.).

Routes of opioid administration

Oral

The majority of opioids are easily absorbed from the gastrointestinal tract with an oral bioavailability of 35% (e.g., morphine) to 80% (e.g., oxycodone) entering the circulation. However, they undergo to a high degree (40–80%) immediate first-pass metabolism in the liver, where glucuronic acid binding makes the drug inactive and ready for renal excretion. Exceptions are metabolites of morphine, e.g., morphine-6-glucuronide, which is itself analgesic, or morphine-3-glucuronide, which is neurotoxic and can accumulate during renal impairment as well as cause serious side effects such as respiratory depression or neurotoxicity. Oral opioids are commonly available in two galenic preparations, an immediate-release formula (onset: within 30 min, duration: 4–6 hours) and an extended-release formula (onset: 30–60 min, duration: 8–12 hours). There is preliminary evidence for ethnic differences, e.g., between Caucasians and Africans, with regard to the hepatic metabolism of opioids, i.e., opioids exert a longer duration of action in Africans. This may be due in part to specific genetic subtypes of the hepatic enzyme cytochrome P-450, and in part due to the individual patient's lifestyle and habits.

Intravenous/intramuscular/subcutaneous

These different forms of parenteral opioid application follow the same goals: a convenient and reliable way of application, a fast onset of analgesic effect, and bypass

of hepatic metabolism. While intravenous application gives immediate feedback about the analgesic effect, intramuscular and subcutaneous routes of administration have some delay (about 15–20 min) and should be given on a fixed schedule to avoid large fluctuations in plasma concentrations. The faster rise in opioid plasma concentration with parenteral versus enteral applications enables better and more direct control of opioid effects; however, it increases the risk of a sudden overdose with sedation, respiratory depression, hypotension, and cardiac arrest. After parenteral administration, a first phase of opioid distribution within the central nervous system, but also in other tissues such as fat and muscles, is followed by a second, slower phase of redistribution from fat and muscles into the circulation with the possibility of the re-occurrence of some opioid effects. This phenomenon is particularly important following repeated administration.

Table 2
Equianalgesic doses of different routes of administrations of opioids

Drug	Dose (mg)	Conversion Factor
Morphine, oral	30	1
Morphine, i.v., i.m., s.c.	10	0.3
Morphine, epidural	3	0.1
Morphine, intrathecal	0.3	0.01
Oxycodone, oral	20	1.5
Hydromorphone, oral	8	3.75
Methadone, oral	10	0.3
Tramadol, oral	150	0.2
Tramadol, i.v.	100	0.1
Meperidine, i.v.	75	0.13
Fentanyl, i.v.	0.1	100
Sufentanil, i.v.	0.01	1000
Buprenorphine, s.l.	0.3	100

Sublingual/nasal

Only highly lipophilic substances such as fentanyl and buprenorphine can be administered by these routes, because they easily penetrate the mucosa and are absorbed by the circulation. Time of onset of analgesia is fast with fentanyl (0.05–0.3 mg; 5 min) but slower with buprenorphine (0.2–0.4 mg; 30–60 min). However, the duration of analgesia is much longer with buprenorphine (6–8 hours) than with fentanyl (15–45 min). Similar to the other parenteral applications, there is no hepatic first-pass metabolism.

Intrathecal/epidural

Opioids administered intrathecally or epidurally penetrate into central nervous system structures depending on their chemical properties: less ionized, i.e. more lipophilic, compounds such as sufentanil, fentanyl, or alfentanil penetrate much (800 times) more easily than more ionized, i.e. hydrophilic, compounds such as morphine. While the lipophilic opioids are quickly taken up, not only by the neuronal tissue, but also by epidural fat and vessels, a substantial amount of morphine remains within the cerebrospinal fluid for a prolonged period of time (up to 12–24 hours) and is transported via its rostral flow to the respiratory centers of the midbrain, leading to delayed respiratory depression. The effects of opioids within the central nervous system are terminated by their redistribution into the circulation and not by their metabolism, which is negligible. Doses for epidural morphine, for example, are a bolus dose of 1.0–3.0 mg, and a 24-h dose of 3.0–10 mg; and for intrathecal morphine a bolus dose of 0.1–0.3 mg, and a 24-h dose of 0.3–1.0–5.0 mg.

Morphine

Morphine, a strong μ-opioid agonist that is recommended in step 3 of the WHO ladder, is commonly used as a reference for all other opioids. It can be applied by all routes of administration. Morphine's active metabolites morphine-6-glucuronide and morphine-3-glucuronide can increase side effects such as respiratory depression and neurotoxicity (excitation syndrome: hyperalgesia, myoclonia, epilepsia), particularly when accumulation occurs due to impairment of renal function. Its main indications of use are for postoperative and chronic malignant pain; however, it is also used for other severe pain conditions (e.g., colic pain, angina pectoris). In acute pain states, morphine can be quickly titrated to optimal pain relief by the parenteral route (e.g., i.v. boluses of 2.5–5 mg morphine), upon which the morphine plasma concentration should be kept constant by regular timed intervals of subsequent administrations (e.g., 6–12 mg i.v. morphine/h). In chronic pain conditions, daily morphine doses should be given in an extended-release formula, and breakthrough pain is best treated by administration of a fifth of the daily morphine dose in an immediate-release formula. Regular monitoring of pain intensity and morphine consumption is desirable.

Oxycodone

Oxycodone is a strong oral μ-opioid agonist belonging to step 3 of the WHO ladder, with 1.5 times the analgesic potency of morphine. Oxycodone has a high oral bioavailability of 60–80%. It is metabolized in multiple steps to different metabolites, of which oxymorphone is the most active and 8 times more potent than morphine. Oxycodone has a similar therapeutic profile to morphine; however, it is only available as an oral extended-release formulation (10–80 mg tablets). Since these tablets have a relatively high dose, they can be pulverized and made into an aqueous solution, which has been misused for its euphoric effects by addicts.

Hydromorphone

Hydromorphone is a μ-opioid agonist belonging to step 3 of the WHO ladder (strong opioids) with 4–5 times the analgesic potency of morphine. After oral application (single dose 4 mg), the onset of analgesia occurs after 30 min and lasts up to 4–6 hours. Because of its high water solubility, it is available as both an oral and parenteral formulation (2 mg/1 amp.) that can be administered i.v., i.m., or s.c. Hydromorphone is extensively metabolized in the liver, with metabolism of approximately 60% of the oral dose. The metabolite hydromorphone-3-glucuronide can cause neurotoxic effects (excitation syndrome: hyperalgesia, myoclonus, epilepsy), similar to morphine-3-glucuronide.

Methadone

Methadone is a μ-opioid receptor agonist with 0.3 times the analgesic potency of morphine. In addition to its opioid receptor activity, it is also an antagonist of the *N*-methyl-D-aspartate (NMDA) receptor, which might be advantageous in chronic pain states such as neuropathic pain in which the NMDA receptor seems to be responsible for the persistent pain hypersensitivity. Methadone is a lipophilic drug with good CNS penetrability and high bioavailability (40–80%). It exists as an oral (5–40 mg tablets) and parenteral formulation (levomethadone: 5 mg/mL). Methadone is metabolized with no active metabolites by multiple different enzymes of the liver in a highly variable manner, which explains its broad variation of half-life (up to 150 h) and makes regular dosing quite difficult for patients. In general, pain relief is better obtained with methadone doses that are 10% of the calculated equianalgesic doses of conventional opioids. Excretion occurs almost entirely in the feces, which makes it a good candidate for patients with renal failure. Methadone has a much lower propensity for euphoric effects and is therefore used in maintenance programs for drug addicts. In addition, there is incomplete cross-tolerance to other opioids. Unfortunately, methadone has the potential to initiate Torsades de Pointes, a potentially fatal arrhythmia caused by a lengthening of the QT interval in the ECG.

Tramadol

Tramadol, a weak opioid, belongs to step 2 of the WHO ladder. Tramadol itself binds to norepinephrine and serotonin reuptake inhibitors, which increases local concentrations of norepinephrine and serotonin, leading to subsequent pain inhibition. In addition, one of its metabolites (M1) binds to the μ-opioid receptor, which elicits additional analgesia. Tramadol has a high bioavailability of 60% and 0.2 times the analgesic potency of morphine. Since the opioid component is dependent on hepatic metabolism to the M1 compound, genetic variations may differentiate poor from extensive metabolizers, and hence the respective differences in analgesic effects. Tramadol exists as an oral (50–100–150–200 mg tablets) and parenteral formulation (50–100 mg). As with all opioids, hepatic and renal impairment may lead to accumulation of the drug with an increased risk of respiratory depression. Because of potential interactions, tramadol should not be given together with monoamine oxidase inhibitors, since the combination may produce severe respiratory depression, hyperpyrexia, central nervous system excitation, delirium, and seizures.

Meperidine

Meperidine, a weak μ-opioid agonist, belongs to step 2 of the WHO ladder with 0.13 times the analgesic potency of morphine and significant anticholinergic and local anesthetic properties. Meperidine is most often used postoperatively, since in addition to its analgesic effects, it has anti-shivering properties. Meperidine exists as an oral (50 mg/mL solution) and parenteral formulation (50–100 mg/2 mL). It is metabolized in the liver to normeperidine with a half-life of 15–30 hours, and has significant neurotoxic properties. Meperidine

should not be given to patients being treated with monoamine oxidase inhibitors (MAOI), since the combination may produce severe respiratory depression, hyperpyrexia, central nervous system excitation, delirium, and seizures.

Fentanyl

Fentanyl, a strong μ-opioid agonist, belongs to step 3 of the WHO ladder with 80–100 times the analgesic potency of morphine. Fentanyl mainly exists as a parenteral formulation (0.1 mg/2 mL); however, sublingual application is sometimes used. A transdermal application system is widely used in industrial countries, but because of its costs and the delayed delivery system with additional risks (delayed respiratory depression), it may only be of use in rare cases. Fentanyl is metabolized in the liver to inactive metabolites. The rapid onset, high potency, and short duration of fentanyl is an advantage in the titration and controllability of perioperative pain. However, incorrect use may lead to large fluctuations in plasma concentration and increase the risk of psychological dependence and addiction. Importantly, repeated administration of fentanyl may lead to drug accumulation due to redistribution from fat and muscle tissue into the circulation with increased risk of respiratory depression.

Sufentanil

Sufentanil, a very strong μ-opioid agonist, with 800–1000 times the analgesic potency of morphine, is exclusively available as a parenteral formulation (0.25 mg/5 mL) and can be given i.v. (10–100 μg boluses) as well as epidurally (initially: 5–10 μg, repeated bolus: 0.5–1 μg). Because of its very high potency, sufentanil is mainly used intraoperatively. In comparison to fentanyl, it is much less prone to drug accumulation, because of its low tissue distribution, low protein binding, and high hepatic metabolization rate to inactive metabolites.

Buprenorphine

Buprenorphine belongs to the mixed agonist/antagonist opioids binding to μ- and k-opioid receptors. It usually has a slow onset (45–90 min), a delayed maximal effect (3 hours), and a long duration of action (8–10 hours). Buprenorphine is available as sublingual (s.l.) (0.2–0.4 mg capsules) and parenteral (0.3 mg/mL) formulations. Its metabolites are inactive and are mainly excreted via the biliary duct. Oral bioavailability is 20–30% and sublingual bioavailability is 30–60%. For acute pain, 0.2–0.4 mg s.l. buprenorphine or 0.15 mg i.v. is applied every 4–6 hours. Because of its very stable and long duration of action, buprenorphine is used for substitution therapy for drug addicts (4–32 mg/daily). Similar to fentanyl, there is a transdermal application system. Buprenorphine's respiratory depressant effects are reversed only by relatively large and repeated doses of naloxone (2–4 mg).

Naloxone/naltrexone

Both substances are classical opioid receptor antagonists with a preference for μ-opioid receptors. Naloxone is available only as a parenteral formulation (0.4 mg/1 mL), and it has a fast onset (within 5 min) and a short duration (30–60–90 min) of action. It is commonly used preoperatively to treat opioid overdosing and needs to be titrated and administered repeatedly under constant monitoring. Naltrexone exists only as an oral formulation (50 mg/tablet) with a delayed onset (within 60 min) and a long duration (12–24 h) of action. Naltrexone is mainly used for maintenance treatment for alcohol and drug dependence. Both substances can precipitate acute life-threatening withdrawal symptoms when improperly used, e.g., hyperexcitability, delirium, hallucinations, hyperalgesia, hypertension, tachycardia, arrhythmia, and increased sweating.

Pearls of wisdom

- Although they have been available for almost 200 years, opioids still remain the mainstay of pain management. While opioids are effective in most postoperative and cancer patients, and in some patients with neuropathic pain, most other noncancer pain is hardly responsive to opioid medication.
- While opioids are regarded with a lot of prejudice because of their side effects and abuse potential, clinical practice and research have demonstrated in the last few decades that opioid medication for short- and long-term treatment can be accomplished safely. There is no evidence about a differential indication of the opioids available. Consequently, availability, costs, and

personal experience should be the guiding principles when choosing an opioid.

- Because there is—as opposed to most drugs used in medicine—no organ toxicity, even at high doses and with long-term treatment, and because some important side effects diminish over time and other potential harmful side effects may be avoided with correct use, it may be that opioids will remain the mainstay of pain management for most of our patients for some time to come.

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Chapter 8
Principles of Palliative Care

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What is palliative care?

Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual. This widely accepted definition of the World Health Organization from 2002 includes some changes compared to an older WHO definition from 1990. The definition explains and reinforces the holistic approach, which not only covers the physical symptoms, but extends to other dimensions and aims of care for patients as they suffers now with their disease, with their own personal story, and in their actual setting and social context.

The WHO provides a similar definition for palliative care for children—the active total care of the child's body, mind, and spirit—and also involves giving support to the family. It begins when illness is diagnosed, and continues regardless of whether or not a child receives treatment directed at the disease. Health providers must evaluate and alleviate a child's physical, psychological, and social distress. Effective children's palliative care requires a broad multidisciplinary approach that includes the family and makes use of available community resources; it can be successfully implemented even if resources are limited. It can be provided in tertiary care facilities, in community health centers, and wherever children call home.

What are the principles of palliative care?

Palliative care is a philosophy of care that is applicable from diagnosis (or beforehand as appropriate) until death and then into bereavement care for the family. Often palliative care is seen as focusing on end-of-life care only, and while this is an important aspect of palliative care, it is only one component of the continuum of care that should be provided. It is focused on the needs of the patient, their families and carers. It is the provision of comprehensive holistic care with the patient at the center of that care, and is dependent on attitudes, expertise, and understanding. It is a philosophy that can be applied anywhere—across a range of skills, settings, and diseases. The WHO has outlined several principles that underpin the provision of palliative care, including statements that palliative care:

- Provides relief from pain and other distressing symptoms;
- Affirms life and regards dying as a normal process;
- Intends neither to hasten nor postpone death;
- Integrates the psychological and spiritual aspects of patient care;
- Offers a support system to help patients live as actively as possible until death;
- Offers a support system to help the family cope during the patient's illness and in their own bereavement;

- Uses a team approach to address the needs of patients and their families, including bereavement counseling if indicated;
- Will enhance quality of life, and may also positively influence the course of illness;
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy, radiation, or antiretroviral therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

How is palliative care provided?

Palliative care can be provided across a range of care settings and models, including home-based care, facility-based care, inpatient and day care. Care can be provided in specialist as well as general settings and should, where possible, be integrated into existing health structures. The concept of palliative care should be adapted to reflect local traditions, beliefs, and cultures—all of which vary from community to community and from country to country.

Palliative care is holistic and comprehensive, and thus ideally it should be delivered by a multidisciplinary team of care givers, working closely together and defining treatment goals and care plans together with the patient and his or her family. In many resource-poor countries the multidisciplinary care team will include community workers and traditional healers as well as nurses, doctors, and other health care professionals. Nurses have a key role in the provision of palliative care due to their availability within resource-poor settings, and they are often the coordinators of the multidisciplinary team. The health care professional may be working alone with little support from others, particularly in rural settings. Community health workers and volunteers can provide support to the health workers and have been trained with good effect to support them with basic medical care. In many resource-limited settings, community workers and volunteers are indispensable for the provision of palliative care and in particular with regard to social support for patients.

There are however, specific situations where professional support from peers or from a team is required. Ethical decision-making in complex situations, disagreeable patients or families, or family systems with complex conflicts may trigger a need for such support. For health care professionals working on their own it is very helpful to identify peers or a support team on which they can fall back if needed, to discuss problems, share responsibility, or get emotional support. This support will enable them to continue in their work for the benefit of the patients.

Case report

Grace is a 43-year-old widow. Her husband died from an "unknown cause" 4 years ago, and she has been bringing up her two children, who are aged 12 and 14, on her own since then. One year ago she noticed that she was getting pain on micturition and that her periods had become irregular and that she was bleeding mid-cycle. She did not seek medical help initially as she thought that this was just part of getting older, and culturally it was not appropriate to discuss such problems with anyone. Six months later, having been to visit a traditional healer first, and not responding to their treatment, she eventually visited her local health center as the pain was getting very bad; she was experiencing bleeding and found that she was unable to keep herself clean and free from odor. On examination at the local health center she was referred to the district hospital, from where she was referred to the national cancer center, where she was diagnosed as having a fungating cervical tumor. Initial diagnosis was of a Stage IV cervical carcinoma, which had spread to her lymph nodes, her pelvis, and her liver. Treatment with surgery was no longer an option, and chemotherapy was not available, so five fractions of palliative radiotherapy was given to try and reduce the pain and the bleeding. She had lost weight over the past 6 months and was suffering from fatigue. While she was an inpatient in the cancer unit she was seen by the local palliative care team because of severe pain in the pelvis and lower back. Pain management included low-fraction radiotherapy and she was commenced on 5 mg oral morphine every 4 hours. This dose was increased gradually to 35 mg of oral morphine every 4 hours with a prescribed rescue dose as required. This regime was combined with 12.5 mg amitryptiline at night for neuropathic pain, and it resulted in significant pain relief. She was also prescribed an antiemetic for nausea and a laxative to prevent her from becoming constipated from the morphine, and to soften her stool to reduce discomfort from the fungating wound on defecation. With the radiotherapy along with a cleansing regimen as well as use of topical metronidazole, the odor disappeared and she felt more comfortable.

The national cancer unit was based in the capital city over 250 km away from her village, and once her pain was controlled and the radiotherapy was finished, she wanted to go back home. As well as being nearer to her children, she could not afford the expense of being in hospital, and she was worried that the children would not be being looked after properly by her elderly mother-in-law. She was aware of her diagnosis of cancer, and the doctors were concerned that she might have an underlying condition of HIV, particularly as her husband had died of "unknown causes." She was, however, reluctant to have an HIV test due to the stigma that she may experience if it came back positive, and due to the advanced stage of her disease, having an HIV diagnosis was unlikely to alter the course of treatment. She was worried about the future of her two children aged 12 and 14 years, and concerned whether her mother-in-law would be able to support them if she died. These problems were addressed with repeated talks with Grace about issues surrounding the health of her children, both of whom seemed to be in good health. Grace was referred to a local home-based care team in her village and was advised as to how she could continue to access oral morphine for pain control, and she was discharged 10 days after having been admitted. She was supported by the home care team, the community, and spiritual leaders at home until she died 5 weeks later with her symptoms under control and having made arrangements for her children's care.

This case report emphasizes what palliative care is about. It is about management of pain and other symptoms, but it is also about psychological, social and spiritual problems. It is about the coordination and continuity of care in different settings and across the disease trajectory. It is about interdisciplinary and cross-sectional team work involving staff from different health care professions as well as volunteer services, including caregivers in their role as partners in the team as well as in their role as family members who require care and support.

How important is the assessment of the patient?

A thorough baseline assessment before the initiation of palliative care interventions as well as regular follow-up evaluations are paramount to ensuring adequate relief of symptoms and distress, and to adapting treatment to the individual patient. The initial assessment will describe the needs of the patient and form the basis not only for a drug regimen, but also for a palliative care plan tailored to individual needs and the patient's situation and context. It is also important to try to assess the cause of any pain or symptoms that the individual might be experiencing, and if the cause is treatable, e.g., an opportunistic infection, then it is important to treat the cause as well as manage the symptom.

What should be done for baseline assessment?

The baseline assessment should include a minimum set of information elicited by the health professional to help provide information about the context of care, e.g., age, sex, underlying disease, care setting, ongoing therapy (medical as well as traditional and complementary therapies), and previous treatments. The description of the care setting should include where the patient lives, who provides care, how many people there are at home, and an overview of financial and emotional resources and the needs of the patient and family. A sociogram can offer a rapid overview of family relations, and important events in the family history including any history of illness.

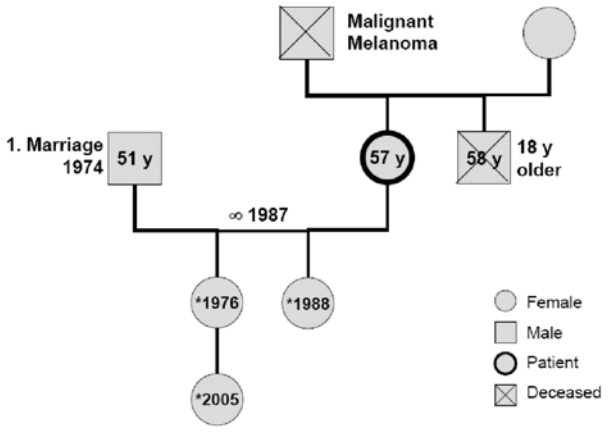

Fig. 1. Sociogram of a family setting of a woman with malignant melanoma.

Along with information about the context of care, the baseline assessment should not be restricted to physical symptoms, but should include several dimensions: physical, psychological, social, and spiritual deficits and resources. Many symptoms such as pain, dyspnea (difficulty breathing), nausea, or fatigue depend on subjective feelings rather than on objective measurable parameters, and so self-assessment by the patient is preferable. Self-assessment can be done with short symptom checklists such as the Edmonton Symptom

Assessment Score (ESAS), which uses numerical rating scales (NRS) or visual analogue scales (VAS) to assess intensity of the most important symptoms. The palliative care outcome score (POS) is a more comprehensive instrument that tries to include all dimensions of care in 12 questions. An African version has been developed that has been used with good effect in resource-poor settings. However, many patients with advanced diseases and with declining cognitive and physical function will not be able to complete even short self-assessment instruments. Assessment by caregivers or staff is usually a close substitute for the patient's self-assessment and should be implemented for such patients.

Assessment of psychological, spiritual, and social issues can be more complex, with limited tools being available to aid the health care professional. However, simple tools can be used for this purpose, such as FICA for assessing spiritual needs, i.e., Faith or beliefs, Importance and influence, Community, and Addressing the issues.

Performance status is an important parameter because it predicts needs. Performance status is also well suited for evaluation and monitoring of services, as it describes the patient population cared for. The Eastern Cooperative Oncology Group (ECOG) Score is an easy four-step categorical scale which is also implemented in the POS (Fig. 2).

0 = Fully active, able to carry on all pre-disease performance without restriction.
1 = Restricted in physically strenuous activity but ambulatory and able to carry out light work, e.g., light housework, office work.
2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3 = Capable of only limited self-care, confined to a bed or chair more than 50% of waking hours.
4 = Completely disabled. Cannot carry on any self-care. Totally confined to a bed or chair.

Fig. 2. Eastern Cooperative Oncology Group (ECOG) Scale.

What follow-up assessments are needed for re-evaluation?

Assessment is an ongoing process, and so after the initiation of treatment, regular re-evaluation is very important. The efficacy of any treatment given for symptom relief has to be monitored, and the treatment, including drug regimen, has to be adapted according to its effect. After the initial phase, with stable symptom relief, regular re-assessment should be maintained, as further deterioration from the underlying disease is to be expected. Cancer patients or HIV/AIDS patients receiving palliative care should be seen weekly, or at least monthly if the situation is stable, by the health care professional. Follow-up assessments can be brief, but should include short symptom checklists to monitor whether new symptoms have appeared. Treatment for new symptoms and problems should be initiated. The POS can be used on a regular basis to assess the patient's status, and ongoing therapies should also be re-evaluated regularly, to see whether they still are indicated or whether careful dose reduction or even withdrawal might be advisable. However, it should be noted that often drugs for the relief of pain, dyspnea, and other symptoms must be continued until the time of death. Symptomatic treatment can be discontinued if treatment of an underlying cause of the symptoms is possible (for example an opportunistic infection in patients with HIV/AIDS).

Following the death of the patient, an evaluation of the overall efficacy of the palliative care delivered is useful for quality assurance purposes. The easiest way is to ask caregivers and family members for an overall evaluation of the patient's care a few weeks or months after the death of the patient, using a simple categorical scale (overall satisfaction with care: very unsatisfied, unsatisfied, neither unsatisfied nor satisfied, satisfied, or very satisfied).

Symptom relief

Why is symptom relief so important?

Management of pain and other symptoms is an essential part of palliative care. With progression of the underlying disease, most patients suffer from physical and psychological symptoms. Cancer, HIV/AIDS, and other chronic infections such as tuberculosis may result in a plethora of symptoms, with severe impairment from pain, dyspnea, nausea and vomiting, constipation, or confusion. Most patients with advanced disease and limited life expectancy suffer from weakness and tiredness (fatigue), caused either by the disease or its treatment. Coping with the diagnosis and prognosis may lead to spiritual and psychological distress, anxiety, and depression. These symptoms can be treated, and with the alleviation of the symptom load, quality of life will be restored.

The following section will provide an overview on the management of the most important and most

frequent symptoms (Table 1). More detailed information on assessment and treatment of symptoms and on other areas of palliative care can be found in the clinical guide to supportive and palliative care for HIV/AIDS in sub-Saharan Africa, and in the WHO Integrated Management of Adult Illnesses Palliative Care module and related materials.

Pain management in palliative care follows the rules of cancer pain management, with analgesic medications according to the principles of the World Health Organization at the center of the therapeutic approach. Opioids such as oral morphine are the mainstay of pain management in palliative care in low-resource settings because they are relatively inexpensive and because effective palliative care is not possible without the availability of a potent opioid. Detailed information is available in Chapter 6.

Is treatment of other symptoms similar to pain management?

Whilst there is no similar tool to the WHO analgesic ladder to help treat other symptoms, many of the principles applied to the pain management can also be applied to other symptoms. For example, reverse what is reversible and treat the underlying cause without increasing the symptoms; use nonpharmacological drug interventions—adjunctively or alone, as appropriate; use medications specific to the types of symptoms; and address associated psychosocial distress. Medication for symptom management should also be given by the clock according to the different dosages available and where possible by mouth, thus making it easier for people to continue with their medications at home, where there is no health professional to give them injections.

How should you treat dyspnea?

Whereas opioids are well established as the mainstay of pain management, it is less well known that opioids also are very effective for the treatment of dyspnea. In opioid-naive patients, oral morphine (5–10 mg) or subcutaneous morphine (2.5–5 mg) will provide quick relief and may be repeated as required. Other opioids can be used for this indication as well, with equipotent dosage. Patients already receiving opioids for pain should have a dose increase to alleviate dyspnea. Continuous dyspnea should be treated with a continuous opioid medication, following similar dose-finding rules as for pain management, although mostly with lower starting dosages.

Respiratory depression is a side effect of opioids, but it does not contradict the use of opioids for dyspnea. Dyspnea is most often related to elevated carbon dioxide in the arterial blood, and less to reduced oxygen. Opioids diminish the regulatory drive caused by elevated carbon dioxide levels, and in consequence patients will feel less hunger for air, even if breathing is not improved. Opioids also reduce pain and anxiety, thus alleviating stress-induced dyspnea.

Dyspnea in cancer patients may also be caused by mechanical impairment, for example from pleural effusion. Mechanical release with pleural puncture will produce rapid relief. Dyspnea can also be related to severe anemia, leading to reduced oxygen transport capacity in the blood, and blood transfusions will alleviate dyspnea in severely anemic patients, though most often only for a few days until the hemoglobin count falls again. Oxygen will be helpful for control of dyspnea only in a minority of patients; however, other nonpharmacological interventions may help, such as repositioning of patients e.g., sitting in an upright position.

In most patients simple measures such as comforting care, allowing free flow of air, for example by opening a window or providing a small ventilator or fan, will be very effective in the treatment of dyspnea.

How should you treat nausea?

Nausea and vomiting can be treated with antiemetics such as metoclopramide or low-dose neuroleptics such as haloperidol. Corticosteroids can be most effective if gastrointestinal symptoms are caused by mechanical obstruction from inflammation or cancer. Nondrug interventions include nutritional counseling. Acupuncture or acupressure at the inner side of the forearm (acupuncture point "Neiguan") is very effective in some patients and has been proven to be as effective as antiemetic drugs in clinical trials.

How should you treat constipation?

Constipation may be caused by intestinal manifestations of the underlying disease, by drugs such as opioids or antidepressants, but also by inactivity, a low-fiber diet, or low fluid intake. Prophylactic treatment with laxatives should be prescribed for every patient receiving chronic opioid therapy. In contrast to other adverse events such as sedation, which most patients report only for the first few days after initiation of opioid therapy or a dose increase, patients do not develop tolerance to constipation. The peripheral opioid antagonist methylnaltrexone

Table 1
The essence of symptom control:
first-line medication for predominant symptoms

Medication	Dosage	Drug Class	Comments
Dyspnea			
Morphine	As required, or 10–30 mg/d initially p.o., titrate to effect; maximum dosage may exceed 600 mg/d	Opioid (μ-agonist)	AE: constipation, nausea, sedation, cognitive impairment
Hydromorphone	As required, or 4–8 mg/d initially p.o., titrate to effect, maximum dosage may exceed 100 mg/d	Opioid (μ-agonist)	AE: constipation, nausea, sedation, cognitive impairment
Lorazepam	As required, or 1–5 mg/d sublingual	Benzodiazepine	Cumulation with repeated use
Respiratory Tract Secretions			
Hyoscine butylbromide (butylscopolamine)	As required, 20–40 mg s.c. (4-hourly)	Antimuscarinergic drug (peripheral action)	No antiemetic effect
Hyoscine hydrobromide (scopolamine)	As required, 400 μg s.c.	Antimuscarinergic drug (central and peripheral action)	Antiemetic effect; AE: sedation
Nausea and Vomiting			
Metoclopramide	30 mg/d; high dose: up to 180 mg/d	5-HT_4 antagonist	Extrapyramidal AE; do not use in patients with gastrointestinal obstruction!
Haloperidol	2 mg/d up to 5 mg/d	Neuroleptic drug	Extrapyramidal AE
Constipation			
Macrogol	1 bag orally		
Sodium picosulfate	10–40 drops orally		
Octreotide	0.3–0.6 mg/d s.c.		Reduces gastrointestinal secretions effectively, indicated for patients with gastrointestinal obstruction
Methylnaltrexone	0.8–1.2 mg/d	Opioid antagonist (peripheral action)	Effective for opioid-induced constipation
Fatigue, Weakness			
Dexamethasone	12–24 mg/d initially, stepwise reduction after a couple of days	Corticosteroid	Gastric ulcers, hallucinations, nightmares, weight gain, only effective for a restricted time period
Anxiety			
Lorazepam	1–5 mg/d	Benzodiazepine	AE: paradoxical effects
Mirtazapine	15 mg initially, stepwise increase after 2–3 weeks up to 45 mg/d	Antidepressant (SNRI)	Also effective for treatment of panic attacks, pruritus; AE: sedation, increased appetite, liver dysfunction
Depression			
Mirtazapine	15 mg initially, stepwise increase after 2–3 weeks up to 45 mg/d	Antidepressant (SNRI)	Also effective for treatment of anxiety, panic attacks, pruritus; AE: sedation, increased appetite, liver dysfunction
Methylphenidate	5 mg in the morning initially, stepwise increase to 30 (40) mg/d	Stimulant	AE: agitation, restlessness, extrapyramidal effects, tachycardia, arrhythmia
Agitation, Confusion			
Haloperidol	2 × 1 mg, up to 20 mg/d	Neuroleptic drug	AE: extrapyramidal effects
Levomepromazine (methotrimeprazine)	25–50 mg, up to 200 mg/d	Neuroleptic drug	AE: sedation, anticholinergic effects

Abbreviations: AE = adverse effect; SNRI = serotonin norepinephrine reuptake inhibitor.

offers a selective and effective option for treatment of opioid-induced constipation, but high costs will prevent its use in resource-poor settings. Nondrug interventions such as increased activity, more fluid intake, or change of diet usually are very effective, if appropriate for the patient's condition.

How should you treat fatigue?

Fatigue has been named as the most frequent symptom of cancer patients, and it is a predominant feature in noncancer palliative care patients as well. As the concept of fatigue is often not clearly understood by patients or by all health care professionals, it is recommended to consider the symptoms tiredness and weakness instead of fatigue. However, there are only a few medical interventions for these symptoms. Treatment with erythropoietin, where available, has been used with good effect in cancer patients, but in the palliative care setting with reduced life expectancy there seems to be no indication for erythropoietin. Drugs such as methylphenidate and modafinil are under investigation. However, the most effective medication seems to be dexamethasone or other steroids. Their effect tends to wear off within a few days or weeks, and often is accompanied by adverse events, so steroids should be reserved for situations where a clear goal is visible within a short time frame, such as a family celebration.

Reduction of other medications may alleviate tiredness dramatically, and a review of the drug regimen is advocated in patients with reduced performance status, as many medications may not be required any more. In selected patients with severe anemia, blood transfusions are an option to reduce tiredness and weakness, with repeated transfusions even over a prolonged period of time.

However, for most patients, nondrug interventions will be effective, such as counseling, energy conserving and restoration strategies, and keeping a diary of daily activities. Physical training has been shown to reduce fatigue effectively. Physical activity is possible even for patients with advanced disease, although it has to be adapted to reduced performance status and cognitive function.

How should you treat anxiety and depression?

Anxiety and depression are among the major psychological problems in palliative care. Patients facing the diagnosis of an incurable disease and limited prognosis may have every right to feel anxious and depressed. However, these symptoms may overburden the patient and will then require treatment to restore quality of life for the remainder of the lifespan.

Anxiety may be most pronounced at night, preventing sleep and adding to tiredness during the day. Benzodiazepines at night provide a good night's rest and prevent endless brooding. Lorazepam offers a profile with rapid onset and little hangover the next day, but other sedatives will do as well. Treatment with benzodiazepines will also help with the treatment of dyspnea and other symptoms, as these symptoms may have been augmented by anxiety.

Some patients with advanced disease suffer from major depression and require treatment with antidepressants. Mirtazapine is included in the IAHPC list of essential drugs for palliative care. Mirtazapine is also indicated for anxiety and panic attacks, and has been reported to alleviate pruritus. However, for treatment of depression, other antidepressants will do as well. Selective serotonin reuptake inhibitors (SSRIs) should be preferred as they produce less side effects compared to older tricyclic antidepressants. Effect of antidepressant therapy usually will take 2–3 weeks, and as treatment should be started at a low dose with stepwise titration until effective, many patients with reduced life expectancy will not live long enough to benefit from antidepressants. For these patients methylphenidate is an alternative, as the onset of action takes only a few hours.

However, many patients will suffer not from major depression, but from feeling depressed, which is not the same. A feeling of sadness and grief may be completely appropriate and may even help with coping with the disease. Treatment with antidepressants for these patients may impede coping and add burdensome side effects such as dry mouth or constipation. The decision to treat depression therefore requires careful balancing of effectiveness and side effects.

How should you treat agitation and confusion?

In the final phase of life, agitation and confusion are frequent symptoms that can cause considerable stress not only on the patient, but also on caregivers and staff. Neurological causes may include focal seizures, ischemic insult, cerebral bleeding, or brain metastases. Many drugs as well as withdrawal of drugs or more frequently of alcohol may lead to delirium, typically with fluctuating symptomatology after sudden onset. Fever, infection, electrolyte disturbance such as hypercalcemia, or dehydration also may trigger or aggravate delirium.

Neuroleptic medication may be required, with haloperidol as a first-line approach. High dosages may be required, with doses as high as 20–30 mg per day. Other neuroleptics such as levomepromazine have more sedative properties and may be beneficial in severely agitated patients. For patients with HIV disease, HIV-related brain impairment can cause agitation and confusion earlier on in the disease trajectory, and thus similar symptoms may have to be controlled prior to the final phase of life.

Emergency interventions

What constitutes an emergency in palliative care?

Exacerbation of pain and other symptoms as well as severe psychological distress with anxiety or even panic may lead to emergency situations that require immediate action. In these emergencies, the onset of symptom relief should not be delayed unduly by prolonged assessment or differential diagnosis. However, the usual medical emergency procedures may also be detrimental, for example when pain exacerbation leads to a hospital admission with transport time as well as radiographic and laboratory investigations, but without analgesic intervention or comforting care.

Emergencies that have to be treated rapidly and adequately are exacerbations of preexisting symptoms, new symptoms with sudden and intense onset, or rare complications such as massive hemorrhage. Individual treatment plans in palliative care should try to foresee such emergencies and provide adequate interventions. Prescription (or even better, provision) of rescue medication for emergencies is especially important when health care professionals are not available out of office hours, and care has to be delivered by auxiliary staff or family caregivers.

What is rescue or breakthrough medication?

Rescue or breakthrough medication should be prescribed for patients with advanced disease, where exacerbations of pain or other symptoms are possible, and rapid treatment of these exacerbations is required. Rescue medications can include different drugs, but for most patients they should include at least an opioid with fast onset for treatment of pain, dyspnea, and anxiety as well as a benzodiazepine such as lorazepam for the treatment of dyspnea, anxiety, and agitation (Table 2).

Respiratory secretions may lead to labored breathing in dying patients, and may cause distress in patients as well as in caregivers. Anticholinergic drugs such as hyoscine butylbromide may alleviate this "death rattle" quickly.

For all drug interventions, the route of administration should be considered. Oral application may be much easier if no professional help is available, but in some patients oral intake is not possible. Opioids as well as many other drugs used in palliative care can be injected subcutaneously, with little risk of complications and with a faster onset of action than with oral application. Intravenous application offers the option for rapid titration with small bolus administrations if trained staff are available.

What should be done in the case of massive hemorrhage?

Cancer growth in the skin or mucous membranes may lead to excessive bleeding if major blood vessels are ruptured. This can manifest with sudden onset or with

Table 2
The essence of symptom control: emergency intervention

Medication	Dosage	Drug Class	Comments
Rescue Medication (Given as Required)			
Morphine 10 mg	10–20 mg orally 10 mg s.c. (or i.v. in small steps)	Opioid (μ-agonist)	Indication: pain, dyspnea
Hydromorphone	1.3–2.6 mg orally 2–4 mg s.c.	Opioid (μ-agonist)	Indication: pain, dyspnea
Hyoscine butylbromide 40 mg	20 mg s.c.	Antimuscarinergic drug	Indication: respiratory tract secretions
Lorazepam 1 mg	1 mg sublingually	Benzodiazepine	Indication: agitation, anxiety
Palliative Sedation			
Midazolam	3–5 mg/h s.c., i.v. or 3–5 mg bolus as required	Benzodiazepine	Paradoxical effect/ inadequate effect

increasing intensity, or with sudden vomiting of clotted blood from gastrointestinal bleeding. With minor bleeding sometimes blood transfusions may be indicated. For more severe bleeding, benzodiazepines or morphine via subcutaneous bolus administration may be indicated, but often they will not take effect fast enough. With massive hemorrhage the patient will quickly become unconscious and die with little distress, and treatment should be restricted to comfort measures. Enough towels or similar material should be available to cover the blood.

What is palliative sedation?

Rarely, patients with extreme distress from pain, dyspnea, agitation, or other symptoms that are resistant to palliative treatment, or do not respond fast enough to adequate interventions, should be offered palliative sedation. This means that benzodiazepines are used to lower the level of consciousness until distress is relieved. In some patients deep sedation is required, rendering the patient unconsciousness. However, for other patients mild sedation may be enough, so that patients can be roused and can interact with families and staff to some degree. Intravenous or subcutaneous midazolam is used most often, as it can be titrated to effect easily.

It should be realized that palliative sedation is the last resort if symptomatic treatment fails. Before the initiation of this treatment, other treatment options have to be considered, and the priorities of the patient should be clarified. Some patients prefer to suffer from physical symptoms instead of losing cognitive capacity, and sedation should only be initiated if the patient agrees. Effective services will find an indication for sedation in only a few selected patients with very severe symptoms.

Psychosocial and spiritual care

What is the impact of psychosocial issues on medical care?

Psychosocial issues are often neglected by medical staff, even though they are paramount for many patients. Fears about the progression of the disease, about death and dying, about financial problems, or about stigmatization with diseases such as HIV/AIDS may overwhelm patients, alienate them from their family and friends, and often aggravate the impact of physical symptoms. For most patients in resource-poor countries the loss of support is an immediate implication of a life-threatening disease, often endangering the survival of the patient as well as of the family. Social support that provides the means to sustain basic requirements is as mandatory as the medical treatment of symptoms.

Most patients with life-threatening disease also have spiritual needs, depending on their religious background and cultural setting. Spiritual support from caregivers as well as from specialized staff, for example religious leaders, may be helpful.

How do you communicate bad news?

Palliative care staff should have special communication skills. Health care professionals should be able to collaborate with other staff and volunteers who care for the patient, and agree on treatment regimens and common goals for the patient. They must also be able to communicate with patients and families on difficult topics, for example ethical decisions such as treatment withdrawal or withholding of treatment. Specific models are available, for example the SPIKES model for breaking bad news (Table 3).

Table 3
SPIKES model for breaking bad news

Setting	Choose the setting for the talk, talk on same eye level with patient, avoid disturbances and interruptions, allow for family members to be present.
Perception	Check the capacity of the patient, impairment from medication or from disease, or from interaction with family members, use verbal and nonverbal cues for perception.
Invitation	Ask the patient about his level of information, what does he know about his disease and about the topic of the talk, and ask the patient how much he wants to know.
Knowledge	Inform the patient about the bad news, in a structured way with clear terminology, allow for questions and give as many details as the patient requires.
Empathy	Leave time for emotional reactions of the patient, explore emotional reactions and react empathically.
Summary	Provide a concise summary, if possible with some written summary, and offer a follow-up talk if possible.

How do you provide bereavement support?

Bereavement support is an important, yet often forgotten, part of palliative care provision, which should not end with the death of the patient. Grief and loss are expressed in a multiplicity of words and languages by different peoples. A wealth of diverse ritual serves to guide people in societies through the grief process, and it is important for the health professional to be aware of such rituals. Grief not only affects relatives, but also patients themselves, who may experience anticipatory grief prior to their death as they grieve the various losses that they are experiencing such as the loss of their future and the loss of seeing their children grow up. Patients need support to work through some of these issues prior to their death and to plan for the future of their loved ones, where possible.

Many different factors can affect the bereavement process for family members, including their relationship with the person who died, the way that they died, whether they were experiencing symptoms and were seen to be suffering, stigma, a lack of disclosure about their illness, local cultural practices and beliefs, personality traits, other stresses that they may also be experiencing, and bereavement overload if they have lost several friends and relatives in a short space of time. Ongoing bereavement support may be provided to relatives, either by the palliative care team or by referral to local community networks and support systems. It is important that the need for bereavement support be recognized and support provided as appropriate.

Ethical decision making

Whereas guidelines and recommendations are available for most areas of symptom control, there are some issues in palliative care that are loaded with ethical implications.

Are nutrition and fluid substitution necessary if oral intake is not possible?

Patients and more often other caregivers and health care professionals insist on enteral or parenteral nutrition or at least fluid substitution if patients are no longer able to eat or drink. If the therapist does not comply with this wish, it is often considered as inhumane, as the patient then will starve or die of thirst. Nutrition often has an overwhelming symbolic significance, and as long as the patient is nourished, caregivers will perceive a chance for the patient to get well. This significance may be supported by medical staff who explain that the withholding of anticancer therapies is linked to the poor nutritional status of the patient. However, it has to be realized that cachectic patients with cancer or with HIV/AIDS most often do not benefit from nutrition. In most cases, a catabolic metabolism is the major reason for cachexia, and the provision of additional calories does not change that status. Patients in the final stage of the disease may even deteriorate with parenteral fluid substitution, when edema or respiratory secretions are increased. Thirst and hunger, on the other hand, are not increased when fluids and nutrition are withheld. In many cases, and nearly always in dying patients, nutritional supplements, parenteral nutrition, and fluid replacement are not indicated and should be withdrawn or withheld. If necessary, small amounts of fluid (500–1000 mL) may be infused with a subcutaneous line.

How should we react if patients ask for hastened death?

Palliative care by definition neither hastens nor postpones death. Active euthanasia is not a medical treatment and cannot be part of palliative care. However, there are a few patients receiving palliative care who ask for assisted suicide or for active euthanasia or for other forms of hastened death.

In most countries, withholding or withdrawing life-sustaining treatment is legally and ethically acceptable, and so treatment reduction may offer an option. In selected cases with intolerable suffering, palliative sedation may be indicated. However, for most patients asking for hastened death, a more detailed exploration and more empathic care should be offered. Often the statement "I do not want to live anymore" means "I do not want to live like this anymore," and communication about problems or fears may help to alleviate the wish for hastened death. For most patients it is possible to find a solution that allows them to spend the rest of their days with an acceptable quality of life.

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International Association for the Study of Pain
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Working together for pain relief

Guide to Pain Management in Low-Resource Settings

Chapter 9
Complementary Therapies for Pain Management

Barrie Cassileth and Jyothirmai Gubili

Is conventional pharmacotherapy always the best option for pain control?

Both acute and chronic pain may be treated with prescription pharmaceuticals, but they also may be controlled by complementary therapies such as acupuncture, massage therapy, and other modalities discussed in this chapter at less cost and typically with fewer side effects.

Each year about nine million cancer patients worldwide experience moderate to severe pain most of the time. Thirty percent of newly diagnosed cancer patients and 70–90% of patients with advanced disease suffer significant pain. Pain experienced by cancer patients can be chronic, caused directly by tumor invasion or by cancer treatment itself, or acute pain, such as following surgery. Pain in terminal stages of disease has its own characteristics and special issues. The World Health Organization (WHO) recommends use of analgesics for pain, starting with nonopioid drugs followed by opioids for uncontrolled and persistent pain. But, pharmacological interventions, although effective, do not always meet patients' needs, and they may produce difficult side effects. They are also costly and may be difficult to obtain. These issues pose a great challenge for patients requiring long-term pain management, often forcing them to choose between living in pain or living with undesirable side effects. Complementary therapies have an important role to play everywhere, and especially in the low-resource setting.

How often are complementary therapies used by the patient?

Complementary therapies are increasingly used to alleviate pain and other symptoms, such as nausea and fatigue. Internationally, 7% to more than 60% of cancer patients use complementary therapies, depending on definitions used in numerous surveys. These therapies also are frequently used for pain that is not cancer-related.

How do complementary therapies work?

Complementary therapies may work by direct analgesic effects (e.g., acupuncture), by anti-inflammatory action (e.g., herbs), or by distraction (e.g., music therapy), to affect pain perception, assist relaxation, improve sleep, or reduce symptoms such as nausea, neuropathy, vomiting, anxiety, or depressed mood, as well as pain. These therapies often work when used alone, but they are also used with pharmaceuticals, often reducing the dosages required, and thus decreasing side effects and cost. When complementary therapies work synergistically with a pharmaceutical pain regimen, effectiveness may be improved and costs reduced.

But do complementary therapies actually work?

Every culture throughout time and in every corner of the world has developed herbal remedies. When subjected to study, some of these remedies are shown to be worthwhile, but others often prove ineffective. In addition, the public internationally is confronted with magical or superstitious remedies. These may have great appeal because they are inexpensive, readily available, and perceived as safe and effective because they are viewed as "natural." However, two false beliefs about "natural" products are seen around the world: the belief that "natural" remedies are harmless; and the belief that remedies in use for decades or centuries must work. Both myths are incorrect. This is a special problem when treatable diseases are not managed properly, as patients may die or their disease may worsen when they fall prey to useless remedies and waste precious time.

For many reasons, therefore, it is important to distinguish between evidence-based, helpful therapies and those that have no value. Baseless promises may come from well-intended people, or they may be promoted by unscrupulous vendors, as has been recognized in many parts of the globe, especially in Western Europe, Australia, and the United States. Early in the 21st century, the WHO named 2001 to 2010 the decade for modernization of African traditional medicine. Africa would thereby join Western nations, China, and other areas of the world in a dedicated effort to modernize traditional medical practices: The WHO advised Africa to establish standards and process for intellectual property rights, research herbal compounds to determine their value, formalize the training of traditional medicine practitioners, and deal with quackery. Quackery in Africa may be similar to that in other continents, where it is a lucrative business that preys on vulnerable people facing pain, cancer, or other serious health problems. Robert L. Park, University of Maryland, writes about quackery in several publications, including his book *Voodoo Science: The Road from Foolishness to Fraud.* He talks about the seven "Warning Signs of Bogus Science and Medicine." These are:

1) The discoverer pitches the claim directly to the media or the public. The integrity of science rests on the willingness of scientists to expose new ideas and findings to the scrutiny of other scientists. An attempt to bypass peer review by taking a new result directly to the media or the public suggests that the work is unlikely to stand up to examination by other scientists. A health-food company marketed a dietary supplement called Vitamin O in full-page newspaper advertisements. Vitamin O turned out to be saltwater.

2) The discoverer may say that powerful people are trying to suppress his work. Often, he claims that mainstream medicine is part of a larger conspiracy that includes industry and government.

3) The scientific effect involved is difficult to detect.

4) The evidence is anecdotal. The main thing that modern science has learned in the past century is not to trust anecdotal evidence. Because anecdotes have a strong emotional impact, they keep superstitious beliefs alive in an age of science. The most important discovery of modern medicine is not vaccines or antibiotics—it is the randomized trial, which shows what works and what does not. The plural of "anecdote" is not "data."

5) The discoverer says a belief is credible because it has endured for centuries. There is a persistent myth that long ago, before anyone knew that blood circulates throughout the body or that germs cause disease, our ancestors possessed miraculous remedies that modern science cannot understand. In fact, much of what is ancient cannot match the results of modern scientific study.

6) The discoverer works in isolation. In fact, scientific breakthroughs are almost always the work of many scientists.

7) The discoverer proposes new laws of nature to explain how it works. A new "Law of Nature," invoked to explain some extraordinary result, must not conflict with what is already known. If new laws are proposed to account for an observation, the observation is almost certainly wrong.

The seven "signs" noted above separate quackery from helpful therapies. To identify useful therapies, including complementary and traditional methods, seven other signs may be used:

1) The therapy was studied and shown to be useful for a particular problem.

2) The study included a methodologically sound trial in humans, such as a randomized clinical trial.

3) Safety and efficacy were established.

4) Results were made public, preferably through a peer-reviewed medical journal.

5) Agents taken by mouth were standardized and active ingredients documented.

6) It is helpful, but not necessary, to have information about mechanisms of action. First it is determined that something works, and then its mechanism (how it works) is explored.

7) Risk/benefit ratio is an important aspect to consider. Most of the non-oral complementary therapies are low-risk and beneficial.

What is the first step in choosing complementary medicine ?

In selecting a particular traditional or complementary therapy, the patient's preferences for use of a passive therapy (e.g., massage or acupuncture) versus an active therapy (e.g., meditation or self-hypnosis) should be considered—each of these is effective in relieving pain. Herbal medicines must be considered in terms of any prescription medication the patient is using.

Would acupuncture be a good choice?

Acupuncture, an important component of Traditional Chinese Medicine, originated more than 2,000 years ago. It involves the stimulation of predetermined points on the body with sterile, filiform, disposable needles, sometimes using heat (moxibustion), pressure (acupressure), or electricity to enhance therapeutic effect. The ancient theory underlying acupuncture assumed that "qi" (pronounced "chee"), or life energy flows through meridians, which were thought to connect the body organs. It was believed that disease occurs when the meridians become blocked. Acupuncture was thought to relieve the blockage and permit the normal flow of qi, thereby restoring health. The idea of "life energy" or "vital energy" has never been substantiated by scientific understanding. Instead, physiological and imaging studies indicate that acupuncture induces analgesia and activates the central nervous system. Additional studies of acupuncture's mechanisms are underway.

The WHO supports the use of acupuncture as an effective intervention for low back pain, postoperative pain, and adverse reactions to radiotherapy and chemotherapy. A 1997 Consensus Conference at the U.S. National Institutes of Health (NIH) concluded that acupuncture is effective in relieving pain, nausea, and osteoarthritis. Since that conference, a large research literature has expanded the evidence for additional benefits, and the NIH continues to support clinical trials of acupuncture as well as studies of its mechanisms. Substantial data support acupuncture's ability to alleviate pain.

What about massage therapy?

Massage therapy dates back thousands of years and is practiced by cultures around the world. It involves manipulating, applying pressure to, rubbing, or stroking soft tissue and skin to promote circulation, relaxation, and pain relief. Particular techniques and degrees of pressure may vary in each of the many types of massage therapy. Swedish massage is the predominant style used in the Western world. Sports massage, Shiatsu, and deep tissue massage are modalities that involve deeper pressure, whereas Reiki (very light touch therapy) involves the gentle brushing of hands over the body. The degree of pressure used must be adjusted to ensure that no damage is done to wounds, fractures, and the like. Reflexology (massage of the feet, hands, or scalp) is especially useful for people who are frail or are recovering from surgery. All types of massage therapy relieve and loosen sore muscles, as human touch itself is usually beneficial and can reduce pain. The many physiological effects of massage include enhanced immune function, as measured by increased levels of natural killer cells, decreased cortisol and epinephrine, and improved blood and lymph circulation, in addition to patients' self-reports. In studies, massage effectively reduced pain and other symptoms, including nausea, fatigue, depression, stress, and anxiety associated with cancer treatments.

And mind-body therapies?

Mind-body medicine includes teaching patients how to control aspects of their physiology to help reduce pain, anxiety, tension, and fear. This category encompasses yoga and hypnosis, where a therapist suggests changes in perceptions of sensations, thoughts, and behaviors. Guided imagery and relaxation techniques such as progressive muscle relaxation and controlled deep breathing are also types of mind-body medicine. These therapies can be learned and used by patients. Training may be given by therapists, but training often is available on compact disk (CD).

And hypnosis?

Hypnosis is a state of focused attention or altered consciousness in which distractions are blocked, allowing a person to concentrate intently on a particular subject, memory, sensation, or problem. It helps people relax and

become receptive to suggestion. A CD developed at Memorial Sloan-Kettering teaches patients self-hypnosis for use prior to surgery or at any time to control pain.

Hypnosis has been studied extensively and found effective for a wide range of symptoms, including acute and chronic pain, panic, surgery, burns, post-traumatic stress disorder (PTSD), irritable bowel syndrome (IBS), allergies, and certain skin conditions, and for controlling unwanted habits. In 1996, the U.S. National Institutes of Health judged hypnosis an effective intervention for alleviating pain from cancer and other chronic conditions. Research suggests that hypnotic sensory analgesia is at least in part mediated by reduction in spinal cord antinociceptive mechanisms in response to hypnotic suggestion. Hypnotic analgesia also may be related to brain mechanisms that prevent awareness of pain once nociception has reached higher centers via brain mechanisms. It also may reduce the affective dimension, perhaps as the subject reinterprets meanings associated with the painful sensation.

And yoga?

Yoga is a physical and mental exercise that combines postures and meditation to calm the mind, body, and spirit. The practice promotes relaxation and blood flow, keeping the spine limber and the muscles flexible. Sessions, usually conducted in small groups, are tailored to individual capabilities, with gentle, meditative classes for cancer patients and others with severe pain. The combined aspects of yoga—its gentle postures, deep breathing, meditation, and group interaction—reduce pain perception and assist coping and recovery. For example, in a small study of women with metastatic breast cancer, participants reported significantly lower levels of pain and fatigue the day after yoga practice.

And music therapy?

Music can reach deep emotional levels, and particular types of music may hold special meanings for each individual. Music therapy is particularly effective in the palliative care setting, where it improves quality of life and enhances comfort and relaxation. Music may involve active patient participation such as singing, song writing, or playing musical instruments, or private listening. The use of music to ease pain, anxiety, and depression is increasingly popular, and its effects on pain intensity and distress associated with pain have been documented in studies.

Does physical activity or exercise reduce cancer pain?

Exercise has shown to provide multiple benefits, and the advantages of exercise for patients is well documented for both noncancer pain and cancer pain. In addition to pain reduction, there are positive effects on mood, as well as on muscular, pulmonary, and cardiovascular functioning. Studies have shown that cancer patients may even reduce fatigue symptoms with exercise.

Herbs and other dietary supplements: what should be considered?

Herbs are used in medical practices around the world. Some of today's most powerful pharmaceuticals are plant-derived. Herbs and herbal compounds should be viewed as dilute, unrefined pharmaceuticals. They may produce physiological effects, and those effects can be positive or negative, depending on a patient's specific clinical situation. Herbal agents also may contain harmful constituents, and in patients on prescription medication, serious adverse effects may result from herb-drug interactions. Numerous herbal agents are said to relieve pain. When studied, some are found to be useful and others useless.

Concerns about topical agents

Allergic reactions

Some common essential oils, such as tea tree, lavender, bergamot, and ylang-ylang, are capable of causing contact dermatitis.

Transdermal absorption of phytoestrogens

Many herbal skin products, like lavender or tea tree oil, have mild estrogenic effects. When applied in large quantities over prolonged periods of time, significant amounts can be absorbed through the skin. Patients with estrogen-receptor-sensitive cancer should avoid these products.

Direct toxicity on skin

Some herbs can cause necrosis of skin tissues. Bloodroot, which contains sanguinarine, is an example. Topical use of bloodroot can lead to severe adverse effects including disfigurement. Patients should be advised not to use this product.

Herbs and other dietary supplements: what to use?

White willow (*Salix alba*), also known as willow bark, bay willow, black willow, and white willow bark, is in common use in Africa. The active preparation is derived from the bark of the tree. Willow bark contains salicin, the phytotherapeutic precursor of aspirin (acetylsalicylic acid). Products should be standardized to the content of salicin with daily doses ranging from 60–120 mg per day. Caution should be exercised in patients with known allergy or intolerance to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs). Willow bark should not be administered to children with a fever, because of the risk of Reye's syndrome. Adverse reactions are analogous to those seen with aspirin, including gastrointestinal bleeding, nausea, and vomiting. Willow bark may have additive effect with aspirin and NSAIDs and should therefore not be administered concurrently. Clinical studies demonstrate efficacy of willow bark in the management of back pain and osteoarthritis. A systematic review of clinical trials suggests that it may also be effective in treating low back pain.

Boswellia preparations, used to treat inflammation, come from the gum of the *Boswellia serrata* tree. Randomized controlled trials show that they reduce pain and swelling in osteoarthritic knee joints. Animal studies suggest these effects may result from the agent's suppression of pro-inflammatory cytokines.

Corydalis rhizome was studied in only one trial. Conducted in human patients, the results showed that after a single, oral administration of *C. yanhusuo* or *A. dahuricae* extracts, pain scores significantly decreased.

Devil's claw (*Arpagophytum procumbens*). Analysis of commercial products reveals wide variation in chemical components. Limited side effects are reported. A clinical study suggests that devil's claw may benefit patients with osteoarthritis of the hip or knee.

Henbane (*Hyoscyamus niger*) can be toxic and even fatal, even at low doses. Common effects of henbane ingestion in humans include hallucinations, dilated pupils, and restlessness. Less common problems (tachycardia, convulsions, vomiting, hypertension, hyperpyrexia, and ataxia) are reported. Henbane is a toxic plant and should not be ingested!

Passion flower (*Passiflora incarnate*) is used primarily to treat insomnia, anxiety, epilepsy, neuralgia, and withdrawal syndromes from opiates or benzodiazepines. It has not been studied in humans for pain control.

Poison hemlock (*Conium maculatum*) apparently is used in parts of Africa for neuralgia and cancer pain, but it has not been shown to be useful for this purpose. Instead, its historic role in producing death is corroborated in literature reports.

Prunus africana (*Pygeum africanum,* Rosaceae) is a plum tree found in tropical Africa and widely used in Europe and the United States to treat benign prostate hypertrophy (BPH). Mice fed *Pygeum africanum* showed a significant reduction of prostate cancer incidence, but no prostate cancer human studies have been conducted.

Valerian (*Valeriana officinalis*), although a popular remedy in Africa, was found no better than placebo when studied.

Verbena (*Verbena officinalis*) has been studied only for the treatment of topical inflammation. Its topical analgesic activity was less than the analgesic activity of methyl salicylate ointment.

Pearls of wisdom

- Complementary therapies serve as adjuncts to mainstream cancer care and can relieve physical and mental symptoms for people with pain and other symptoms.
- They address body, mind, and spirit and enhance patients' quality of life.
- They are low-cost, minimally or non-invasive, and comforting, and they allow patients a choice of treatment.
- Their largely favorable risk-benefit ratio suggests that complementary therapies can play an important role in physical and emotional rehabilitation and can be especially useful in pain management.
- Oral agents should first be determined to be safe. Some plants used for medicinal purposes have no benefits and are dangerous; physicians and patients should be alerted to the serious negative effects, including death, that these agents may produce. Herbs may be contraindicated for patients on prescription medication.

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Websites

A CD developed at Memorial Sloan-Kettering teaches patients self-hypnosis for use prior to surgery or at any time to control pain: www.mskcc.org/mskcc/html/5707.cfm

Because accurate information is essential, the Integrative Medicine Service at Memorial Sloan-Kettering Cancer Center developed and maintains a free website with continually updated and objective data on more than 240 entries: www.mskcc.org/mskcc/html/11570.cfm

Information on traditional medicine may be accessed via: www.who.int/mediacentre/factsheets/fs134/en/

Physical and Psychological Patient Evaluation

Chapter 10
Pain History and Pain Assessment

Richard A. Powell, Julia Downing, Henry Ddungu, and Faith N. Mwangi-Powell

The effective clinical management of pain ultimately depends on its accurate assessment. This entails a comprehensive evaluation of the patient's pain, symptoms, functional status, and clinical history in a series of assessments, depending on the patient's presenting needs. Such assessments rely in part on the use of evaluation tools. To varying degrees, these tools attempt to locate and quantify the severity and duration of the patient's subjective pain experience in a valid and reliable manner to facilitate, structure, and standardize pain communication between the patient and potentially different health care providers.

How do you learn about a patient's pain? What is the pain assessment process?

Where pain levels permit (i.e., where severe clinical needs do not demand *immediate* intervention), the assessment process is essentially a dialogue between the patient and the health care provider that addresses the nature, location, and extent of the pain, looks at its impact on the patient's daily life, and concludes with the pharmaceutical and nonpharmaceutical treatment options available to manage it.

Is pain assessment a one-off process?

Rather than an isolated event, the assessment of pain is an *ongoing process*. Following the initial assessment, treatment may be delivered to manage the pain. It is important, however, that this treatment intervention be evaluated via subsequent pain assessments to determine its effectiveness. The patient's pain should therefore be assessed on a regular basis and the resulting treatment options modified as required to ensure effective pain relief.

Are there key elements to the pain assessment process?

Bates (1991) suggests that the critical components of the pain assessment process include a determination of its: location; description; intensity; duration; alleviating and aggravating factors (e.g., the former might include herbal medications, alcohol or incense); any associative factors (e.g., nausea, vomiting, constipation, confusion, or depression), to ensure that the pain is not treated in isolation from comorbidities; and its impact upon the patient's life.

These components are most commonly embodied in the "PQRST" approach: *P*rovokes and *P*alliates, *Q*uality, *R*egion and *R*adiation, *S*everity, and *T*ime (or *T*emporal). In this approach, typical questions asked by a health care provider include:

P = *Provokes* and *Palliates*

- What causes the pain?
- What makes the pain better?
- What makes the pain worse?

Q = *Quality*
- What does the pain feel like?
- Is it sharp? Dull? Stabbing? Burning? Crushing?

R = *Region* and *Radiation*
- Where is the pain located?
- Is it confined to one place?
- Does the pain radiate? If so, where to?
- Did it start elsewhere, and is it now localized to one spot?

S = *Severity*
- How severe is the pain?

T = *Time* (or *T*emporal)
- When did the pain start?
- Is it present all the time?
- Are you pain-free at night or during the day?
- Are you pain-free on movement?
- How long does the pain last?

At the patient's first assessment, the pain assessment process should be a constituent part of a wider comprehensive patient assessment that could include additional questions:
- Is there a history of pain?
- What is the patient's diagnosis and past medical history (e.g., diabetes, arthritis)?
- Is there a history of surgical operations or medical disorders?
- Has there been any recent trauma?
- Is there a history of heart disease, lung problems, stroke, or hypertension?
- Is the patient taking any medication (e.g., to reduce the pain; if so, did it help the patient?)
- Does the patient have any allergies (e.g., to food or medicines)?
- Does the pain hurt on deep inhalation?
- What is the patient's psychological status (e.g., depression, dementia, anxiety)?
- What is the patient's functional status, including activities of daily living?

What can be done to ensure an effective pain assessment process?

First, in general, accept the patient's self-reported pain as accurate and the primary source of information. Pain is an inherently subjective experience, and the patient's expression of this experience (be it behavioral or verbal) can be influenced by multiple factors (e.g., gender differences, socially acceptable pain thresholds, culturally acceptable levels of "complaining," a sense of hopelessness, diminished morale, coping and adaptation abilities, and the meaning attached to the experienced pain). Consequently, the health care provider should accept the patient as an expert on his or her own body, and accept that while some patients may exaggerate their pain (e.g., to be seen earlier in a hospital), this will generally be the exception rather than the norm. Moreover, evidence suggests that health care providers' observational pain report cannot be assumed to be an accurate indicator of the patient's pain.

Second, as much as is possible within a time-constrained service setting, allow patients to describe their pain *in their own words* (the fact that patients may report socially acceptable answers to the health care provider demands a sensitive exploration of what is expressed). For patients who feel uncomfortable expressing themselves, the health care provider can provide a sample of relevant words written on cards from which the patient can select the most appropriate descriptors. The primary intention here is to *listen to the patient* rather than make any potentially false assumptions and erroneous clinical decisions.

Third, listen actively to what the patient says. Rather than engage the patient in a distracted manner, the health care provider should focus attention on the patient, observing behavioral and body language, and paraphrasing words when necessary to ensure that what is expressed is clearly understood. In emotionally charged encounters, the health care provider must also actively listen for nonverbal descriptors.

Fourth, the location of the pain across the body can be determined by showing the patient a picture of the human body (at least the front and back) (see Appendix 1 for an example of a body diagram), requesting that they indicate the primary and multiple (if appropriate) areas of pain, and demonstrate the direction of any radiated pain.

Fifth, pain scales (of varying complexity and methodological rigor) can be used to determine the severity of the expressed pain (see below for some examples).

Sixth, while it is important to manage an individual's pain as soon as is possible (i.e., one is not obligated to wait for a diagnosis), in the assessment process the health care provider should also diagnose the *cause* of that pain and treat if possible, thus ensuring a longer-term resolution to the presenting pain problem.

How long should an assessment take?

The time needed for assessment will vary according to individual patients, their presenting problems, and the specific demands on clinic time. For example, the patient may be in such severe pain that they are unable to provide any meaningful information to produce a comprehensive pain history. Similarly, there will be occasions when the assessment has to be relatively brief (investigating the intensity, quality, and location of the pain) so that urgently required effective pain management can be provided quickly.

It is also important to remember that, in general terms, it is the *quality* of the pain assessment that results in effective pain management rather than the *quantity* of time spent on it.

Does pain assessment differ with children and young people?

The response to this question is mixed. On the one hand, no, it does not, because, despite the previously held misconception that children do not experience pain due to underdeveloped neurological systems, *children do feel pain*. Consequently, an effective pain assessment process is as important for children as it is for adults.

On the other hand, yes it does, because the expression and detection of children's pain can be more challenging than it is for adults (see below).

Is there a specific assessment process for children and young people?

The specifics of assessing pain in children have given rise to the "QUESTT" approach:

*Q*uestion the child if verbal, and the parent or guardian in both the verbal and nonverbal child.

*U*se pain rating scales if appropriate.

*E*valuate behavior and physiological changes.

*S*ecure the parent's involvement.

*T*ake the cause of pain into account.

*T*ake action and evaluate the results (Baker and Wong 1987).

What are the challenges for pain assessment with the young?

The term "the young" refers to children of varying ages and cognitive development: neonates (0–1 month); infants (1 month to 1 year); toddlers (1–2 years); preschoolers (3–5 years); school-aged children (6–12 years); and adolescents (13–18 years). Children at each stage of development pose distinct challenges to effective pain assessment.

Neonates (0–1 month)

At this age, behavioral observation is the only way to assess a child. Observation can be conducted with the involvement of the child's family or guardian, who can advise on what are "normal" and "abnormal" behavior patterns (e.g., whether or not the child is unusually tense or relaxed). Importantly, for all children, the health care provider should follow national ethical guidelines concerning the presence of a parent or guardian at the assessment process and any associated issues (e.g., informed consent). Additionally, it must be remembered that behavior is not necessarily an accurate indicator of the patient's pain level and that the absence of behavioral responses (e.g., facial expressions such as crying and movements indicating discomfort) does not always equate with the absence of pain.

Infants (1 month to 1 year)

At this age, the child may exhibit body rigidity or thrashing, exhibit facial expression of pain (e.g., brows lowered and drawn together, eyes tightly closed, mouth open and squarish), cry intensely or loudly, be inconsolable, draw the knees to the chest, exhibit hypersensitivity or irritability, have poor oral intake, or be unable to sleep. The issues raised above for neonates resonate for infants, too.

Toddlers (1–2 years)

Toddlers may be verbally aggressive, cry intensely, exhibit regressive behavior or withdraw, exhibit physical resistance, guard the painful area of the body, or be unable to sleep. While toddlers may still be unable to communicate their feelings verbally, their behavior can express their emotional and physical disposition. At this age, generating an accurate assessment of the location and severity of the child's pain may require the use of play and drawings, offering children a nonverbal means of expressing what they are feeling and thinking. However, some children,

even at this age, are able to express their pain using simple language. Health care providers should be sensitive to such developmental differences.

Preschoolers (3–5 years)

Preschool children may verbalize the intensity of their pain, see pain as a punishment, thrash their arms and legs, attempt to push stimuli away before they are applied, be uncooperative, need physical restraint, cling to their parent or guardian, request emotional support (e.g., hugs and kisses), or be unable to sleep.

At this age, as for school-aged children (see below), the child needs to be able to trust the health care provider, who needs to overcome the child's potential reservations concerning strangers and perceived authority figures. This aim can be achieved by conducting the assessment process at a tempo, in a language, and with a demeanor that is suited to the child (e.g., taking more time, where possible, using open-ended questions to encourage children to discuss what they are experiencing, and using appropriately supportive and encouraging body language).

School-aged children (6–12 years)

The school-aged child may verbalize pain, use an objective measure of pain, be influenced by cultural beliefs, experience pain-related nightmares, exhibit stalling behaviors (e.g., "Wait a minute" or "I'm not ready"), show muscular rigidity (e.g., clenched hands, white knuckles, gritted teeth, contracted limbs, body stiffness, closed eyes, or wrinkled forehead), engage in the same behaviors as preschoolers, or be unable to sleep. At this age, the child may be more reserved, feeling genuine fears and anxieties (e.g., they may deny the presence of pain because they fear the consequences, such as a physical examination or injection).

However, school-aged children are more articulate and cognitively advanced. As such, they are more curious about their own body and health and may ask spontaneous questions of the health care provider (e.g., "What is happening to me?" "Why do I have a stomachache?"). They can also begin to understand cause and effect issues, enabling the health care provider to give them age-sensitive explanations (e.g., "You have a pain in your stomach because you have a lump there which is making it hurt"). They also may want to be involved in their own clinical care and, where possible, be given choices about what will happen to them.

Adolescents (13–18 years)

Adolescents may verbalize their pain, deny pain in the presence of their peers, have changes in sleep patterns or appetite, be influenced by cultural beliefs, exhibit muscle tension, display regressive behavior in the presence of their family, or be unable to sleep.

At this age, the child can appear relatively uncommunicative or express a disdainful disposition. This tendency can in part be countered by the health care provider expressing genuine interest in what the adolescent has to say, avoiding confrontation or generally negative sentiments (which can cause anxiety and avoidance), focusing the conversation on the adolescent rather than the problem (e.g., by asking informal questions about friends, school, hobbies, family), and avoiding deliberate moments of silence, which generally prove unproductive.

As a consequence of this diversity across age groups (especially in children's cognitive abilities to comprehend what is being asked, and verbal abilities to articulate what is being thought or felt), the pain evaluation tool selected for the assessment process must be appropriate to the individual child. Moreover, given that behavior alone is not necessarily a reliable indicator of experienced pain, and self-reporting has potential limitations, a pain rating scale should ideally be used in conjunction with an investigation of physiological pain indicators, such as changes in blood pressure, heart rate, and the patient's respiratory rate (see Chapter 26 on Pain Management in Children for additional information).

Does pain assessment differ with the aged?

Aged patients present additional challenges in that they may be visually or cognitively challenged, hearing impaired, or influenced by socially determined norms regarding the reporting of negative feelings (e.g., not wanting to appear to be a social burden). Geriatric patients (i.e., patients with advanced biological age with multiple morbidities and—potentially—multiple medications) are especially problematic when they have dementia. Such patients normally receive inadequate analgesia due to their inability to communicate their need for it. (Defining "the aged" in low-resource settings can be problematic. The United Nations definition of "older people" is commonly associated with a legal entitlement

to age-specific pension benefits arising from the formal employment sector, but in regions such as sub-Saharan Africa such a chronological definition is problematic, often replaced by more complex, multidimensional sociocultural definitions, such as the person's seniority status within their community and the number of grandchildren they have.)

Consequently, the principal rule, especially for the geriatric patient, is to *ask for pain*. Among those who have sufficient cognitive functioning to express themselves, the health care provider can increase the text size of word descriptors for the visually impaired, include relatives in the pain assessment process where it is considered appropriate and helpful, and avoid "mental overload" (i.e., discussing multiple topics and providing insufficient explanatory guidance in the pain assessment).

In noncommunicative patients, however, assessments of the extent of presenting pain will be primarily based on behaviorally based proxies (e.g., facial impression, daily activity, emotional reactions, the effect of consolation, and vegetative reactions) rather than relying upon any scale whose use is premised on communication (see Chapter 27 on Pain in Old Age and Dementia for additional information).

How do you measure a patient's pain?

A number of unidimensional and multidimensional tools exist that to varying degrees lend themselves to everyday use. One-dimensional assessment tools simplify the pain experience by focusing on one particular aspect or dimension, and in a challenging low-resource, nonresearch, clinical setting they take less time to administer and require less patient cognitive functionality than do multidimensional instruments. Often these tools have been validated in linguistically and culturally diverse settings. Additionally, they are not usually used in isolation (e.g., a body diagram may be used in conjunction with a scale indicating the severity of the pain experienced). (Examples of multidimensional tools not discussed in this chapter, which could be used for clinical and research purposes, include the McGill Pain Questionnaire (short- and long-form); the Brief Pain Inventory; the Dartmouth Pain Questionnaire; the West Haven-Yale Multidimensional Pain Inventory; the Minnesota Multiphasic Personality Inventory; the State-Trait Anxiety Inventory; the Beck Depression Inventory, the Self-Rating Depression Scale, the Depressivity Scale; the University of Alabama in Birmingham (UAB) Pain Behavior Scale, the Neonatal/Infant Pain Scale, and the Children's Hospital Eastern Ontario Pain Scale.) Importantly, it is essential that the health care provider selects the most appropriate tool (depending on the aims of the pain assessment, and on the practicality, applicability, and acceptability of the instrument to particular patient populations) and uses it consistently over time.

The most commonly used tools for assessing pain in cognitively unimpaired adults and the elderly are the visual analogue scale (VAS), the numerical rating scale (NRS), the verbal descriptor scale (VDS). A tool that has been evaluated in a low-resource setting, the APCA (African Palliative Care Association)'s African Palliative Outcome Scale (POS). One tool used among cognitively impaired adults is the Pain Assessment in Advanced Dementia (PAINAD) Scale. The most commonly used tools for assessing children's pain, in addition to the VAS, NRS, and VDS (for some children aged over seven years old), include the FLACC (i.e. Face, Legs, Activity, Cry, and Consolability) Behavioral Pain Scale, the Touch Visual Pain (TVP) Scale, the Wong-Baker FACES Pain Rating Scale, and the Pain Thermometer. These tools, and how they are used, are described below, along with an outline of the comparative advantages and disadvantages of each.

Adult pain tools

i) Visual analogue scale (VAS)

The VAS pain rating scale uses a 10-cm-long horizontal line, anchored by the verbal descriptors "No pain" and "Worst pain imaginable," on which patients make a mark to indicate what they feel best represents their perception of the intensity of their current pain (Fig. 1).

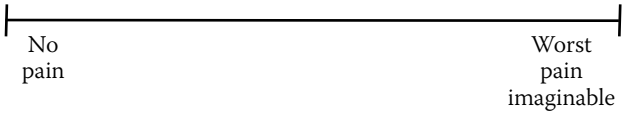

Fig. 1. Visual analogue scale.

ii) Numerical rating scale

Using this scale, the health care provider asks patients to rate their pain intensity on a numerical scale that usually ranges from 0 (indicating "No pain") to 10 (indicating the "Worst pain imaginable").

Fig. 2. Numerical rating scale.

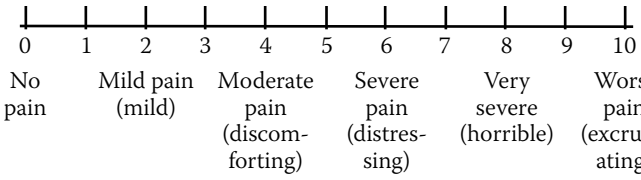

Fig. 3. Verbal descriptive scale

iii) Verbal descriptor scale

When using this scale, the health care provider describes the meaning of pain to the patient (e.g., significant feelings of unpleasantness, discomfort, and distress, and the significance of the experience for the individual).

Then either verbally or visually, the patient is asked to choose one of six descriptors (i.e. "No pain," "Mild pain," "Moderate pain," "Severe pain," "Very severe pain," and "Worst pain possible") that best represents the level of pain intensity he or she is experiencing. Sometimes (as in Fig. 3), numbers are also used to ease the recording of the results.

iv) African Palliative Outcome Scale

The APCA African POS is a simple and brief multidimensional outcome measure, specifically for palliative care, that uses patient-level indicators that include pain, but do not focus exclusively on pain. The health care provider interviews patients and their carers using a 10-item scale over four time periods on a scale of 0–5 that can also be completed using the "hand scale." Promoted by the WHO, the hand scale ranges from a clenched hand (which represents "No hurt") to five extended digits (which represents "Hurts worse"), with each extended digit indicating increasing levels of pain. A pediatric version of the APCA African POS is currently being developed.

v) Pain Assessment in Advanced Dementia (PAINAD) Scale

The PAINAD is an observational tool that assesses pain in patients who are cognitively impaired with advanced dementia, who as a result of their condition

APCA AFRICAN PALLIATIVE OUTCOME SCALE

PATIENT NO. _____	POSSIBLE RESPONSES	Visit 1 DATE	Visit 2 DATE	Visit 3 DATE	Visit 4 DATE
ASK THE PATIENT					
Q1. Please rate your pain (from 0 = no pain to 5 = worst/overwhelming pain) during the last 3 days	0 (no pain) to 5 (worst/overwhelming pain)				
Q2. Have any other symptoms (e.g., nausea, coughing, or constipation) been affecting how you feel in the last 3 days?	0 (not at all) to 5 (overwhelmingly)				
Q3. Have you been feeling worried about your illness in the past 3 days?	0 (not at all) to 5 (overwhelming worry)				
Q4. Over the past 3 days, have you been able to share how you are feeling with your family or friends?	0 (not at all) to 5 (yes, I've talked freely)				
Q5. Over the past 3 days, have you felt that life was worthwhile?	0 (no, not at all) to 5 (yes, all the time)				
Q6. Over the past 3 days, have you felt at peace?	0 (no, not at all) to 5 (yes, all the time)				
Q7. Have you had enough help and advice for your family to plan for the future?	0 (not at all) to 5 (as much as wanted)				
ASK THE FAMILY CARER					
Q8. How much information have you and your family been given?	0 (none) to 5 (as much as wanted) N/A				
Q9. How confident does the family feel caring for _____?	0 (not at all) to 5 (very confident) N/A				
Q10. Has the family been feeling worried about the patient over the last 3 days?	0 (not at all) to 5 (severe worry) N/A				

Fig. 4. APCA African Palliative Outcome Scale (used with permission).

Items*	0	1	2	Score
Breathing independent of vocalization	Normal	Occasional labored breathing. Short period of hyperventilation	Noisy labored breathing. Long period of hyperventilation. Cheyne-Stokes respirations.	
Negative Vocalization	None	Occasional moan or groan. Lowlevel speech with a negative or disapproving quality.	Repeated troubled calling out. Loud moaning or groaning. Crying.	
Facial expression	Smiling or inexpressive	Sad. Frightened. Frown.	Facial grimacing.	
Body language	Relaxed	Tense. Distressed pacing. Fidgeting.	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out.	
Consolability	No need to console	Distracted or reassured by voice or touch.	Unable to console, distract or reassure.	
			Total**	

Fig. 5. Pain Assessment in Advanced Dementia Scale. Used with permission. Copyright, Elsevier.

can experience more pain or prolonged pain due to its undertreatment.

The tool consists of five items (i.e. breathing, negative vocalizations, facial expressions, body language, and consolability), with each item assessed on a three-point score ranging in intensity from 0–2, resulting in an overall score ranging from 0 (meaning "No pain") to 10 (meaning "Severe pain").

Children's pain tools

Children under 3 years old

i) The FLACC Behavioral Pain Scale

The FLACC Behavioral Pain Scale (Fig. 6) is a pain assessment instrument for use with patients who are verbally unable to report their pain. Each of the scale's five measurement categories—i.e. *F*ace; *L*egs; *A*ctivity; *C*ry; and *C*onsolability—is scored from 0–2, which results in a total score per patient of between 0 and 10 (Merkel et al, 1997). Scores can be grouped as: 0 = Relaxed and comfortable; 1–3 = Mild discomfort; 4–6 = Moderate pain; 7–10 = Severe discomfort/pain.

Before deciding upon a rating score, for patients who are awake, the health care provider observes the patient for at least 2–5 minutes, with their legs and body uncovered. The health care provider then repositions the patient or observes their activity, assessing their body for tenseness and tone. Consoling interventions are initiated if needed. For patients who are asleep, the health care provider observes for at least 5 minutes or longer,

DATE/TIME						
Face 0 – No particular expression or smile 1 – Occasional grimace or frown, withdrawn, disinterested 2 – Frequent to constant quivering chin, clenched jaw						
Legs 0 – Normal position or relaxed 1 – Uneasy, restless, tense 2 – Kicking, or legs drawn up						
Activity 0 – Lying quietly, normal position, moves easily 1 – Squirming, shifting back and forth, tense 2 – Arched, rigid or jerking						
Cry 0 – No cry (awake or asleep) 1 – Moans or whimpers; occasional complaint 2 – Crying steadily, screams or sobs, frequent complaints						
Consolability 0 – Content, relaxed 1 – Reassured by occasional touching, hugging or being talked to, distractible 2 – Difficult to console or comfort						
TOTAL SCORE						

Fig. 6. FLACC Behavioral Pain Scale (used with permission). Copyright 2002, The Regents of the University of Michigan.

with the patient's body and legs uncovered. If possible, the patient is repositioned, with the health care provider touching their body to assess for tenseness and tone.

ii) Touch Visual Pain (TVP) Scale

The 10-point TVP Scale, which uses touch and observation to assess not only a child's pain but also any anxiety or discomfort that may be experienced, is based on a search for signs of pain and anxiety that can be assessed either by looking at, or touching, an ill child. Signs of pain and anxiety include an asymmetrical head, verbalizations of pain, facial tension, clenched hands, crossed legs, shallow breathing, and an increased or irregular heartbeat.

On the first assessment, the health care provider assigns a score of 1 (for present) and 0 (for not present) across 10 items to establish a baseline score. Depending on the degree of pain and anxiety, medication is administered *when necessary*. After 20–30 minutes, the child is assessed once more using the TVP scale. If there is no positive change in these signs, a different approach to managing the child's pain can be considered. Importantly, whilst the TVP has yet to be rigorously validated, it is being used in low-resource settings.

Children over 3 years old

i) Wong-Baker FACES Pain Rating Scale

This scale (Fig. 8) comprises of six cartoon faces, with expressions ranging from a broad smile (representing "No hurt") to very sad and tearful (representing "Hurts worst") (Wilson and Hockberry 2008), with each becoming progressively sadder. The health care provider points to each face, using the words to describe pain intensity, and asks the patient to choose the face that best describes the pain they feel, with the number assigned to that face recorded by staff.

Fig. 8. Wong-Baker FACES Pain Rating Scale. Used with permission. (Wilson and Hockberry 2008.)

Children over 7 years old

i) Pain thermometer

An adaptation of the VDS (Fig. 9), this tool aligns a thermometer against a range of words that describe varying levels of pain intensity. This scale was developed for patients with moderate to severe cognitive deficits, or with difficulty communicating verbally, but a subsequent revised version (the Iowa Pain Thermometer) has been shown to be useable among the young, too. Patients are shown the tool and asked to imagine that, just as temperature rises in a thermometer, pain also increases as you move to the top of the scale. They are then asked to indicate which descriptors best indicate the intensity of their pain, either by marking the thermometer or circling the relevant words.

The health professional documents the relevant descriptor and evaluates changes in pain over time by comparing the different descriptors chosen. Some researchers have converted the indicated descriptors into a pain score by attributing scores to each.

Tactile and visual score	present
1. Toes bent down or upwards and tense under soles, ankles tightly crossed	
2. Knees tightly together or tightly crossed	
3. One leg protecting nappy area	
4. Thoracic and/or irregular breathing, and/or mouth breathing and/or intercostal muscles and/or nasal flaring and/or crackles	
5. Heart rate increased and/or irregular	
6. Arms tight against body or guarding or crossed over face, chest or stomach	
7. Fists (impossible or difficult to open with finger)	
8. Neck asymmetrically positioned on shoulders, shoulders pulled up	
9. Head asymmetrical	
10. Facial tension (fearful or painful expression); tense mouth, eyes tense or anxious, distressed look	

Fig. 7. Touch Visual Pain Scale (Used with permission. Copyright, Dr Rene Albertyn, School of Child and Adolescent Health, University of Cape Town, South Africa.)

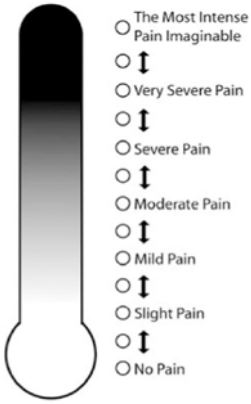

Fig. 9. Pain thermometer. (Used with permission. Copyright, Dr Keela Herr, PhD, RN, FAAN, College of Nursing, The University of Iowa, 2008.)

Case studies

Case 1

You are working in a small, rural hospital when a 7-year-old girl is brought in by her 13-year-old brother. She has AIDS and is not on antiretroviral therapy. She appears to be in some pain. How do you assess that pain?

Answer: The imperative in this instance is to control the patient's pain as quickly as possible; to achieve this, the health care provider has to assess her pain. Because she is 7 years old, the patient should be able to verbalize her pain. As such, the body diagram and the Wong-Baker FACES Pain Rating Scale could be used in combination to achieve an initial assessment of the location, radiation, and severity of her pain. Depending on how severe the patient's pain is, the health care provider may be unable to complete a full assessment until the pain has been managed. The assessment process should, subject to her agreement, involve both the girl and her older brother. It would additionally be important to explore a brief family history to determine if the child has an adult carer or whether she is being looked after exclusively by her older brother to ensure that appropriate consent is obtained to undertake possible therapeutic interventions with the child. If an adult carer cannot be located quickly, it may be necessary to assess and treat the girl's pain while waiting for the carer to begin to make her comfortable.

Case 2

You are working in a home-based care team that visits people in a rural setting. You have arrived at a house to find an elderly woman with end-stage cancer curled up on her bed and crying, who periodically drifts into a semi-conscious state. How do you assess her pain?

Answer: From the patient's initial presenting behavior (crying and in a fetal position), it would appear that she is in pain. The severity of her condition means that she is unable to respond verbally to a pain chart or scale. The health care provider would therefore need to take a history from one of the patient's carers (assuming that one is present), asking what makes her pain better or worse, how long she has been in pain, where they think the pain is, and whether they think it is localized or referred, and using an observational tool such as the PAINAD. Additional questions should explore how long the patient has been in a curled position and crying, whether she is on any medication (including pain medication), and whether her pain is getting worse. In moments of consciousness, even if the patient is unable to verbalize responses to questions based on a pain scale, she may be able to respond by squeezing the health care provider's hand or by nodding. In that instance, the health care provider should provide the patient with closed questions (e.g., with simple "Yes" and "No" responses), providing very clear instructions on, for example, squeezing their hand if the answer is "Yes." This questioning could be supplemented by a quick physical examination to determine what might be causing the patient's pain. Consequently, the health care provider's assessment would be based on observation, a physical examination, simple questions for the patient, and a more comprehensive history from her carer.

Case 3

You are working in a regional hospital. A week-old baby boy is brought in by his mother. He is experiencing projectile vomiting (a symptom typical of congenital hypertrophic pyloric stenosis, a condition that 1 out of 500 babies are born with) and will need surgery. The baby appears tense and agitated and you suspect that he is in pain. How do you assess the pain?

Answer: The FLACC scale could be used to assess the baby's pain. What is the expression on the baby's face? Is he lying with his legs in a relaxed position, or are they restless and tense, or is he kicking? Is he lying quietly, or is he squirming or rigid? Is he crying and inconsolable?

Alongside the FLACC score, the health care provider should speak to his mother to determine how long he has been in this condition, whether he has

any other symptoms, whether he has a known medical condition, when the pain started, and what makes it worse or better? While it is possible that the underlying cause of the pain may be treatable (and it is important to ascertain what the underlying cause is), it is critical to manage his pain quickly, which should also allow him to become more relaxed, making it easier to ascertain the cause.

Pearls of wisdom

- An understanding of the need to undertake an assessment of pain that is sensitive to the individual patient (e.g., age, regarding cognitive ability, and literacy).
- An appreciation of the potential value of standardized pain assessment scales.
- The ability to use pain assessment tools and make decisions within the clinical setting of the most appropriate in different situations.
- Pain assessment is not an academic exercise! Every question potentially provides the therapist with essential information about the etiology of pain and certain first steps to be undertaken to treat it.
- Pain intensity: asking for pain intensity helps you to assess the need for treatment: 0–3 would mean generally that no change of therapy is necessary, 4–7 that analgesic therapy has to be changed, and 8–10 that analgesic therapy has to be changed immediately (a pain emergency).
- Pain quality: this helps you to differentiate the etiology of pain ("burning," "shooting," "electrical," etc. would be indicators of neuropathic pain; "dull," "aching," etc. would be indicators of nociceptive pain; and "terrible," "unbearable," etc. would suggest an affective valuation of pain).
- Pain increase: pain increase after certain movements or at certain times of the day helps to identify the etiology of pain (e.g., pain because of inflammation will be often worst in the early morning hours, while constant high pain levels might suggest a chronic pain disease).
- Pain decrease: positions or situations in which the pain decreases are also helpful for assessment; e.g., if only rest—and no other coping strategies—is considered useful for the patient, this is important information for the therapist that chronic pain may be present and that cognitive restructuring will be indicated. Another example would be a decrease of pain with movement, when possibly osteoarthritis might be present.
- Localization: probably the most important question. Localization of the pain may differentiate between a radicular and nonradicular etiology of pain.
- The items mentioned are only rough indicators of certain etiologies. Further questioning and examination must to be undertaken to confirm suspicions.

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Websites

International Association for Hospice and Palliative Care: www.hospicecare.com/resources/pain-research.htm

National Institute of Health Pain Consortium: http://painconsortium.nih.gov/pain_scales/index.html

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) www.immpact.org

Appendix 1

When using the body diagram (in children a broad equivalent is the Eland Colour Scale), patients are requested to indicate, using a marker, the location of their pain (which could include several sites) by shading the relevant areas. The severity of pain experienced can then be determined using one of the adult pain assessment tools (Appendix 2).

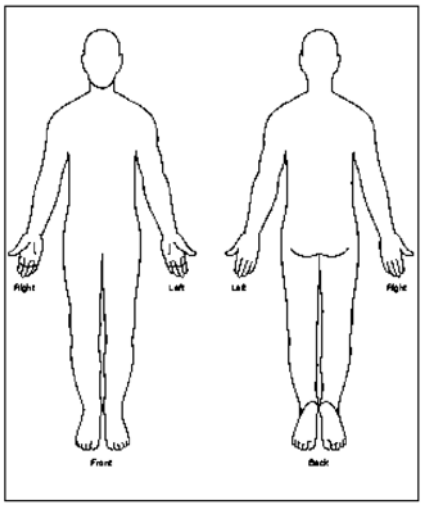

Fig. 10. Body diagram.

Appendix 2: Pain intensity scales

Children's pain intensity scales

Scale	Advantages	Disadvantages
(i) Faces, Legs, Activity, Cry and Consolability Scale	This tool is useful among children who are unable or unwilling to report pain; it is quick to use and easily reproducible.	It has not been validated among children with special needs, neonates, or ventilated children.
(ii) Touch Visual Pain Scale	This tool is useful among children who are unable or unwilling to report pain; it is quick to use and easily reproducible.	Additional research is required to validate the tool in different populations and settings.
(iii) Wong-Baker FACES Pain Rating Scale	This tool is simple and quick to administer, is easy to score, requires no reading or verbal skills, is unaffected by issues of gender or ethnicity, and provides three scales in one (i.e., facial expressions, numbers, and words).	The tool is sometimes described as measuring mood instead of pain, and sad or crying faces are not culturally universal.
(iv) Pain Thermometer	The tool is simple and quick to use and is intuitively preferred by some patients instead of attempting to express their pain intensity numerically.	While overcoming some of the limitations of the VDS by providing an accompanying illustration of pain intensity, the tool may be problematic among the cognitively or visually impaired.

Adult pain intensity scales

Scale	Advantages	Disadvantages
Cognitively Unimpaired		
(i) Visual analogue scale	The tool is quick and simple to administer, is easy to score and compare to previous ratings, is easily translated into other languages, has been validated extensively, and is considered one of the best tools for assessing variations in pain intensity.	The tool is highly sensitive to changes in pain levels, which can hinder its use. Some adults can find the tool too abstract to understand, especially among patients with cognitive dysfunction, non-English-speaking patients, postoperative patients (whose levels of consciousness and attention may be altered after receiving general anesthesia or certain analgesics), and patients with physical disability such as reduced visual acuity or manual dexterity (the health practitioner marking the scale can introduce bias).
(ii) Numeric rating scale	The tool is quick and simple to use, and it is easy to score and document the results and compare with previous ratings. The tool is well validated, can be translated into other languages, and can be used to detect treatment effects. It is easy to teach patients its correct use. Unlike the VAS, the scale can be administered verbally, thereby overcoming problems for those with physical or visual impairments and enabling those who are physically and visually disabled to quantify their pain intensity over the telephone.	Some patients are unable to complete the tool with only verbal instructions. Consequently, there is decreased reliability at the age extremes and with nonverbal patients and the cognitively impaired.
(iii) Verbal descriptor scale	The tool is quick and simple to use, easily comprehended, well validated and sensitive to treatment effects, and intuitively preferred by some patients instead of attempting to express their pain intensity numerically.	Based on the use of language to describe pain, the tool depends upon a person's interpretation and understanding of the descriptors; which can prove to be a challenge in different cultures. The tool is problematic for use among the very young or old, the cognitively impaired, and the illiterate.
(iv) APCA African Palliative Outcome Scale	The tool is quick and simple to use, and provides three scales in one (i.e. numbers, words, and the physical hand).	This tool, which only addresses pain as a single domain in addition to others affecting a patient's life, requires a degree of staff training to ensure its consistent application. Additional research is ongoing to validate the tool in different populations and settings.
Cognitively Impaired		
(v) Pain Assessment in Advanced Dementia Scale	This tool is useful among adults who are unable to report pain; it is quick to use and easily reproducible.	Relies upon proxy indicators of pain rather than verbal self-reporting.

Note: The table above draws on McLafferty and Farley (2008).

International Association for the Study of Pain
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Working together for pain relief

Guide to Pain Management in Low-Resource Settings

Chapter 11
Physical Examination: Neurology

Paul Kioy and Andreas Kopf

Why do a neurological examination?

The main objective in a neurological examination for a patient with pain is to identify the abnormality in the nervous system that may be related to the pain experience and separate central nervous from peripheral nervous lesions. It is also important not only to establish a clinical diagnosis, but also to follow this up with anatomical, pathophysiological, etiological, and possibly pathological diagnoses, if possible. Pain is the most common reason that patients seek medical consultations, and it should be remembered that the pain may not be neurological. Indeed, in origin it often is not. In a general overview, a quick evaluation of the mental state and psychological makeup of the patient must be included as part of the neurological examination as these factors may have a significant impact on pain behavior.

In the history, the presenting symptoms are evaluated in the usual manner, which we exemplify here using one of the most common symptoms in pain patients—headaches. Headaches are important as they are a very common type of pain and one that alerts patients to a potential neurological problem, although fortunately the cause is rarely neurological. Headache still calls for a thorough neurological examination, however, as missing those uncommon neurological headaches (raised intracranial pressure, meningitis, tumors, etc.) may have catastrophic consequences.

Find out the type of headache, its character, anatomical site, severity, frequency, and duration; the nature of onset, timing and periodicity; precipitating factors (straining, coughing, posture, sex, etc.); relieving factors; and associations (visual, auditory, tactile, and dysautonomic associations etc.). Other symptoms can largely be evaluated along the same lines with variations as necessary, since not all aspects apply to all symptoms. A history of common neurological symptoms such as loss or impairment of consciousness, visual disturbances, speech and language disturbances, sensory disturbances, and motor disturbances (including sphincters) should be obtained along the same lines where possible. Further details regarding individual symptoms can be added as appropriate during direct questioning to establish potential etiological factors, including exposure to drugs (alcohol included), environmental toxins, past injuries, and systemic illnesses.

In conclusion, at least basic neurological examinations are indicated in every patient to detect somatic etiologies of pain, mainly lesions of the cerebrum, spinal cord, and peripheral nerves, including myopathies. Although in pain management the psychological factors and symptomatic treatment options are emphasized, it is crucial for the adequate understanding of the patient's pain to take a thorough history and perform a thorough physical examination. It would be harmful to our patients to overlook pain etiologies that could be treated causatively! Therefore,

an basic neurological examination is inevitable for everybody dealing with pain patients (together with an orthopedic and psychosocial evaluation).

What is a systematic diagnostic procedure in a neurological examination?

The examiner has to use a certain systematic approach when examining the patient. Starting with the *symptoms* presented by the patient, it is advisable to continue trying to identify a *syndrome,* which includes all symptoms. A *topical diagnosis* may then be made (which is the "level" of neurological dysfunction), which should lead to the final *etiological diagnosis*. Paraclinical testings, such as electrophysiology and imaging techniques, help by confirming or ruling out a certain etiological diagnosis. However, the availability of such technical examinations is not a prerequisite to make a diagnosis in many cases. Therefore, in environments without the possibility for further testing, careful and thorough history taking and physical examination will be able to collect relevant and most often sufficient findings to make a diagnosis, helping the clinician to understand and possibly treat neurological diseases causing pain.

How do I prepare the patient for the examination?

In the usual clinical manner, establish a rapport with the patient and explain the nature and purpose of the examination to reassure him or her. Endeavour to gain the patient's confidence and trust in order to achieve the level of cooperation that is essential for the interpretation of findings. The patient should be comfortable on the examination couch and adequately but decently exposed.

How can I draw conclusions from the neurological examination?

To be able to draw conclusions from the neurological examination, it is advisable to follow a certain stepwise approach to avoid imperfection. However, following a stepwise approach does not mean being overly schematic!

It is important to explain the examination to the patient before starting because the patient's cooperation and alertness are necessary to ascertain the neurological status. If cooperation is impaired, it should be noted in the progress notes (e.g., "unexpected/inadequate finding"). Thus, objective findings such as muscle atrophy have greater value, since they may not be voluntary influenced!

Every examiner will experience at times "inadequate" or "unexpected" results from the examination. To diagnose a "psychogenic" etiology, however, thorough experience is needed. The patient should never be confronted with the suspicion of aggravation or simulation, so as to avoid an irreversible loss of mutual trust, but the suspicion should be integrated into the whole picture of the patient evaluation.

What technical support do I need for the physical neurological examination?

Everything necessary for an orientating neurological examination should be easily available. A small collection of instruments should be at hand. With a patellar hammer, a sharp instrument (e.g., a wooden stick or sterile cannulas), a soft brush or a piece of cotton wool, a wooden tongue depressor, a small flashlight, a tuning fork (128 Hz), spatulas, and a pair of glass test tubes it should be possible to detect relevant motor, coordination, trophic, and vegetative dysfunctions of the nervous system. If available, an ophthalmoscope would complete the test battery. Remember that in a very busy clinic, one may not be able to do a thorough examination for all patients. But with experience, one develops a quick and efficient personal examination protocol.

What is the stepwise approach to performing a neurological examination?

The physician normally begins the examination of any patient with an examination of the appearance of the subject in general, his/her skin and mucous membranes, followed by palpation for lumps, lymph nodes, pulses, and any superficial points of tenderness. An evaluation of vital functions should normally be done at this time, including blood pressure, pulse, respiration, and temperature. Care should of course be exercised during palpation to avoid the obvious points of severe pain and tenderness this early in the examination so as to retain the patient's cooperation.

The examiner develops a quick plan of the sequence of steps in the examination, which should be followed, because otherwise important aspects of the examination may be missed. A checklist of activities is often useful for the non-neurologist who is not yet experienced. For many, it is easy to follow the examination in a rostral caudal direction, but one may find other methods equally effective. As a bare minimum, the areas listed below must be assessed in an adult patient.

What items do I look for in the neurological examination?

- Higher functions and general examination: (look for level of consciousness, maybe use the Mini-Mental State Examination [MMSE] to test cognitive function, and check vital functions)
- Examination of the head and neck: (look for meningeal irritation, such as neck stiffness or a positive Kernig's test, check neck muscle function and neck movement)
- Examination of the cranial nerves
- Examination of the motor and musculoskeletal system (look for deformities, bulk, muscle tone, and bilateral strength)
- Examination of the sensory system (distinguish radicular and nonradicular deficits or pain radiation; check deep tendon reflexes and the "primitive" reflexes)
- Cerebellar functions (test coordination with rapid alternating hand movements, finger-nose and heel to shin test, tandem walk, one-leg stance, and Romberg test)
- For special diagnostic questions only, certain "technical" testing could be useful (laboratory tests, blood tests, cerebrospinal fluid, electrophysiology, electroencephalography, electroneuromyography, testing of autonomic functions, and imaging)

How do I evaluate "higher functions"?

The patient's degree of consciousness should be evaluated and established as this is probably the most important point in the evaluation of a patient neurologically. Most patients who will be reviewed outside the emergency department presenting with pain will not be in a coma, and an elaborate description of how to evaluate a patient in a coma may not be necessary. Nevertheless, a general familiarization with a coma scale (such as the famous Glasgow Coma Scale) may be useful.

Establish that the patient is fully conscious, able to understand and follow instructions, and fully oriented in time, space, and person. The patient's mood and emotional state (level of anxiety, depression, apathy, disinterest, posturing, and behavior) should be assessed. If any impairment is noted, a full description should be recorded as precisely as possible.

Cognitive skills can quickly assessed using simple observations during history taking and can then be supplemented by direct examination of specific skills. Assessment of language pattern and fluency can easily pick up those patients with motor dysphasia, while ability to follow instruction in the course of general examination may raise the suspicion of receptive dysphasia.

The MMSE examination of Folstein et al (Mini-Mental State Examination) is a quick formal test consisting of some 30 items which can quickly be carried out in less than 10 minutes, should suspicion of a cognitive deficit be raised. With this tool, orientation, memory and recall, abstraction, comprehension, reading, drawing, and writing ability can be assessed. Where dysphasia is marked, testing other elements of cognition is difficult, if not impossible.

How do I examine the head and neck?

Observe and palpate for deformities and tenderness in the scalp and over the muscles—especially the temporalis muscles. Tenderness over the insertion of the paraspinal and mastoids on the skull may be elicited in patients with neck muscle spasms, while occasional tenderness at the vertex may be elicited in patients with tension and depression headaches.

Check for meningeal irritation by flexing the neck and observing for stiffness and pain along the spine, and follow this with the Kernig's test. Brudzinski's sign is rarely observed in adults. Palpation for the carotid pulse will establish the presence and symmetry of the pulsations. Superficial and deep palpation of the neck muscles may elicit spasticity and tenderness and should then be followed by an assessment of neck movements in all directions, which may be restricted by pain, spasms, and/or osteoarthritis of the spine. Lhermitte's sign may occasionally be elicited in patients with multiple sclerosis and spinal canal stenosis, among other pathologies.

What does examination of the cranial nerves tell us?

The first cranial nerve is commonly examined using aromatic non-irritant or pungent materials, such as soap, which is easily available. Each nostril should be examined separately with the other blocked, and the patient is asked to determine the smell by sniffing. Abnormalities of smell are more commonly from local pathologies in the realm of otorhinolaryngology, but they can occur with base of skull and anterior fossa pathologies such as fractures and tumors.

Examination of the second cranial nerve is the most involved, but it affords the best source of information about intracranial pathology. The optic pathways traverse the whole of the brain from the frontal to the occipital pole, with the optic radiation opening out to traverse the parietal as well as the temporal lobes. Assess visual acuity roughly using a newspaper, which conveniently has type of different sizes. More accurate visual acuity measurements can be done using hand-held Snellen charts (i.e., eye charts).

Visual fields can be examined using the confrontation method in all four quadrants separately for each eye. The method compares the visual fields of the patient with that of the examiner using a colored object—usually a pin head advanced from the periphery of each quadrant. More accurate assessment can be carried out using perimetry or tangent screens.

Examination of the optic fundus may reveal invaluable information regarding raised intracranial pressure and the state of the arteries. All patients with headaches should have a funduscopy done. The state of the arteries, silver-wiring, venous pulsations, disc color and margins should be examined and noted together with hemorrhages and exudates if present.

The examination of the papillary reactions and eye movements yields further information on the second, the third, the fourth, and the sixth cranial nerves. Pupil size, shape, and reaction should be checked using a bright light for direct, consensual, and accommodation reactions and noting the symmetry and promptness of the responses. Check for ptosis (eyelid droop), and note whether it is partial or complete. Eye movements should be tested in all directions and include tests of conjugation. The presence of nystagmus should be noted and described, remembering that nystagmus at extremes of lateral gaze may be normal. Abnormalities of nystagmus reflect abnormalities in the vestibular (8th nerve) system and occasionally cerebellar lesions, although mentioned here with the eye motor nerves.

The fifth nerve is examined by assessing sensation in the face and part of the scalp in front of the ear, together with motor activity of muscles of mastication (jaw clenching and opening against resistance). Fast (touch) and slow (pinprick) sensations are handled separately as they follow different pathways and may be impaired differentially. The corneal reflex has its afferent arm in the ophthalmic division of the trigeminal nerve and would normally be included as part of its assessment.

The seventh nerve is examined by observing for facial symmetry at rest and when the patient attempts to wrinkle the forehead (lift the eyebrows), close the eyes, show the teeth, or blow out the cheeks. Taste, which is also a function of the seventh nerve, is rarely tested routinely, but it can be tested in the anterior two-thirds of the tongue using sugar or salt on the protruded tongue.

The eighth nerve function may crudely be tested using a ticking watch or by rubbing the fingers near the ear. If a hearing deficit is suspected, ensure the patency of the external auditory meatus and then carry out more elaborate tests such as Weber's test or Rinne's test to distinguish conduction from nerve deafness, or refer the patient for more sophisticated audiometry.

The ninth, 10th, and 12th nerves are examined together. One should note the presence of dysphonia, palatal movement symmetry (when the patient says *aaah*), the gag reflex, and tongue movement symmetry. Pharyngeal sensation may be tested using a wooden probe tipped with cotton wool, testing each side separately, normally as part of the gag reflex.

The 11th nerve or the spinal accessory nerve is normally examined with the rest of the motor system. The movement of shrugging the shoulders and turning the neck against resistance applied to the side of the jaw will give an indication of any weakness in the trapezius or the sternocleidomastoid muscles, respectively.

How do I examine the motor and musculoskeletal system?

General observation for muscle wasting or hypertrophy, deformities, posturing, and presence of involuntary movements (fasciculations, tremors, chorea, or athetosis) should be done. When necessary, changes

in muscle mass can further be evaluated by palpating as the muscle contracts and/or by measuring the girth of the limbs. Localized atrophy may be due to disuse because of chronic pain and should be kept in mind as a non-neurological cause of changes in muscle mass. Ensure the patient is calm and comfortable before testing tone and limb mobility. Decreased tone is usually a feature of lower motor neuron pathology, whereas increased tone (spasticity, rigidity) is a feature of upper motor neuron pathology. Limb mobility at joints should be tested in all directions allowed by the joint and any restrictions noted. One should be aware that there may be some modifications of tone and limb mobility by pain.

Muscle power is then tested in muscle groups around the joints and in the axial musculature. A good knowledge of segmental and peripheral nerve innervation of the various muscles or muscle groups is essential in evaluating the etiopathology of any weakness. If nerve-related weakness is noted, then it is imperative that it be graded according to an established scaling system such as the Medical Research Council (MRC) scale. Also, establish whether it is upper motor neuron or lower motor neuron and whether it is segmental, diffuse, distal, or peripheral in distribution. Myopathic weakness does not respect peripheral nerve or segmental demarcations and is usually more marked proximally. Neuropathic weakness needs to be delineated and assessed for the anatomical site of the pathology (spinal cord, roots, specific peripheral nerve, or diffuse neuropathy). Subtle weakness in the lower limbs may occasionally be picked up by requesting patients to rise from a squatting position, walk on their tiptoes or on their heels, while in the upper limbs one may look for pronator drift.

Other tests may be done to elicit specific deficiencies such as the straight leg raise to identify lumbar disk protrusion or the femoral stretch if higher disk pathology is suspected. There are numerous maneuvers in clinical practice aimed at eliciting specific joint or structure pathology, and these can be obtained from books on neurology and orthopedic surgery if they are needed.

How do I examine the sensory system?

The sensory system is examined guided by function and anatomy. There are two types of sensations physiologically:

Fast (posterior column, lemniscal, or discriminatory) sensations that include light touch (tested with a wisp of cotton wool), joint position sense, two point discrimination, and vibration.

Slow (spinal thalamic) sensations that traditionally are represented by pain (pinprick) and temperature sensations.

The patient is normally requested to close his/her eyes during the tests. The stimulus is applied on one side initially and then on two sides simultaneously in corresponding parts of the body. The latter tests for sensory extinction where the patient may fail to register stimulation of one side (the left usually) in lesions of the nondominant hemisphere. If any abnormalities are detected, attempts should then follow to accurately map the area of the deficit and establish the anatomical site of the lesion or the structure involved.

Pain and temperature tests yield information on the same systems, and therefore it may not be necessary to test for both in the routine patient without neuropathic pain. However, a positive increase or pathological increase in sensation (like *dysesthesia*) that may have partly been picked up during history taking will need to be elucidated further. Regions of *hyperesthesia* and *allodynia* need to be mapped out accurately, noting that skin hypersensitivity to various stimuli (touch, cold, and warmth) may be different and therefore should be tested separately.

Light touch, joint position, and vibration should be tested even though they are physiologically related in that they are all fast sensations, because they may be affected differentially in certain clinical situations.

Higher sensory functions such as two point discrimination, graphesthesia (recognition of numbers or letters drawn on the skin), and stereognosis (ability to recognize familiar objects placed in the hand) are not normally part of a routine neurological examination but can be performed where a cerebral lesion is suspected.

What does examination of the reflexes tell us?

The deep tendon reflexes are normally tested after the examination of the sensory systems. The jaw jerk, the supinator, the biceps, the triceps jerks in the upper limbs and the knee and the ankle jerks in the lower limbs are routinely tested. Others like finger flexion and adductor reflexes in the upper and lower limbs respectively are not routine. Their responses are usually graded in a simple

five point system from 0 to 4: 0 = absent, 1 = decreased, 2 = normal, 3 = increased, and 4 = increased with *clonus.* Of particular interest is the symmetry of responses and the least force necessary to elicit the responses which may be a more sensitive measure than the grading system above. Comparison between the upper limbs and the lower limbs may yield some information regarding spinal cord lesions. Before recording a reflex as absent, a re-enforcing technique (like contracting muscles in other limbs or clenching the jaws) should be tried. The hall mark of upper motor neuron deficit remains the increased deep tendon reflexes, disappearance of superficial reflexes and appearance of pathological reflexes.

The pathological reflexes include Hoffman's reflex, the Trömner reflex, the abdominal reflexes, and the plantar responses, which are useful in identifying upper motor neuron deficits. The so-called primitive or frontal lobe release reflexes (grasp, pouting, rooting, etc.) are hardly ever part of a routine clinical examination (with the possible exception of neonates) but can be carried out if the clinical situation demands it.

The cerebellum coordinates muscle contractions and movements in all voluntary muscles, and cerebellar dysfunction results in symptoms of ataxia that is truncal if the flocculonodular lobe is affected or limb ataxia if the hemispheres are at fault. Truncal ataxia is associated with disturbed gait that is typically broad based and reeling and does not get worse when eyes are closed. This can be observed when the patient walks into the examination room or when he/she is requested to walk naturally in the room. Tandem walking (10 steps), heel walking, and one leg stances (holding form more than 10 seconds) can also be tested. The Romberg's test is usually included among the tests of coordination, although it largely assesses the posterior column functions and joint position sense rather than strict cerebellar function.

The neurophysiological process of movement coordination is a complex one requiring an intact ascending sensory system, basal ganglia, the pyramidal system and the vestibular apparatus. Lesions in one of these structures may impair one or other aspect of coordination. Fortunately such lesions will usually be accompanied by other neurological manifestations that help discriminate lesions. Limb coordination to assess cerebellar function may be tested using a variety of tests: the finger-nose test, rapid finger tapping, and rapid alternating hand movements in the upper limbs, and the heel to shin test and foot tapping in the lower limbs.

Pearls of wisdom

Suggested neurological examination tests for the pain patient by the non-neurologist:

Trendelenburg-test: descending of the hip to the unaffected site with pain when walking for longer distances (insufficience of the gluteal muscles)

"Nerve stretching" tests: the Lasègue test is performed in the sitting and the supine position, and is positive if pain is felt in the back radiating to the leg with <70° of straight leg raise, especially if flexing the foot on the ipsilateral site increases the pain (Bragard test), which would be highly positive if pain starts at <35° and/or if pain is provoked with contralateral testing (malingering should be suspected if the test has different results in the sitting and supine position, or if flexion of the head does not increase the pain).

- Allocation of nerve roots:
  Hip flexion (when sitting) and patellar reflex is negative (L2)
  Knee extension (when sitting) and patellar reflex is negative (L3)
  Supination in ankle joint (when supine) and heel standing negative (L4)
  Extension of big toe (when supine) and heel standing negative (L5)
  Atrophy of gluteal muscles and standing on one leg negative (L5/S1/S2)
- Valleix pressure point test: provoking radiating pain in the leg when palpating along the pathway of the sciatic nerve on the dorsal site of the thighs
- Leg-holding test: lifting of the straight leg by 20° in the supine position for >30 seconds (if <30 seconds, suspicious for myelopathy, especially when the Babinski test is positive)
- Tuning fork test: vibration sensitivity (negative result indicates polyneuropathy)
- Babinski test: forced brushing of the sole of the foot, positive when slow extension of the big toe is observed (indicates myelopathy with pyramidal lesion)
- Brudzinski test: reflexive flexion in the hip and knee joints when bending the head
- Jackknife test: no spasticity at rest, but after passive movement of the joints, increasing spasticity followed by a sudden muscle relaxation
- Paresis grading test: the severity of paresis is graded according to Janda at six levels (0= no muscle contraction, 1 = <10%, 2 = <25%, 3 = <50%, 4 = <75%, 5 = normal strength)

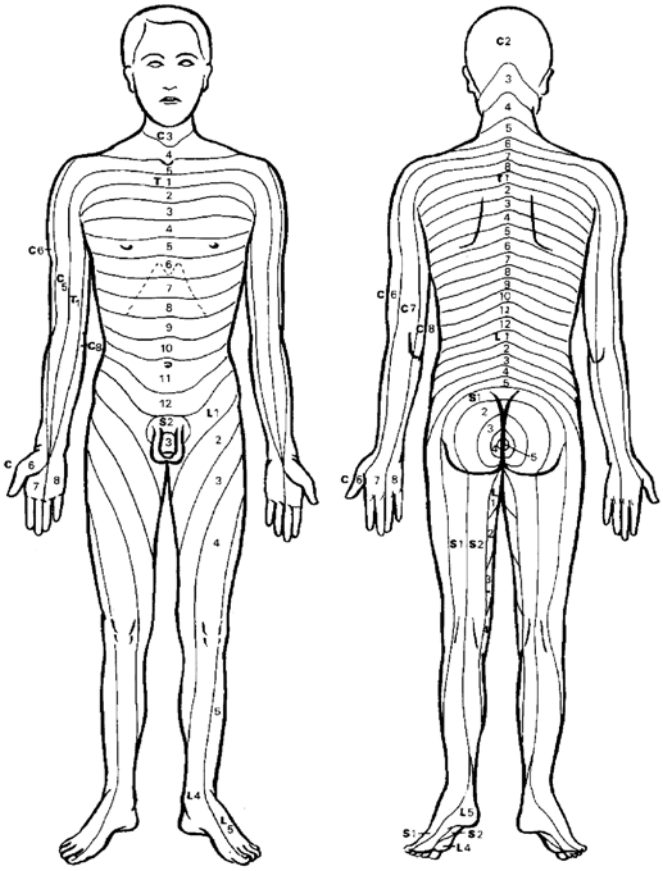

Fig. 1. A neurological body scheme, useful for differentiating and localizing radicular and nonradicular pain with the patient's subjective reports and the results from the physical examination.

- Reflex testing: biceps = C5–6, triceps = C6–7, finger II + III flexion ("Trömner") = C7–T1, patellar ligament = L2–4, and Achilles tendon = L5–S2
- Finger-nose test: a test for coordination, and the patient trying to touch his nose with his index finger in a uninterrupted ample movement with his eyes closed
- Romberg test: the patient should be able to stand stable with eyes closed, feet together, arms extended 90° to the front
- Use a simple body scheme to document the pain reported from the patient and your findings (see Fig. 1)

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Chapter 12
Physical Examination: Orthopedics

Richard Fisher

Clinical case story 1 (extremities)

You have been asked to see a patient in the emergency room of your hospital. The patient is a 46-year-old male who was pinned between a loading dock and a truck bumper several hours ago. His left lower extremity is in a temporary cardboard splint, and after a primary evaluation, he seems not to have other significant injuries. He is alert and will talk to you.

Your initial examination of the left lower extremity shows a swollen calf with a mild angular deformity and bruised but closed skin. Examination of the knee shows no effusion, but range of motion and ligament testing are not possible because of calf pain. Likewise, the range of motion of the hip cannot be tested.

The patient can move his toes and ankle in both directions. He states he can feel you touch the toes and foot, but they have a tingling feeling; slightly different than the right. The left foot is slightly cooler and seems paler. You cannot palpate a dorsalis pedis or posterior tibial pulse. Capillary refill at the toes seems slower than on the right, but intact.

X-ray is available, so you ask to have an X-ray taken of the tibia and fibula. The X-ray shows transverse mid-shaft fractures of both bones with some angulation and minimal displacement—but little comminution.

You decide that the fracture should be "reduced" [placed in proper alignment], and so you contact the on-call anesthesiologist and instruct the operating theater to perform a closed manipulation of the fracture and apply a long leg plaster splint. They tell you they will be ready in 2 hours.

The manipulation seems to work, and you apply a plaster splint to three sides of the limb—leaving the anterior aspect open to allow room for swelling. The patient is comfortable with oral or intramuscular pain medication, and things seem to be going well. The vascular and neurological function of the left foot and ankle seems to be improved following your reduction, although not completely normal.

The next day, just before you begin rounds, the nurse calls you because the patient is having extreme pain in his left calf. She has given all the pain medication ordered, and it is not helping. You go quickly to examine him and find that his splint is intact, but his left leg below the knee is swollen and tense. He cannot extend or flex his toes. You can passively extend them with mild discomfort, but if you try to passively flex them he screams with pain. There is a diffuse decrease in sensation about the foot and calf, and there is no feeling between the first and second toes on the dorsal surface of the foot. Yesterday you could palpate weak posterior tibial and dorsalis pedis pulses, but now there is no dorsalis pedis pulse by palpation. His capillary refill is slower, and the foot feels cooler and looks paler than yesterday.

Do you think this pain pattern is typical for a fractured tibia, or should you look for another cause?

After examining him on rounds, so you suspect the problem is located:

- in the posterior deep compartment?
- in the venous system, probably from a deep vein thrombosis?
- in the anterior compartment?
- in the tibial nerve distribution?

How do you reach a diagnosis?

The calf muscles are organized around four compartments, and the muscles are contained within substantial fascial sheaths. As the muscles become ischemic they swell, increasing the pressure within their compartment. As the pressure increases, it eventually exceeds the capillary perfusion pressure, and no blood can flow to the muscles—and the cycle goes on. If the pressure is not released by dividing the surrounding fascia, the muscle will become permanently nonfunctional. A compartment syndrome is one of the few surgical emergencies affecting the musculoskeletal system. The compartment's fascial sheath should be released as soon as possible.

The tissues manifesting the patient's symptoms include artery, nerve, muscle, vein, ligament, and joint. The symptoms are caused primarily by the ischemic muscle. They can be remembered by the "7 P's":

Pallor—decreased blood flow, slow capillary refill

Pain—from pressure on the muscle

Paresthesia—from early nerve ischemia causing decreased or abnormal sensation

Pressure—the compartment involved will feel tight, and the pressure will measure high

Passive stretch—stretching the muscles of the involved compartment will cause extreme pain; in this case, plantarflexing the ankle and toes

Palsy—the involved muscles will be weak or have no function.

Pulselessness—the pulse will not be palpable if the pressure is high enough, but this is a late sign and is not reliable for early diagnosis.

Why is musculoskeletal pain such an important medical problem?

Pain is an essential component of musculoskeletal function. It is the signal we use to limit activities, which if continued, will lead to damage of the functional elements of the system—muscle, nerve, blood vessel, tendon, ligament, bone, and articular cartilage. The value of this feedback loop is better appreciated in situations where pain perception is impaired and a rapid disintegration of musculoskeletal elements ensues. This is seen in congenital syndromes, acquired neuropathic conditions (diabetic neuropathy), and situations of anesthetic use to enhance performance during athletic activities. Pain produced by musculoskeletal pathology, trauma, infection, or tumors must be managed as a component of the treatment of those conditions. The pain associated with certain chronic pain syndromes appears out of proportion to the initial stimulus. The history and physical examination provide the key to establishing a working differential diagnosis.

Pain is the most common symptom of patients seeking medical help for a musculoskeletal problem. It is often accompanied by other complaints such as swelling, discoloration, or the inability to perform certain tasks, such as walking up stairs, lifting the arm over one's head, or gripping chopsticks, fork, or spoon, but pain is commonly involved. Thus, pain is a useful tool for diagnosis and treatment and a way to measure progress and healing as function is restored. In treating patients we are always working on this edge of comfort versus function.

Pain provides the starting point for the orthopedic examination; both the history and physical components. Where does it hurt? For how long? How did it begin? What makes it worse? What makes it feel better? The answers provide the clues we need to begin the physical examination. Fortunately the basic orthopedic exam is not complex. It consists of a rather limited set of maneuvers, coupled with some knowledge of the anatomy involved. The goal is to understand the abnormality and provide the advice or treatment necessary to restore pain-free or comfortable function. This is an important concept, because if you had continued to increase the pain medication for the patient in the above case history without understanding the meaning of the physical findings, the most likely outcome would have been loss of the extremity. After all, tibial fractures hurt. Why not just treat the pain? The physical examination is important and it is not difficult, but the extremity examination maybe easier than the spine examination, so let's start there.

How to perform an examination of the extremities

The extremity examination should include a careful evaluation of the important tissues. In general order of importance, these include the skin, vascular supply, nerve, function, muscle, joint function, including ligament stability, and bone. The parameters to examine are listed in Table 1.

Judgment is an important skill to practice. If a bone is obviously broken, it may not be prudent to attempt to evaluate range of motion or ligament stability in a nearby joint. However, it is possible to examine the joint for swelling, effusion, tenderness, and deformity and gain an understanding of whether the joint is or is not likely to be involved in the injury. Likewise, the skin may show redness, increased temperature, induration, mild or extreme tenderness, some swelling, or tenseness, all indicating the degree of underlying pathology; from a mild bruise to severe infection. Systemic signs of fever, weight loss, or chronic fatigue, along with basic laboratory tests, should also be used.

Table 1
Evaluation of the extremities

Skin	Look for swelling, redness, induration, open wounds, palpate for tenderness
Vascular system	Palpate major pulses, evaluate capillary refill, temperature, and color
Nerves	Evaluate skin sensation, muscle function, and major deep tendon reflexes; try to determine if there is loss in a dermatome or peripheral nerve distribution
Muscles	Palpate for tenderness and swelling; test for strength
Joints	Evaluate for swelling (fluid in the tissue around the joint), effusion (fluid within the joint), range of motion (active/passive), stability (test major ligament groups), tenderness (around the joint and the ligament and tendon attachments)
Bones	Look for alignment: normal, angled, or rotated; look for localized swelling and tenderness

The following is a simple checklist to follow when performing the basic extremity examination. When possible, it is easiest to do with the patient sitting.

Shoulder:

1) Palpate the surface of the clavicle, the acromioclavicular joint, the subacromial space, the coracoid process, and the deltoid muscle insertion.

2) Test shoulder joint range of motion actively or passively: flexion/extension, abduction and internal and external rotation.

3) Test rotator cuff impingement (shoulder flexion/abduction against resistance).

4) Evaluate sensory nerve function of the axillary, median, ulnar and radial nerves. Hint: the volar tip of index finger = median; the little finger tip = ulnar; the dorsal thumb web space = radial, the tip of the shoulder = axillary.

Elbows:

1) Palpate the surface location of the medial and lateral epicondyles, the radial head, the olecranon process, and the olecranon bursa.

2) Check elbow range of motion: flexion/extension and pronation/supination.

3) Test the biceps muscle strength with elbow flexion and supination.

4) Tap the ulnar nerve beneath the medial epicondyle ("funny bone")—increased tenderness signifies compression.

5) Check the biceps and triceps reflexes.

Hands and wrists:

1) Palpate the surface location of the radial and ulnar styloid processes, the thumb abductor tendons, and the anatomical "snuffbox."

2) Palpate the radial and ulnar pulses.

3) Evaluate the range of motion of the wrist joint: flexion/extension, pronation/supination, radial/ulnar deviation.

4) Assess for carpal tunnel syndrome: tap the median nerve at the wrist (Tinel's test), test sensation as above, flex the wrist and hold to create tingling, and palpate the thenar muscle mass.

Hip and pelvis:

It is easiest to do tests 1–3 with the patient supine and test 4 with the patient standing.

1) Palpate the surface location of the pubic tubercle, the anterior superior iliac spines, the greater trochanters, and the ischial tuberosities.

2) Check hip range of motion (passive is easiest): flexion/extension, internal and external rotation, and adduction/abduction.

3) Palpate pulses—femoral, popliteal, and anterior and posterior tibial.

4) Test hip abductor strength—with the patient standing, ask them to lift one leg off the floor. Normally the ipsilateral pelvic rim will elevate. If the abductor

muscles are weak or if there is a painful hip problem the pelvis will fall and the patient will lean the upper body in the opposite direction.

Knee:

The knee can be examined with the patient sitting or supine.

1) Palpate the surface location of the patella, the patellar tendon, the head of the fibula, and the medial and lateral joint lines.

2) Check knee range of motion—flexion/extension.

3) Test the stability of the medial and lateral collateral ligaments with the knee in full extension and flexed to 30°.

4) Test the integrity of the anterior and posterior cruciate ligaments with the knee in 30 and 90° of flexion.

5) Evaluate meniscus integrity.

6) Check for pain with compression across the knee joint while flexing, extending, and rotating the joint.

7) Check for tenderness along the meniscus insertion at the joint line.

8) Check for an impediment to full extension.

9) Check the patella reflex.

Ankle and foot:

1) Palpate the surface location of:
   a. the medial and lateral malleoli and the collateral ligaments.
   b. the insertion of the plantar fascia
   c. the major tendons (Achilles, anterior/posterior tibial, peroneal, and toe extensors)

2) Check the range of motion of the ankle, midfoot, and hindfoot joints.

3) Evaluate the Achilles reflex.

Clinical case story 2 (spine)

A patient in the clinic tells you he has been bicycling about 12 miles to and from school each day for the past year. He says that last month as the weather was becoming cooler he noticed tightness in his lumbar muscles and had difficulty standing up straight when arrived at school. For a while only his back was affected, but recently he has developed pain in the right posterior thigh and calf, which is increased by sitting in class, bending forward, or sneezing.

Last week he tripped several times when his right toes caught on a carpet edge, and he says that he has been embarrassed by a slapping sound his foot makes walking down the halls at school. His right foot feels tingly at times, but he has noticed no problems with bowel or bladder control, and his left leg seems fine. He does take anti-inflammatory medication when his back hurts a lot, but usually not every day.

You notice he gets up slowly to move to the exam table but can stand up straight. His spine alignment looks satisfactory, but he has limited range of motion, with only a few degrees of flexion and lateral bending to 20°. There is mild tenderness to palpation over the lumbar muscles only.

Sensation is intact to sharp/dull discrimination, except on the lateral right calf and the dorsum of the right foot. You ask him to walk on his heels and toes. He does this with no difficulty, except he cannot walk on his right heel while keeping his toes off of the ground. Big toe extension is weak to manual testing. Deep tendon reflexes at the knee and ankle are normal and symmetrical. The straight leg raising test (sciatic nerve stretch test) is not painful on the left to 80°, but on the right it produces pain into the calf at 40°.

Where do you suspect his primary problem lies?

- Muscles of the calf?
- Sciatic nerve posterior to the hip joint?
- The intervertebral disk between the last lumbar and the first sacral vertebral bodies?
- Knee and ankle joints?
- The intervertebral disk between L4 and L5 vertebral bodies?

How do you reach a diagnosis?

Potentially abnormalities of the calf muscles (especially those in the anterior compartment) or of the sciatic nerve in the thigh could produce some of these symptoms. However, the patient tells you that the pain first began in his back and then spread to the posterior thigh and calf. Also, the positive straight leg raising test indicates irritation at the nerve root level as it is stretched over a protruding disk.

The patient's neurological symptoms and signs suggest a pattern of function loss that you can trace. His sensory loss involves the lateral calf and dorsum of the foot—look at the dermatome map—L5 root. Similarly the slapping foot and toe extensor weakness involve anterior compartment muscles—this could result from anterior compartment compression, peroneal nerve injury, or the L5 root. Reflexes at the knee (L4) and ankle (S1)

are intact (there is a reflex associated with the L5 root, but it is difficult to evaluate).

Usually—although there are exceptions—the L5 root is compressed by an abnormal L4–5 disk and the S1 root by an abnormal L5–S1 dis,. This relationship can be seen anatomically.

What is the cause of the slapping foot?

- Gait incoordination secondary to pain?
- Weakness of the muscles in the anterior compartment of the leg?
- Compression of the common fibular nerve at the knee?
- Weakness of ankle plantar flexor muscles?
- Peroneal muscle weakness?

How to reach a diagnosis

This is a common symptom and a significant problem for the patients because the weakness of ankle extension tends to make them trip over curbs and carpet edges and makes an embarrassing noise walking on tile floors. As mentioned above, it can result from injury to the L5 root as in this patient, from a tight anterior compartment (as in case 3), or from compression of the peroneal nerve. The most common location for such compression is at the fibula neck, and it may result from a tight cast or splint or positioning on the operating table—look at this area on your dissection.

Sequentially, the nerves most likely to be involved are:

- L4 root: femoral nerve: posterior tibial nerve
- L5 root: sciatic nerve: posterior tibial nerve
- S1 root: sciatic nerve: common peroneal nerve
- L5 root: sciatic nerve: common peroneal nerve

How to examine the back

Back pain is a universal problem, which must be addressed carefully in order to separate musculoligamentous mechanical back discomfort from other significant problems for which more aggressive treatment is needed, such as infection, fractures, tumors, or neurologic involvement from disc disease as the case illustrates. Fortunately the initial assessment can be done simply and still provide a great deal of information.

Radiographic assessment is helpful in evaluating deformity or destruction of bone. Magnetic resonance imaging is useful in evaluating soft-tissue problems such as tumor, infection, and nerve root impingement. Computerized axial tomography imaging is of value in assessing spinal fractures and dislocations.

How to examine the spine

- Look for systemic findings such as fever, chills, weight loss.
- Observe as the patient enters the room: look for gait abnormalities, response to your greeting, and general state of well-being.
- Evaluate alignment and symmetry from the front, back, and side. Check for scoliosis by observing thoracic symmetry with the patient bending forward and for kyphosis by a break in the smooth spinal curve in the side view.
- Palpate landmarks: sacroiliac joints, spinous processes, paravertebral muscles, sacrum.
- Check the range of motion with forward flexion, extension, lateral bending & rotation.
- Elicit deep tendon reflexes at the knee and ankle.
- Perform the straight leg raising test: with the patient supine elevate one leg at a time with the knee straight. Pain felt in the calf is a positive test indicating tension on the involved nerve.

In general, mechanical back pain will show only a loss of normal spinal motion. Disk disease with nerve root involvement will present with the above signs plus sensory, motor, or reflex changes and a positive straight leg raising test, as in Case 2. Tuberculous infection presents with systemic signs, spinal deformity, usually kyphosis, and may have neurological changes. The neurological involvement from tuberculosis involves the spinal cord, rather than nerve roots, and the physical findings may include hyperactive reflexes, clonus, and spasticity. Spinal tumors often cause the same neurological abnormalities. Adolescent patients may present with either an isolated kyphosis or scoliosis. These are usually of unknown cause, idiopathic, and while they may progress, they do not cause severe pain; just some mild discomfort. If the pain is significant, other causes such as tumor or infection should be considered.

Pearls of wisdom

- There are a few particular problems involving musculoskeletal pain for which a physical examination is helpful. Chronic or recurrent back pain is especially difficult to treat unless a clear diagnosis such as tuberculosis, pyogenic infection, tumor, or disk disease is established.

- Pain is often the presenting symptom in patients with a musculoskeletal abnormality. Take a careful history of the onset and quality of the discomfort.
- The physical examination is easily performed, but be sure to include the evaluation of all important structures: nerve, vessel, skin, muscles, tendons, joints, ligaments, and bone.
- Systemic signs (fever, weight loss, fatigue) provide a clue to possible infection or tumor.
- Special radiographic and imaging studies are helpful, but try to the make the diagnosis without them if they are not available.
- There are only a few common chronic pain syndromes involving the musculoskeletal system, and a physical examination is the key to their diagnosis.
- If deformity or significant abnormality is present on the physical exam with little associated pain, consider an underlying neuropathy.

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Guide to Pain Management in Low-Resource Settings

Chapter 13
Psychological Evaluation of the Patient with Chronic Pain

Claudia Schulz-Gibbins

Why is psychological assessment of pain important?

People who have painful conditions or injuries are often additionally affected by emotional distress, depression, and anxiety. Chronic pain involves more than the subjective experience of the intensity of pain. In the last 30 years a biopsychosocial model for understanding chronic pain has evolved. According to this model, chronic pain is a syndrome with consequences such as physical and psychosocial impairment. This model contains variables such as central processes on the biological dimension as well as on psychological dimensions, including somatic, cognitive, and affective dimensions.

The cognitive dimension contains, besides attention processes, attempts to come to terms with the pain experienced. For example, thoughts like "the pain is unbearable" or "the pain will never end" can have an effect on the affective dimension and intensify reactions like anxiety.

Suffering from chronic pain has social consequences, for example, on activities of daily living, family environment, and cultural factors, or it may be affected by previous treatment experiences. Illness can be viewed as the effect of the complex interaction of biological, psychological, and social factors [2]. Emotional and cognitive aspects like anxiety or helplessness in coping with chronic pain are correlates that can significantly strengthen pain perception and intensity.

The cause of increased pain perception can include emotional components such as despair, sadness, anger or fear, but it can also be a reaction to impairment due to pain. In correlation with these processes, the cognitive component is the belief that it is not possible to have any relief of pain after unsuccessful treatments. Believing this can, for example, increase feelings of helplessness. The loss of belief in the functionality of one's own body is experienced as a psychological threat. Thoughts will increasingly focus on the apparently unchangeable pain problem. Very often the result is a restriction of one's whole perspective on life through the focus on pain. The consequence is that the person concerned very often retires from physical and social activities. Family conflicts arise because of the feeling of being misunderstood. Self-esteem is affected by the subsequent inability to work. The main focus is on consulting a doctor and obtaining a cure. The increasing consumption of medication is accompanied by fear and apprehension of side effects. Inactivity because of the impairment by the pain and the whole symptomatology can cause and intensify depressive reactions such as passivity, increasing cogitation, lack of sleep, and decreased self-esteem. In a vicious circle, chronic pain can lead to depressive reactions, which influence the perception of and reactions to the pain. For example, biological processes such as muscle tension can cause pain but can also be caused by increased depression. Depression can lead to more physical passivity, and in

consequence the lessened activity leads to an increase of pain because of degeneration of muscles. The result can be chronic pain. The main aims of treatment depend on the complexity of chronic pain and demand consideration of all the factors involved.

Case report 1

A 40-year-old farm worker suffers years of increasing back pain. All attempts at treatment have so far been without success. He says that a doctor told him that he could not find the exact cause of his pain, but that probably has a "crumbling" spine, and he can see no way to treat him or relieve his pain. Because of the pain, he has been unable to work and earn enough to support his family. He rarely has enough money to buy pain killers. Increasingly, he feels helpless, he cannot sleep at night because of his pain, and he worries about the future. For the past year, he has tried as much as possible to avoid strenuous movements, and as soon as he gets home he goes to bed. He says he has no strength left, and his wife feels helpless. It makes him even sadder to see how his wife suffers because she cannot help him. He does not know how to continue, and he fears that, if his physical restrictions and pain increase further, he will not be able to care for his family. His employer has told him that he cannot be lax at work, and he fears for his job. He has not yet told his wife of his problems at work, fearing that she might leave him. His colleagues have complained to his employer that they had to take over some of his work. His social life is poor because of his pain.

What are the dimensions of the biopsychosocial concept within this case report?

Biological dimensions:

Possibly some early degeneration of the vertebral column and muscular dysfunction, enhanced by physical inactivity.

Psychological dimensions:

a) Affective dimension: increased sadness and anxiety.

b) Cognitive dimension: feelings of helplessness, "pain and impairment will go on, and no one can help me," and decreased self-esteem, "I am not able to care for my family," "physical activity harms my body."

Social dimensions:

Possible loss of work, conflicts with his colleagues and employer, and family conflicts.

The "vicious cycle" of pain is begins: The pain leads to physical inactivity out of fear that the pain could increase through strain. Fear for the future leads to constant increased muscle rigidity and increased agitation at night, resulting in sleep disturbances, which weaken the body additionally. The patient retreats due to depression and avoids social contact. Attempts to solve problems are avoided, which increases the anxiety and helplessness.

What are the consequences for patient assessment?

The complex interactions of somatic and psychological processes make it very difficult for any one individual to be aware of all relevant information and to appraise their relevance. Psychological assessment should be an inherent part of the pain diagnostic investigation, in a multidisciplinary setting[9]. A thorough medical assessment is an important part of any chronic pain management protocol, but a psychological interview should be integrated as promptly as possible. Patients should not get the feeling that they are being sent to a psychologist because nothing was diagnosed on the somatic level that could explain the pain and its intensity. Patients may interpret such a referral as being "shoved off" or stigmatized.

As mentioned earlier, pain affects the whole "body and soul" of our patients. Since the perception of pain is always more than just a signal from our nerves, every patient with chronic pain should be evaluated thoroughly. To accomplish this goal, in the diagnostic process, "somatic" and "psychological" aspects should be included from the beginning. The physician will then have a complete picture of the patient and will be able to understand several things better: the nature of the pain, how the pain is perceived by the patient, and how it affects the life of the patient. On the other hand, the patient may learn from the beginning that his pain may be more than just an alarm sign for an injury. From the beginning, pain and its psychological implications should be part of the conversation between the patient and the physician: the patient should never feel that the physician doubts his pain and its effect on his or her life.

What would be an appropriate technique for taking the history of a patient?

The psychological assessment includes the clinical interview, the use of standardized psychological questionnaires, and early supervision of the patient's behavior. In clinical practice, the interview is an important way

to detect the patient's complaints and attitude. It is not possible to gather all information within an interview, because of the different issues surrounding response to pain. Highly structured methods exist in the field of research, which are often not practical in daily use due to time constraints. Nonstandardized formats make it easier to focus on topics that are discovered to be essential during the discussion. It is easier to diagnose nonverbal actions such as avoidance of movements or facial expressions of emotions within the interview, along with emotions like sadness or anger.

What is the format for an interview specific to chronic pain with underlying psychological aspects?

An interview should include questions about previous pain experience and about the development of pain, individual explanations about the origin of the pain, and the treatment objectives for the patient. Assessment of the patient's behavior includes information on reduction of activities and the avoidance of everyday activities, including physical activities, because of the fear of an increase in pain. It is also important to evaluate the use/overuse of medication and compliance [16], in order to detect possible hints of drug abuse. Questions might include:

- "When do you have to take the medication?"
- "How often do you take it?"
- "How much do you have to take for pain relief?"
- "What other medications have you tried?"

The assessment of possible comorbid disorders such as depression, anxiety, somatoform disorders and posttraumatic stress disorder (PTSD) is another important purpose of the psychological interview, along with assessment of risks of chronification.

What are further possible risks of chronification?

A helpful system for the identification of psychosocial risk factors, known as "Yellow Flags," was developed by Kendall et al. [4], mainly for patients with back pain, but it may also be applicable to other pain syndromes:

Cognition/Beliefs

- Exercise/strain is harmful
- Pain must disappear completely before activity is resumed
- Catastrophizing
- Conviction that pain is uncontrollable
- Fixed ideas on development of treatment

Emotions

- Extreme fear of pain and impairment
- Depressive reactions
- Increased awareness of physical symptoms
- Helplessness/resignation

Behavior

- Distinctly cautious behavior
- Withdrawal from normal daily activities
- Distinctly preventive behavior
- Extreme pain behavior (including intensity)
- Disturbance of sleep
- Abuse of medication

Family

- A partner who is overprotective and too caring
- A history of dependency (medication/drugs)
- A family member is also a "pain patient"
- Serious conflicts in partnership or family

Workplace

- Conviction that work damages the body
- Little support in job
- No interest shown by boss or colleagues
- Dissatisfaction with job
- Motivation to relieve strain

Given Diagnosis/Treatment

- Cautious behavior/impairment supported by doctor
- Numerous (partly contradictory) diagnoses
- Fear of malignant disease
- Passive treatment prescribed
- High level of health care utilization
- Conviction that only somatic treatment will lead to alleviation
- Dissatisfaction with previous treatment

Why is it important to assess individual models of explaining pain and its expression?

Individual models of explaining the development of pain are dependent on sociocultural and ethnic aspects. The meaning and expression of pain and suffering are determined by social learning. Response to and expression of pain are determined by culture as a conditioning influence. An early belief in the development of pain was the "foreign body theory," where pain that did not have an identifiable cause, such as headache, was thought to be connected to supernatural powers. Magical objects were thought to enter orifices and be responsible for

pain. In ancient sophisticated cultures, magical beliefs were connected directly to punishment as a result of insulting the gods. The perception of pain as "punishment by God" within the framework of religious structures is still widespread today; for example, pain patients feel "less desire to reduce pain and feel more abandoned by God" [14]. Lovering [7] investigated cultural beliefs with regard to causes of pain in various cultures and reports of references by the patients to "the evil eye" (Filipino, Saudi, and Asian cultures) or the power of the ancestors (Tswana culture). The handling of pain is influenced not only by the patient's attitude toward pain, but also by the attitude of the health professional. In an explanatory model, "Patients and health professionals bring their own cultural attitudes to the communication and interpretation of the patient's pain experience." In this interaction, it is the health professional's knowledge and attitudes that dominate the response to the patient's experience of pain [7]. The consideration of subjective assumptions with regard to the development of pain—such as belief in magical, biomedical, or biopsychosocial approaches to pain—make it possible to develop relevant therapy concepts by incorporating the wishes and targets of patients. Understanding the personal experience narrative means understanding the outcome.

Consequently, what are the functions of psychological assessment?

The chief purpose of psychological assessment is to get a complete picture of the pain syndrome with all affected dimensions: somatic, affective, cognitive, behavioral, and above all, the individual consequences for the patient. The complete information and the analysis of conditions of pain maintenance enable us to fix targets for treatment. For example, a patient with a diagnosis of back pain and avoidance behavior needs education to understand why it makes sense to minimize such behavior. A patient with back pain, avoidance behavior, and depressive reactions needs a good explanation of the biopsychosocial model. For example, what are the consequences of depression in the context of pain? A better understanding can enable the patient to develop better strategies of coping and minimize helplessness.

What are psychological models for explaining conditions of pain development and maintenance?

Cognitive and behavioral factors, as well as classical conditioning, are factors we have to think about in this respect. Within the theoretical understanding of pain, classical conditioning according to Pavlov, based on stimulus and reaction, builds the foundation for further considerations. The feeling of pain is primarily a reaction to a pain stimulus and thus has a response. In this regard, a primarily neutral stimulus, for example, a rotation of the body with evidence of relevant muscular malfunction, is connected to feeling an unpleasant psychophysiological reaction such as increased heart rate or a painful increase of tension in muscles. The consequence is to avoid this type of rotation of the body, which can make sense when the pain is felt for the first time. However, if this behavior is maintained, an increase in the muscular malfunction leads to a strengthening of the mechanism. If both stimuli are often experienced together, then the body reacts to the original neutral stimulus. Receptiveness for a given stimulus is determined by the individual's life and illness history. For example, stress stimuli, which are often accompanied by pain, can be the cause of subsequent pain.

Does operant conditioning also play an important role?

Operant conditioning has been explored in the work of B.F. Skinner in the 1930s and 1940s. In this paradigm, it is hypothesized that behavior increases in frequency if reinforced. A decrease follows if this behavior is not rewarded or punished. In the late 1960s, Fordyce first explored the principles of operant-behavioral therapy (OBT) as a treatment for patients with chronic pain.

The operant model assumes that one's reaction to pain is not determined by somatic factors but as a result of psychosocial consequences. The longer pain persists, the greater the likelihood that the pain experience is primarily influenced by reactions to the environment. Behavioral attitudes will more than likely emerge when they are directly positively strengthened or when negative effects can be avoided. The awareness of pain can thus be affected by positive strengthening, for example, by increased care and attention by third parties. A negative strengthening of pain awareness can be caused by the absence of unpleasant activities or by avoidance of conflicts as a result of expressing pain. This behavior can be sustained even after alleviation of pain and thereby lead to a renewed sustainment of the vicious cycle, for example, by sustained avoidance of beneficial behavior such as activity.

What are typical cognitive factors influencing pain?

The classical as well as the operant conditioning model presuppose the existence of pain. The flaw in both models is that they do not take cognitive-emotional factors into account. Moreover, physiological processes are not considered in the operant model. An extension occurs in the theory of the cognitive-behavioral approach. In this model the interaction between pain and cognitive, affective, and behavioral factors is the central point. The central assumption here is that the affective, as well as the behavioral, levels are decisively determined by a person's convictions and attitudes toward pain. Within the cognitive framework of pain, it is necessary to differentiate between self-verbalization, which refers to the moment, and metacognition, which refers to a long period of time. The tendency to a single cognition generally leads to behavioral consequences. Attributable self-verbalization such as catastrophizing, such as, "The pain will never end" or "Nobody can help me" leads to an overestimation of pain. Hypothetically, as a result of an overestimation of the level of pain, avoidance tendencies may result, as a consequence further pain stimuli are not freshly evaluated, and adaptive strategies to cope with pain will not be carried out. Maladaptive metacognitions such as fear-avoidance beliefs are accompanied by the assumption that the pain scenario will definitely not proceed favorably and by the assumption that every strain for the body will affect the state negatively. There is no longer a belief in the restoration of physical functionality [13].

What is meant by observational learning?

The concept of model learning stems from social learning theory. Within this concept, the approach to pain in one's family of origin is of central importance. Learning does not only occur as a result of imitation of behavioral models, for example, that one should lie down as soon as a headache is evident. Yet expectations and attitudes are adopted, such as the overinterpretation of all somatic symptoms as dangerous and in need of treatment.

What are possible influences of coping strategies?

Since the development of the multidimensional concept of psychological coping by Lazarus and Folkman [6], there has been increasing interest in the concept, particularly in the development of psychological interventions, such as cognitive-behavioral therapy. Coping with pain includes all attempts made by a person to influence the pain, whether by thought or deed. Coping strategies can be positive (adaptive) or negative (maladaptive). Adaptive thinking strategies include: "I know the pain will be better tomorrow" or "I'll try to think about something pleasant, to take my mind off the pain." Examples of maladaptive thinking strategies are: "I can't bear the pain any longer—there's nothing I can do by myself" or "I have no future if the pain goes on." Thoughts also have an effect on the pain behavior of the patient. Adaptive behavioral strategies include: "After my work is done, I will take a short break, and after that I can do something I want to do," or "After a little walk in the sun I will feel better." Maladaptive coping strategies can be problematic behaviors: "Drinking alcohol will reduce my pain" or avoidance behaviors: "After only a hour's activity I have to have a rest of not less than two hours." Assessment of coping strategies allows having an influence on the education of the patient in order to support adaptive strategies. For example: 'It is better to do the work of the day in short periods of time and have a little rest, rather than to do all the work in two hours and have to rest for the remainder of the day."

In this area there are cultural differences, which depend, among other factors, on access to the health system. Murray et al. [12] examined cultural differences between patients with diagnosed cancer and the pain involved with qualitative interviews. Patients in Scotland reported as the main issue the prospect of death, saying that suffering of pain is unusual and spiritual needs are evident. In comparison, patients in Kenya reported physical suffering as the main issue, especially as analgesic drugs are unaffordable. They feel comforted and inspired by belief in God. Taking these findings into account, it is necessary to take a close view of patients' resources and problems in coping with pain.

Within the field of research, common instruments to assess coping strategies of patients with chronic musculoskeletal pain are the Coping Strategy Questionnaire [15] or the Chronic Pain Coping Inventory [3].

What are possible social impacts that can influence healing in a negative way?

Constant chronic pain not only leads to physical and psychological impairment but can also cause multiple problems in daily social life, and sometimes the patient is alone in coping with the pain alone. Social problems in combination with poor coping strategies can also intensify the risk for chronicity of pain.

More often than not, conflicts of goals may arise; existing and resulting psychosocial problems can come into conflict with the aim of possible recovery. Often the patient is not aware of, or else has no abilities to cope with, the existing physical failures of daily functioning. The problems cannot be compensated for on one's own. The patient is under extreme psychological and physical stress. If conflicts of goals exist, it is helpful to discuss these conflicts and any possible negative consequences with the patient during the course of the treatment and explore possible solutions.

Do financial compensation/legal issues interfere with recovery from chronic pain?

Possible risk factors making treatment and subsequent recovery more difficult are accidents at work, accidents caused by third parties, or unsuccessful medical treatment. Results can be post-traumatic stress disorders or adjustment disorders with a long-lasting depressive reaction. Legal problems, such as lengthy proceedings, compensation for injury at the workplace, or injury caused by a third party can prolong the healing process. The desire for compensation, in the sense of approval of the damage suffered, can have psychic as well as financial aspects. Often, a financial settlement is considered as a partial compensation for the pain and lost work. If a settlement is not made, there is further psychological upset, resulting in anger, despair, and increased pain. The patient feels that the pain he or she personally suffered is not acknowledged.

Case report 2

A 62-year-old salesman, Mr. Andrew, reports increased back pain after a back surgery. In the same room, he says, there has been another patient who had the same operation. His roommate was mobilizing 2 days after the operation and was almost pain free at the time of discharge. Mr Andrew believes that during his own operation, an error must have occurred. He considered that this was no surprise, given the number of procedures that were done daily and the stress on the doctors. He has tried to speak with his surgeon several times, only to be told that the pain would settle down soon. The surgeon, he thought, seemed quite abrupt with him, and did not really take time to explain things. He cannot understand the explanation of the surgeon because his former roommate at the hospital felt fine immediately afterwards. He has talked to a lot of people with similar problems, and most had better results. He is now considering suing the surgeon.

During his stay, further discussion was arranged between him and the surgeon. The surgeon apologized that the operation in this case did not bring about the desired result. Although the operation was quite similar, Mr. Andrew had a much more progressive disease, and the operation itself was technically difficult. This was explained with the help of pictures and models. Afterwards Mr. Andrew said he would refrain from suing, since he was better informed now. The pain does still exist, but Mr. Andrew knows now that he has to live with the impairment and has a more positive outlook.

What would be a typical case of intense stress within the family?

In a biopsychosocial framework, the immediate social environment, such as the patient's family, has to be taken into account. In this framework, diverse problems exist that have an additional effect on the pain syndrome. In the literature, there are three main theoretical approaches evaluating the importance of family in the co-creation and maintenance of chronic pain. Within the psychoanalytical approach, there is an emphasis on the intrapsychic processes and conflicts as well as early childhood experiences that may influence and perpetuate the experience of pain. Here, it is assumed that suppressed aggressions and feelings of guilt, as well as early experiences of violence, both sexual and physical, along with deprivation, can lead to psychosomatic conflict.

Case report 3

A 32-year-old bank accountant, Mrs. Agbori, describes abdominal pain of several years' duration. She had been diagnosed as having endometriosis and has had several surgeries, which were unsuccessful in relieving her pain. The only measure that had any effect on her pain, each time for several months, was treatment with a "hormone preparation," which, however, has made her "sterile." This upsets her very much because she and her husband wanted children. Apart from the pain she has no other physical problems, she says. The relationship with her husband is stable, and Mrs. Agbori is very content at work. Her entire family is very loving and caring, and support her.

During further interviews, Mrs. Agbori reports of having constant back pain for several years. As a 10-year-old she had to wear a body cast for almost half

a year. She knows that her back is "unstable and endangered," but she can deal with that; only the abdominal pain is a burden to her as it also impairs her sexual relationship with her husband. Since about a year ago she has tried to avoid sex, because of increasing abdominal pain afterwards. In a subsequent interview, Mrs. Agbori reports that she has a pronounced fear of becoming pregnant. She could not talk to anyone about this fear because everyone in the family wanted her to have children. She is afraid that she will not be able to go through the pregnancy and look after her child properly. In other words, she would not make a good mother. She also fears that hear back might "break apart" and she would be confined to a wheelchair.

What does this case report show us?

This case report illustrates how an innate psychological conflict can contribute to the chronicity of pain. The patient has a pronounced fear of pregnancy, although she, as well as her family, had a strong desire for her to have a child. At the same time she harbors guilty feelings because she could not fulfil this desire. *The pain in this context is probably made more intense by a feeling of guilt.*

In the framework of a family-based therapeutic approach, the family is considered as a system of relationships in which the well-being of each member depends on that of the others. This system strives for homoeostasis. A sick member of the family can, for example, have a stabilizing effect when the illness is a distraction from other problems, such as marital or pregnancy problems. The conflict of goals, here, could be that it is not easy for the sick person to "give up the disease" without risking the stability of the family. In behavioral theory, operant, respondent, and model-learning mechanisms can play a role in the chronicity of pain. An increase in illness behavior may, for example, happen when a partner gives too much emotional support. The illness behavior thus ensures also the attention and emotional support of third parties, which might not happen without the disease. It is more useful if the partner helps to cope with pain, for example, by supporting daily activities.

Case report 4

A 38-year-old man reports increasing headaches since his wife has become pregnant. He cannot understand it, he says, because the expectation of becoming a father has made him very happy. The increasing intensity and frequency of his headaches can interfere with everyday life, which puts a lot of strain on him. His wife cares about him very much and tries her best not to stress him, and has taken over doing more housework. He worries that this may cause problems in the relationship. Usually, he has looked after everything; but now his self-esteem is starting to be affected. Additionally, he has become very irritable because of the headaches. He has begun to lash out at small things, which he would regret afterwards.

Further psychological analysis reveals that the patient has suffered from headaches since early childhood. His single mother had been very ill, and he had to take over the responsibility for the family since a very young age. Since her pregnancy, his wife has stopped working. This has conflicted with his wishes to offer his child a better childhood that he has had himself. Financially supporting the family on his own would be very stressful; it creates feelings of being overwhelmed, and he often feels that he is not up to his tasks. During the further course of counseling, issues such as sharing responsibilities and feelings of guilt were discussed.

What conflicts may prevent healing?

A significant conflict of goals that may impede the treatment of chronic pain is the desire for retirement. Often, continuing disability leads to long periods of absenteeism at work. If the individual is forced to return to work, there are further periods of increased absenteeism. This can cause a change in attitude toward work and the workplace, including colleagues. Restoration of an amiable attitude to work now seems impossible. Patients very often start to think that continuing work will affect their health, and retirement is the only possibility for a sane existence. Sometimes, employers and insurers demand a solution different from ongoing further treatment, which is expensive for them.

How do we implement psychological treatment?

According to current knowledge, multimodal treatment concepts should be considered as soon as possible when risks of chronification become evident. A precondition for psychological pain therapy is the results of the somatic examination and the psychological diagnosis. The aim is to reach an adequate description of the chronic pain syndrome and an analysis of the sustained conditions of the illness process, so that an individual care plan can be plotted and discussed with the patient, along with a relative if possible.

What are specific indications for a psychological pain therapy and interventions?

- Evidence of a psychiatric disorder such as depression, anxiety, somatoform disorders, and posttraumatic stress disorder, which is causing or contributing to the chronification of pain.
- Inability to cope with chronic pain.
- High risk of chronification (yellow flags).
- Abuse of or addiction to medication.
- Psychosocial impacts (e.g., death or illness of relatives, financial problems, loss of job) in connection with or independent of the pain.

Pearls of wisdom

- After a trusting relationship has been developed, the indication for psychiatric or psychological treatment should be discussed with the patient. Particularly, educative aspects (for example, the provision of a biopsychosocial treatment concept) play an important role within the framework, in helping the patient to acquire a better understanding of the complexity of pain.
- Strategies should be developed to enable the patient to cope with pain.
- Guidelines for the management of chronic low back pain offer similar advice: Maintain physical activity and daily activities, return to work on a permanent basis, and avoid passive careful behavior [1,5,17].
- The aim is not freedom from pain but support in developing improved quality of life and coping with pain.

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Management of Acute Pain

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Guide to Pain Management in Low-Resource Settings

Chapter 14
Pain Management after Major Surgery

Frank Boni

What types of surgery are we talking about?

Surgery can be grouped into four grades, as follows:

Grade 1: Minor: examples are excision of skin lesions and evacuation of the uterus;

Grade 2: Intermediate: examples are inguinal hernia repair and tonsillectomy;

Grade 3: Major: examples are thyroidectomy, hysterectomy, and bowel resections; and

Grade 4: Very major: examples include cardiothoracic surgery and joint replacements.

This grading depends on the extent and complexity of the surgical operation. There may be some problems with the classification when endoscopies and some newer surgical techniques are used. We will consider grades 3 and 4 for our discussions.

Case report 1

An 18-year-old male had small-bowel resection for multiple typhoid perforations. He has not regained consciousness fully, 6 hours after the operation.

Does he need pain relief? How would you manage his pain, if any? What objectives do we hope to achieve with our pain management?

Although communicating with the patient may be a problem, we still have to provide a pain-free period during which the patient recovers from this multisystem infectious disease. The patient should be able to tolerate diagnostic and therapeutic procedures in the postoperative period and have calm periods of wakefulness or sleep. The pain management should not have any detrimental effect on the already compromised vital organs.

What problems do we have to deal with during the pain management plan?

The patient may be unresponsive or confused and uncooperative because of his altered state of consciousness. He was probably ill for about 2–3 weeks and has had various kinds of treatment.

Septicemia comes with gastrointestinal tract, cardiac, respiratory, renal, and other organ dysfunctions. There may be hypovolemic, cardiogenic, or septic shock with their associated problems. Fluid and electrolyte and nutritional problems are very common in these patients.

Effect of the operation and anesthesia

The sympathetic system might have been stimulated to the extreme by the illness, and any further stress may cause the patient to decompensate. The patient may therefore get worse temporarily in the postoperative period as a result of the added stress of the surgery and anesthesia.

Methods of pain relief options

Postoperative pain management must start with drugs given intraoperatively.

Local anesthetic infiltration of the wound, however, may not be advisable because of the generalized systemic nature of the disease and the increased risk of wound infection, and the reduced effectiveness and increased chances of undesirable effects of the local anesthetic drugs.

After the operation, intravenous, intramuscular, or rectal paracetamol (acetaminophen) will be preferred to nonsteroidal anti-inflammatory drugs (NSAIDs) or dipyrine for analgesia and antipyretic effects. This is because of the high incidence of multiple organ failure.

These patients will need to have small regular intermittent doses or continuous infusions of tramadol, fentanyl, morphine, or any other suitable opioids that are available in combination with the mild to moderate analgesics mentioned above. There is little evidence that one opioid is superior to another in the postoperative setting as long as equipotent doses are used and application is according to the specific drug kinetics. If the clinician is very worried about hypotension and respiratory depression, small doses of ketamine can be given intermittently, as a continuous infusion with a drip or infusion pumps. Small analgesic doses should limit the unwanted effects, and the sympathetic effects may actually be beneficial. It must be stressed that all drugs have to be carefully titrated according to response. Many patients in low-resource countries have had limited exposure to opioids and can be very sensitive to them. This applies especially to very ill patients like this one. Poor renal and liver function could lead to reduced metabolism and excretion, increasing the cumulative effects of drugs.

What other special actions should we take regarding his pain?

Very poor-risk patients like this one ideally will require respiratory and cardiovascular support in a high-dependency or intensive care unit. Since most hospitals in low-resource countries do not have these facilities, great caution must be exercised when using any drugs for pain relief, and careful monitoring of the cardiovascular, respiratory, and urine output should be routine. Central nervous system manifestations such as agitation or coma may make it difficult to interpret the sedation score. The delayed recovery of consciousness could also be due to the cumulative effects of sedatives and long-acting opioids used for sedation and ventilation.

The take-home message would be: the general poor state of the patient and the fear of hypotension should not be reasons to avoid the use of opioids in this patient. The fact that the patient cannot complain does not mean there is no pain! Careful titration, use of multiple analgesics, and good monitoring hold the key to safe and successful management.

Case report 2

A 75-year-old man is due for bilateral total knee replacement. How would you manage his pain perioperatively?

What objectives do we hope to achieve with pain management in this patient?

This patient must be pain-free to mobilize quickly and have physiotherapy in the perioperative period. Preexisting comorbidity should be considered at all times. Complications from drug interactions and complications from multiple drug usage should be avoided.

What is the incidence and severity of postoperative pain in joint replacement patients?

Joint replacements constitute some of the most destructive types of surgery and are usually very painful. Most of these patients have been in a lot of pain even before surgery and are already on many drugs and other forms of treatment. Their pain will be moderate (Grade 3) or severe (Grade 4), and bad enough to limit movement and normal activity. There are other associated problems of old age and immobility. Many patients come for surgery as a last resort to get rid of their pain. We can therefore assume that most will have unbearable pain after their surgery, especially when physiotherapists start mobilizing them within one or two days after the operation.

What other problems do we have to consider regarding pain management?

These patients are usually on analgesics which may include combinations of acetaminophen (paracetamol), NSAIDs, and opioids. Some may be on steroids and other drugs for rheumatoid arthritis and other medical conditions. These drugs may have been taken for long periods, and side effects or drug interactions are not uncommon in the perioperative period. The elderly have considerable multisystem pathology, and they may be on cardiovascular, respiratory, central nervous system, and genitourinary drugs. They may be on blood-thinning drugs such as warfarin, aspirin, and any of the heparins, which may affect our regional and local anesthetic blocks.

The socioeconomic status of these patients is very important. The patients may not have family and financial support. If they have dementia and cannot communicate very well, pain management can be very difficult.

What are the best pain management options for this patient?

For pain relief during and immediately after the operation, regional anesthesia is probably best for this group of patients. The duration of the operation, patient cooperation, and technical difficulties, as well as anticoagulant therapy, may make general anesthesia mandatory. Spinal anesthesia with long-acting local anesthetic drugs together with intrathecal opioids will provide a simple and effective anesthesia and good postoperative analgesia. This method is well suited for any low-resource country because patients receiving this type of anesthesia require less resources and care than patients who have general anesthesia. Small doses of diamorphine given intrathecally with the local anesthetic drugs can provide good analgesia for up to 24 hours postoperatively. Diamorphine may, however, not be freely available in low-resource countries. Morphine may be easier and cheaper to procure and can be an alternative. The clinician should, however, only use preservative-free morphine in the intrathecal or epidural space and should be aware of the problems associated with morphine use, which include delayed respiratory depression, itching, nausea, vomiting, and urinary retention.

Patients on aspirin and some prophylactic anticoagulation can have spinal anesthesia, provided that hematological profiles are kept within normal ranges and that care is taken with timing and concurrent use of prophylactic heparins. Clopidogrel and some newer drugs used in richer countries cause more problems and have to be stopped at least 7 days before surgery and regional anesthesia. The timing of the dural puncture should not be within 2 hours of giving low-molecular-weight heparin (LMWH) such as enoxaparin. Unfractionated heparin is more affordable but not as effective as LMWH in preventing deep vein thrombosis in these patients.

The single-shot spinal may, however, not be suitable for a bilateral knee replacement in this patient, and so a combined spinal epidural (CSE) can be used. This treatment is more expensive, and the incidences of complications with anticoagulants are higher. If the duration of the operation or the patient's condition do not favor a regional technique, general anesthesia should be carefully conducted. In this situation, strong opioids combined with NSAIDs can provide good intraoperative and postoperative analgesia.

Syringe and volumetric pumps are expensive and difficult to maintain, but large teaching hospitals should have them for patient-controlled analgesia (PCA) or continuous infusions in operations such as joint replacement. Regular acetaminophen, either intravenously or orally, should be given with other oral analgesics such as codeine, tramadol, or NSAIDs as soon as patients can take oral medications. Antiemetics, antacids, and mild laxatives may be prescribed as required. Intravenous acetaminophen is now more affordable and convenient than rectal acetaminophen and should be used more often, even in low-resource countries. It is probably the safest multipurpose analgesic that we have at the moment.

What roles should the patient, relatives, and medical personnel play in the pain management of this patient?

Perioperative pain management plans should be meticulously put in place well in advance of operations like this one. The surgeon, anesthetist, and acute pain team (if available) should involve the patient and the relatives before the operation to discuss the options. Special forms, written instructions, and guidelines make things easier for patients and hospital staff. The appropriate scoring systems, and the use of equipment like PCA pumps, should be practiced with the patient before the operation. In uncooperative or demented patients with no family support, the safest and most appropriate techniques should be used, and extra care should be taken in monitoring them.

These are just two examples of major surgery that one can come across in poorly resourced countries. There are many other operations, types of patients, and issues that one will come across in managing pain after major surgery in these countries. Some of these issues will now be discussed.

Why is postoperative analgesia an issue?

Major surgical operations normally cause considerable tissue damage and pain. It only became possible to perform major operations safely and painlessly after modern anesthesia was introduced about a century ago. In the perioperative period, certain pathophysiological

changes caused by pain threaten the wellbeing and the rehabilitation of the patient. Pain is part of the "stress response complex" to prepare the patient for "fight or flight." Poorly administered analgesia can have some unwanted effects. When we decide to treat pain, we have to consider the cost implications involved. One must therefore understand the pain process and make good use of available resources judiciously, wherever one is practicing.

Some frequently asked questions regarding pain after major surgery include:

- How common is pain after major surgery?
- What is the nature of pain and how do we measure the severity?
- What are the consequences of inadequate analgesia after major surgery?
- What are our goals in postoperative pain management?
- How do patients and type of surgery affect our pain management?
- Do newborn and unconscious patients have pain after surgery?
- What are the pain therapy methods available to us after major surgery?
- What roles can patients, relatives, and medical staffs play?
- Can we justify the costs and the risks involved in the management of pain?
- Does opioid use postoperatively lead to addiction in later life?
- Should strong opioids be avoided in very ill poor-risk patients?
- Is pain threshold higher in patients in less affluent countries?

There are many more questions, some of which have been partly answered by the two case scenarios presented. These questions can, however, be generalized to cover a wider range of patients and issues found in poorly resourced countries.

What is the incidence of pain after major surgery?

Moderate pain has been estimated to be present in about 33% and severe pain in 10% of patients after major surgery. If all patients with moderate and severe pain need treatment, these figures suggest that only about half of patients will need postoperative analgesia after major surgery. A closer look at publications, which are mostly from developed countries, reveals that these figures are for patients who have had analgesia during and after operations and yet still had pain. A good proportion of patients in developing countries will not complain of pain—although they may be in agony—because of cultural and other reasons.

In the absence of reliable data in poorly resourced countries, we can only assume that most patients will have moderate to severe pain after major surgery. The real incidence of untreated postoperative pain may never be known because it would be unethical to carry out properly controlled studies by deliberately allowing some patients to have pain after major surgery.

What type of pain is caused by surgical trauma?

All patients (except a few with abnormal physiology) will have acute pain due to actual tissue damage. Most pain experts will call such pain "nociceptive pain." The tissue damage will provoke chemical and nerve stimulation at the local as well as the systemic levels, which can provoke many complex responses.

The pain may be due to surgical incisions, tissue manipulation, injury during operations, or positioning of the patient. On the other hand, the pain may have nothing to do with the surgery or the positioning on the operating room table. It may, for example, be due to preexisting arthritis, chest pain, or headache from any cause.

Whatever the cause or nature of the pains, it is the severity that matters most to the patient. A simple and frequently used classification has four levels of pain:

No pain	Grade 0
Mild pain	Grade 1
Moderate pain	Grade 2
Severe pain	Grade 3

It is generally accepted that grades 0 and 1 may not need any treatment, but grades 2 and 3 should be treated because they can cause significant morbidity.

What consequences of pain do we expect after major surgery?

Pain, as part of the so-called "postoperative stress syndrome," can cause considerable morbidity and even mortality. Pain is usually accompanied by hormonal,

metabolic, and psychological responses to trauma. Examples include the neuroendocrine changes involving hypophysis-adrenal responses, which can have profound effects on the body. Some of these detrimental effects are summarized below.

Cardiovascular system

Pain can cause a number of different types of arrhythmias, hypertension leading to myocardial ischemia, and congestive cardiac failure, especially in the elderly and those with cardiac disease.

Respiratory system

Tachypnea and low tidal volume due to painful respiratory efforts, reduced thoracic excursions, and sputum retention can lead to atelectasis or chest infections.

Gastrointestinal system

Delayed gastric emptying can lead to nausea, vomiting, and bowel distension.

Metabolic effects

Sympathetic stimulation can lead to hyperglycemia and acid-base abnormalities such as respiratory acidosis or alkalosis, which can lead to electrolyte imbalances and fluid retention.

CNS and socioeconomic effects

Pain can lead to uncooperative patients and can cause anxiety, depression, or agitation. Prolonged stay in the hospital can put stress on individuals, families, and health institutions.

Secondary consequences of pain

There are also some effects that may not initially appear to be linked to pain. Pain delays the mobilization of patients out of bed and, therefore, increases the risk of postoperative complications like thromboembolism, bedsores, and many infections such as chest, gastrointestinal tract, and wound infections. These can be referred to as *secondary consequences*.

Do we have to measure pain postoperatively, and how do we go about it?

It is very useful, but not always possible, to assess pain in the postoperative period. Simple and reliable methods of pain assessment like the verbal, visual, or numeric analogue scales should not be difficult to use routinely in even the poorest environments. The assessment should tell us about the nature and severity of pain and help us to initiate and evaluate treatment.

Quantifying pain may, however, be difficult because pain is subjective and unique to the individual. One has to be able to communicate with patients and measure their responses. Assessor and patient factors are therefore important. To improve the accuracy of the various assessment methods available, we have to educate the patients as well as medical staff in their use. Preferably, patient education and practice in using these methods should take place in the preoperative period.

Is the assessment of pain with an analogue scale sufficient for all situations?

Sometimes one cannot use the most common assessment methods such as the visual analogue scale, or they may not be sufficient for certain situations. In babies, and with uncooperative and unconscious patients, we cannot use the analogue scale. In preschool and older children, modified scales can be used, but one may have to rely on physiological parameters such as pulse rate, respiration, crying, sweating, limitation of movement and many others. Unfortunately, pain is not the only cause of these changes, and they should be interpreted with caution.

In settings like intensive care units, physiological data may be the only methods that can be used. The equipment required can be very expensive to purchase, maintain, and operate.

What are our goals in postoperative pain management?

Clinicians will want to treat pain in order to prevent the detrimental effects mentioned earlier. We would like the patients to be able to mobilize quickly out of bed. Patients should be able to tolerate physiotherapy, tracheal suctioning and coughing, and other potentially painful therapeutic and diagnostic procedures.

Patients want to breathe, talk, walk, and carry out other functions as quickly and comfortably as possible. They also want peaceful uninterrupted periods of rest and sleep. When on pain treatment, they do not want to be unduly drowsy, or have any nausea and vomiting or inconveniences such as constipation.

Whatever the method of analgesia chosen, the method must be:

- Effective,
- Safe, and
- Affordable.

One should try and initiate analgesia before the pain becomes intolerable and established because the pain cycle is more difficult to break once it becomes established. Once good analgesia is achieved, it should be maintained as long as the patient needs it. After major surgery, the first 48 hours will be the critical period, but some patients will need analgesia for weeks. Analgesia can be started with intravenous strong opiates, with or without regional and local anesthetic techniques, and gradually tapered to weaker drugs by the oral or rectal routes over several days. The intramuscular use of drugs immediately after operations is not advisable because the results are not very predictable and they are difficult to control. It is preferable to use more than one technique or drugs to achieve our goals.

Does good acute pain control have any long-term effects?

Although we still do not fully understand the development of chronic pain after surgery, we now know a lot about the incidence of chronic pain after surgery and about ways to prevent its occurrence. Although the numbers tend to vary after most types of surgery, about one out of every 10–20 patients will have long-term pain after surgery, and for half of them, the pain will be severe enough to need treatment. We now know that good pain control, no matter how it is achieved, will reduce the number of patients experiencing long-term pain after major surgery.

We also know that only a negligible number of patients who receive opioids for acute pain after surgery will become addicted or dependent on opioids if the drugs are used in a controlled manner. There is, therefore, no justification for withholding strong opioids from patients because of the fear of addiction, as is done in many developing countries. Ironically, many patients in these countries can barely tolerate the euphoria, drowsiness, and other effects caused by the opioids. Some patients in poorly resourced countries will not accept opioids postoperatively when given the choice.

How do we monitor the side effects of the analgesics we are using?

When using systemic analgesia, we are particularly concerned about the use of opioids. The side effects we should be most concerned about are the respiratory effects. Respiratory depression can be difficult and unreliable to detect at the initial stages. Since excessive sedation usually comes before respiratory depression, if we monitor sedation carefully and regularly, we should be able to prevent respiratory depression. A simple sedation score like the one below should be used for all patients on opioids:

Grade 0	patient wide awake
Grade 1	mild drowsiness, easy to rouse
Grade 2	moderate drowsiness, easy to rouse
Grade 3	severe drowsiness, difficult to rouse
Grade S	asleep, but easy to rouse

The key to safe use of opioids in poorly resourced countries is therefore to monitor the sedation score very closely and avoid Grade 3 sedation. Regular monitoring, e.g., by a nurse, may be considered as safe as monitoring with technical equipment!

What other parameters should we measure in wards after major surgery?

All patients should have the following monitored after all major surgery:

- Level of consciousness
- Position and posture of the patient
- Rate and depth of respiration
- Blood pressure, pulse, and central venous pressure, when indicated
- Hydration state and urine output
- All medications being administered along with analgesics
- Patient activity and satisfaction.
- History, examination, and good record-keeping will reveal any problems.

Complications such as nausea and vomiting can be troublesome and should be controlled with antiemetics. Constipation may be a problem after prolonged use of opioids, and mild laxatives like lactulose can be used.

Renal, bleeding, and other problems can be worsened by the use of nonsteroidal anti-inflammatory drugs and other analgesics, and patients should be

monitored more closely if there is any cause of suspicion from the history and examination.

What pain management options do we have to choose from?

Peripheral analgesics

Peripheral analgesics are sometimes described as weak to moderate analgesics, and they can be used intravenously, intramuscularly, rectally or orally. Examples are acetaminophen (paracetamol), ibuprofen, and diclofenac. Although they may not be able to control pain alone after major surgery, they are very useful in combinations with one another or with opioids and other analgesic techniques. One of the new major developments in postoperative pain management is the regular use of peripheral analgesics after all grades of surgery.

Local and regional anesthetics

These include wound infiltrations during operations, field blocks, nerve blocks, and regional blocks of the limbs and trunk. These are particularly useful in the first 12 to 24 hours, when we are very worried about cardiovascular and respiratory postoperative complications.

"Central" analgesics

Opioids are the most useful in this group, but in some specific situations, general anesthetic drugs such as intravenous ketamine in "subanesthetic" doses can be used for pain relief without making patients unconscious.

"Coanalgesics"

Drugs such as antidepressants and anticonvulsants are frequently used in chronic pain, but they are not very useful in acute pain. Intravenous steroids such as dexamethasone are becoming more popular for use as antiemetics after surgery, but they have not been proven to reduce postoperative pain significantly.

Nonpharmacological methods

Tender loving care ("TLC"), heat and cold applications, massage, and good positioning of the patient can all reduce pain after surgery and do not add much to the costs of treatment. These methods should be used more whenever possible. Transcutaneous electrical nerve stimulation (TENS), acupuncture, and other methods are not currently considered clinically useful after major surgery.

Invariably the following will determine the type of methods to choose

- Type and condition of the patient
- Type of the surgery and healing period
- The training and experience of the anesthetist and other staff
- The resources available to treat and monitor the patient

Which pharmacological alternatives may I choose from?

The drugs included in the table are mostly the drugs from the latest essential drug list proposed by the World Health Organization (WHO). The drugs marked are not included in that list but can be very useful. This applies to diamorphine and some other drugs mentioned in the text.

Should very ill patients receive strong analgesics postoperatively?

Many patients are not well resuscitated and may be hypovolemic after major surgery. Severe pain causes a lot of adrenergic stimulation, which tends to temporarily keep the blood pressure up. This occurs at great cost to the patient because of the accompanying tachycardia and increased oxygen consumption, and also peripheral and renal shutdown. When pain is abolished, these patients may reveal their "true" blood pressure and become hypotensive. Some medical staff therefore avoid opioids in such patients. The hypotension should prompt medical staff to treat the patient more aggressively and correct the real causes. Morphine causes histamine release, which may cause vasodilatation, but it is usually mild and beneficial to the heart.

Some hospital staff looking after very ill patients prefer to see a patient struggling and showing signs of life rather than pain free and sleeping quietly. Some tie up such patients to their beds when they are struggling. Others resort to sedatives and hypnotics, such as diazepam or even chlorpromazine. Many patients are restless because they have pain or a full bladder. Sedating or restraining such patients may do more harm than good and should not replace adequate pain relief.

Is the pain threshold higher in patients from poorer countries?

There is no real evidence for this surmise. Although expressions and the reactions to pain may differ from

Drug	Dose	Route	Frequency
Acetaminophen	0.5–1 g	i.m., i.v., rectal	t.i.d. or q.i.d.
Diclofenac*	50–100 mg	i.m., rectal	b.i.d. or t.i.d.
Ketorolac*	10–30 mg	i.m. or i.v.	
Morphine	2.5–15 mg 0.5–2 mg 2 mg 0.1–0.2 mg better recommend titration	i.m. i.v. Epidural Intrathecal	4–6 hourly Titrate Once daily One dose only
Pethidine (meperidine)	25–150 mg 5–10 mg 10–25 mg	i.m. i.v. Intrathecal	3–4 hourly Titrate One dose only
Dipyrone*	10–15 mg/kg	i.m., i.v.	t.i.d.
Ketamine	0.25–0.5 mg/kg	i.m., i.v., epidural	Titrate i.v. dose
Bupivacaine	1 mg/kg 1–2 mg/kg	Wound infiltration Epidural or caudal	End of operation
Tramadol	50–100 mg	Oral/i.v.	8-hourly p.r.n.
Hyoscine butylbromide	20–40 mg as gastrointestinal or genitourinary antispasmodic	Oral/i.v.	8-hourly p.r.n.

Abbreviations: b.i.d., twice daily; i.m., intramuscular; i.v., intravenous; q.i.d., four times daily; t.i.d., three times daily;
* Not on the WHO essential drug list, but can be useful in poorly resourced countries.

one region to another, one cannot make such generalized statements about pain after major surgery. Many patients in developed countries may be more exposed to analgesics, and their expectations for pain relief may be higher, compared to patients in developing countries. They may, therefore, request more drugs and will be able to tolerate them better. Pain is, however, no respecter of race or class, and every individual must be treated as unique. The modern definition of pain acknowledges the role of the person's environment, culture, and upbringing and these should be taken into account when evaluating or managing pain from any cause.

How to organize pain management after major surgery

Minimum services for maximum effect

Every hospital, no matter how remote or small, should endeavor to provide effective pain relief after every major surgery. Pain relief may require the barest minimum of staff drugs and equipment. The type of acute pain service provided will differ depending on the circumstances. The World Health Organization and other world bodies recognize the need for universal guidelines like those developed for chronic cancer pain. Such guidelines help countries, especially those with the least resources, to carry out audits and compare outcomes to other countries.

Acute pain services may vary but share some basic structures:

- Patients and the general public need to be educated about acute pain and its management in the perioperative period. Consent is not normally required except for experimental and research purposes.
- Protocols and guidelines need to be developed for all health personnel
- The use of mild and moderate analgesics such as acetaminophen, NSAIDs, and dipyrine should be encouraged as much as possible. Intravenous, rectal, or oral routes can be used in an upward or downward stepladder manner depending on the circumstances.
- Intraoperative wound infiltration by surgeon is usually effective in the immediate postoperative period and should be used whenever feasible.
- Local and regional-pain relieving techniques have an important role in any acute pain service and should be encouraged.
- Opioid analgesics should be readily available and used routinely.
- Antagonists to drugs, resuscitation drugs and equipment, and good monitoring are essential in all institutions where major surgery is done.

- The acute pain service should organize regular ward rounds, run emergency services for complications, carry out research, and conduct audits on pain management.

Advanced pain management services in teaching hospitals and other specialized units

- These facilities should aim to have acute pain service with guidelines and protocols to cover children and adults in accident and emergency wards, operating rooms, and recovery wards as well as general wards.
- At least one or two doctors and an identified pain nurse should be able to follow up difficult and problematic postoperative cases and to manage any complications arising from postoperative pain or its treatment.
- A recovery ward and a high-dependency unit and if possible an intensive care unit will be required for some of the major operations or for very ill patients in order to treat pain effectively in the immediate postoperative period. Relying on the sympathetic responses caused by pain to artificially prop up the patient's blood pressure is not acceptable and may cause more harm than good.
- There should be staff training programs to train personnel to manage pain safely at all levels and especially in high-risk patients after major surgery.

What equipment and what drugs are required for postoperative pain management?

- Simple hypodermic needles or preferably cannulas and syringes and intravenous infusion lines may be all that is needed to treat most patients. Syringe and infusion pumps are being increasingly used for continuous, patient-controlled, or nurse-controlled analgesia. The prices and availability of these pumps should improve sooner or later and make it possible for poorly resourced countries to procure them.
- There should be a wide range of drugs to reflect the range of patients and operations carried out. The WHO essential drug list may not be adequate for managing pain after major operations, even in poorly resourced countries.
- Optimum monitoring of the patient should include equipment for respiratory monitoring, including pulse oximetry and cardiovascular monitoring, and fluid input/output charts.
- It should, however, be emphasized that the best monitors are the doctors, nurses, and other health personnel with the help of relatives and any other persons around. Simple sedation observation charts and early warning charts for adverse events will help manage even the most difficult patients in the least well-resourced areas.

What are pain considerations after some specific major surgical operations?

General surgery (e.g., thyroidectomy, gastric and bowel resections, major burns, and abdominal trauma)

Patients will have moderate to severe pain (Score 2–3). It does not matter if they are emergency or elective cases. More care must be taken with emergency cases because systemic analgesic drugs may mask symptoms and signs of diseases.

- Antispasmodics such as hyoscine butylbromide are useful in colic pains.
- General surgery covers a wide spectrum of operations and pain-relieving techniques. Local and regional anesthetic blocks are grossly underused.

Obstetrics and gynecology (e.g., abdominal hysterectomy, cesarean sections, pelvic clearance for cancer)

Patients will have moderate to severe pain (Score 2–3). Considerations include:

- First trimester. Choose drugs carefully and avoid those that affect the fetus.
- Before delivery of the baby by cesarian section, opioid use should be avoided as it affects the fetus.
- Deep vein thrombosis, bleeding, and other hematological problems affect pain management.
- Women may seem to tolerate pain better than men, but this is not a general rule.
- Nausea and vomiting are very common and should be adequately treated.

Trauma and orthopedic operations (e.g., fractures of the neck of the femur with moderate pain or shoulder, knee, or hip reconstruction with very severe pain)

- Head injuries. Some clinicians are reluctant to use opioids, but they can be used safely.

- Acute abdomen. Analgesics may mask acute abdomen signs perioperatively.
- Regional and nerve blocks can be used in many clinical situations.
- Multi-organ failure must be considered when choosing and titrating drug doses.

Major pediatric operations (e.g., cleft palate repair with severe pain, pyloric and bowel surgery with moderate to severe pain, anal and genitourinary malformation repair with severe pain, exomphalus and gastroschisis with severe pain, and thoracic surgery such as diaphragmatic hernia and tracheoesophageal fistulae with very severe pain)

Problems related to the management of pediatric patients include:

- Technical, physiological, and biochemical differences from adult patients.
- Drugs doses and drug delivery systems require special training.
- Parents and staff role are more critical than in adults.
- The view that newborns do not need pain relief is no longer valid.

Cardiothoracic operations (facilities for cardiopulmonary bypass are not usually found in poorly resourced countries, but one may still need to do thoracotomies and lung resection for tuberculosis and chest tumors. Chest trauma, repair of aneurysms, esophageal surgery, and some valve repairs and closure of congenital malformations can all be very painful, especially when the sternum and ribs are split).

Special problems include:

- Use of anticoagulants and problems with regional and local anesthetic blocks.
- Heavy sedation and ventilation ideally will require intensive care units.
- Heart and lung function may be compromised, but good pain management can prevent or control major complications and help with physiotherapy.

Neurosurgical operations (e.g., major spinal surgery with severe pain, craniotomy and resection of brain tumors with moderate pain, trauma and skull fractures with moderate pain)

- Care should be taken in interpreting the Glasgow Coma Scale with opioids.
- Large doses of opioids can cause hypoventilation and increase intracranial pressure.
- It may be advisable to avoid nonsteroidal anti-inflammatory drugs.
- Scalp and other head and neck nerve blocks can be very useful.
- Nausea and vomiting may be a problem.
- Dihydrocodeine or other "weak" opioids are preferred by some health workers to stronger opioids, because of the view that they causes less respiratory depression. However, if doses are titrated carefully to the desired effect and adequately monitored, any opioid may be used safely.

Ear, nose, throat, dental, and maxillofacial operations (e.g., jaw fracture fixation with moderate pain, tonsillectomies with moderate but sometimes severe pain)

Common problems include:

- Airway concerns, especially with bleeding, increased secretions, and opioids.
- Danger of sleep apnea, restlessness, or diminished states of consciousness.
- Nausea, vomiting, and retching are to be avoided as much as possible.
- Pethidine (meperidine) may have advantages of anticholinergic effects over other opioids.

Genitourinary operations (e.g., prostatectomy, urethral reconstruction, and nephrectomy, which can all be very painful, but fortunately these are easy to manage with regional techniques)

- The patients are usually elderly with geriatric and major medical problems.
- Intrathecal and epidural local anesthetics with opioids are commonly used.
- Some theoretical problems, such as spasm of sphincters caused by morphine, are rarely encountered.

Septicemia

Septic patients are common in poor countries. Many of these patients may not be suitable for regional and local anesthesia and analgesia if there is frank septicemia.

There may also be unpredictable drug effects from opioids, nonsteroidal anti-inflammatory and other potent drugs because of multiorgan failure. Acetaminophen and dipyrine, if they are not contraindicated, will help with the pain and the pyrexia seen in septic patients.

Pearls of wisdom

- Acute pain after major operations provides few benefits and numerous problems for patients and should be treated whenever possible.

- Treatment of pain may, however, cause its own problems and should be planned and practiced with clear written guidelines and protocols.
- Education and involvement of the patient, the family, and all medical staff are all important for any pain management program to succeed.
- Universal acute pain management protocols and guidelines need to be encouraged by WHO and other professional and regulatory bodies. Regional and local modifications will be required to reflect the type of patients and the type of surgery, as well as the resources available.
- Even in poorly resourced countries, efforts should be made to provide enough funds to improve standards of postoperative care, especially pain management.
- All medical personnel should be trained to overcome the fear of strong opioid analgesics and other methods of pain relief, and to develop a positive attitude toward all patients who have had major surgery.
- More use of local anesthetic drugs and techniques, and also the use of peripheral analgesics, should be encouraged after all types of surgery.
- International and national drug regulatory bodies in partnership with governments and local suppliers should make opioids more available and reduce restrictions on their use for pain management in developing countries.

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Anesthesia, pain, and intensive care management

www.postoppain.org
Good site for pain management in ideal situations

www.nda.ox.ac.uk/wfsa
Updates aimed at poorly resourced countries

www.who.int/medicines
Drug policies and control, including essential drugs list

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Guide to Pain Management in Low-Resource Settings

Chapter 15
Acute Trauma and Preoperative Pain

O. Aisuodionoe-Shadrach

When acute trauma occurs, the diagnosis and purposeful management of pain should be of paramount concern.

Case report

A 38-year-old man, John Bakor, is brought to the accident and emergency room after being knocked down by a small vehicle. He was transported in the back seat of a saloon car without any splint to his injured leg and had jolts of pain every time the car stopped on its bumpy ride to the hospital.

John is received by Dr Omoyemen, the attending resident, who after putting a full-length aluminium gully-splint to immobilize his left lower limb, asks for a helping hand to move him onto a hospital stretcher. Fracture immobilization on its own minimizes pain due to the fracture injury by limiting movement of the affected parts. A quick review reveals that John had sustained an open fracture with dislocation of the left ankle and has multiple skin bruises over his left forearm and thigh. He is fully conscious, knows who he is, and is well oriented as to time and place. He is then checked for other injuries that he may have ignored as inconsequential or may be unaware of, such as other bruises or lacerations. Dr Omoyemen obtains a brief history of the nature of the accident and proceeds to specifically evaluate for secondary injuries such as blunt abdominal injuries, or chest wall or pelvic fractures. The benefit of this evaluation is to identify injuries that may pose a potential danger to life besides the obvious left ankle injury.

Intravenous access is obtained for the administration of fluids and/or medications, and Dr Omoyemen then performs a thorough evaluation of the patient's pain using a standardized assessment tool, the verbal rating scale (VRS). John's VRS = 7/10, suggesting that he is having acute severe pain. The doctor administers 50 mg of pethidine (meperidine) intramuscularly (i.m.) as a preliminary analgesic before the injury is formally reviewed and dressings are changed, and i.m. tetanus toxoid is administered to prevent tetanus.

After dressings are complete, adequate regular analgesia is commenced (pethidine 50 mg i.m., 6-hourly). Finally, while John is awaiting formal orthopedic surgical review, his pain is reassessed regularly to determine the effectiveness of the analgesic regimen, which is also periodically reviewed as required.

Questions you should ask yourself and their probable answers

What is pain?

Acute pain results from tissue damage, which can be caused by an infection, injury, or the progression of a metabolic dysfunction or a degenerative condition. Acute pain tends to improve as the tissues heal and responds well to analgesics and other pain treatments. We know that pain is a subjective sensation, although

several assessment tools have been designed to objectively measure it. Pain has multiple dimensions with several descriptions of its qualities, and its perception can be subjectively modified by past experiences.

Acute pain leads to a stress response consisting of increased blood pressure and heart rate, systemic vascular resistance, impaired immune function, and altered release of pituitary, neuroendocrine, and other hormones. This response could limit recovery from surgery or injury. Adequate relief or prevention of pain following orthopedic surgery has been shown to improve clinical outcomes, increase the likelihood of a return to preinjury activity levels, and prevent the development of chronic pain. Undertreatment of acute pain can lead to increased sensitivity to pain on subsequent occasions.

Furthermore, the sources of pain in acute trauma and preoperative settings are mostly of deep somatic and visceral origin, as may occur in road traffic accidents, falls, gunshot wounds, or acute appendicitis. Pain in the acute trauma and preoperative settings is usually caused by a combination of various stimuli: mechanical, thermal, and chemical. These stimuli cause the release of nociceptive substances, e.g., histamine, bradykinin, serotonin, and substance P, which activate pain receptors (nociceptors) to initiate pain signals.

How should pain be assessed?

Because of its complex subjectivity, pain is difficult to quantify, making an accurate assessment problematic. However, a number of assessment tools have been developed and standardized to identify the type of pain, quantify the intensity of pain, and evaluate the effect and measure the psychological impact of the pain a patient is experiencing.

A pain scale may be either one-dimensional or multidimensional. In the acute trauma/preoperative setting, where the cause of pain is obvious and pain is expected to resolve more or less promptly, one-dimensional scales are recommended. Examples include the following:

- Numeric rating scale (NRS), in which the patient rates pain from 0 to 10 in increasing order of intensity
- Visual analogue scale (VAS), in which the patient marks the severity of pain on a line
- Verbal rating scale (VRS)
- Illustrative scales such as the Faces Pain Scale, which consists of drawings of facial expressions. This type of scale is useful in children, the cognitively impaired, and persons with language barriers.

Although the multidimensional pain scale was developed for pain research, it can be adapted for use in the clinic. An adapted version of the Brief Pain Inventory questions patients about pain location, intensity as it varies over time, past treatments, and the effect of pain on the patient's mood, physical function, and ability to function in various life roles.

Is there an obligation to manage pain in the acute trauma and preoperative setting?

The commitment to manage a patient's pain and relieve suffering is the cornerstone of a health professional's obligation. The benefits to the patient include shortened hospital stay, early mobilization, and reduced hospitalization cost.

Pain is not merely a clinical symptom but evidence of an underlying pathology. In the acute trauma and preoperative setting, there is a temptation to overlook pain and its specific management, while all efforts are geared toward treating the underlying pathology. The challenge is to help the health professional realize that the management of both symptoms (pain) and underlying pathology (acute appendicitis) should go hand in hand. Using the WHO analgesic ladder, a rational systematic approach to pain management in the acute trauma and preoperative setting can be developed and implemented.

Is pain an important issue to the patient who is in the acute trauma/preoperative setting?

Yes. Freedom from pain can be considered a human right. As fanciful as that may seem, it must be emphasized that pain is a natural accompaniment of acute injury to tissues and is to be expected in the setting of acute trauma. In such a scenario, the goal of the physician is to ensure that the patient's pain is tolerable.

In a study conducted at an accident and emergency room department of a university hospital in sub-Saharan Africa, 77% of patients who had preoperative analgesia considered the analgesic dosage inadequate, and 93% of those patients blamed this inadequacy of pain relief on inadequate analgesic prescription by their doctors. The 77% of patients who had preoperative analgesia admitted they would have preferred a lot more than what they were given.

What should the attitude of the attending physician be regarding the specific management of pain in this scenario?

Concern. Often, paying attention to adequate analgesic coverage for this category of patients is overlooked in

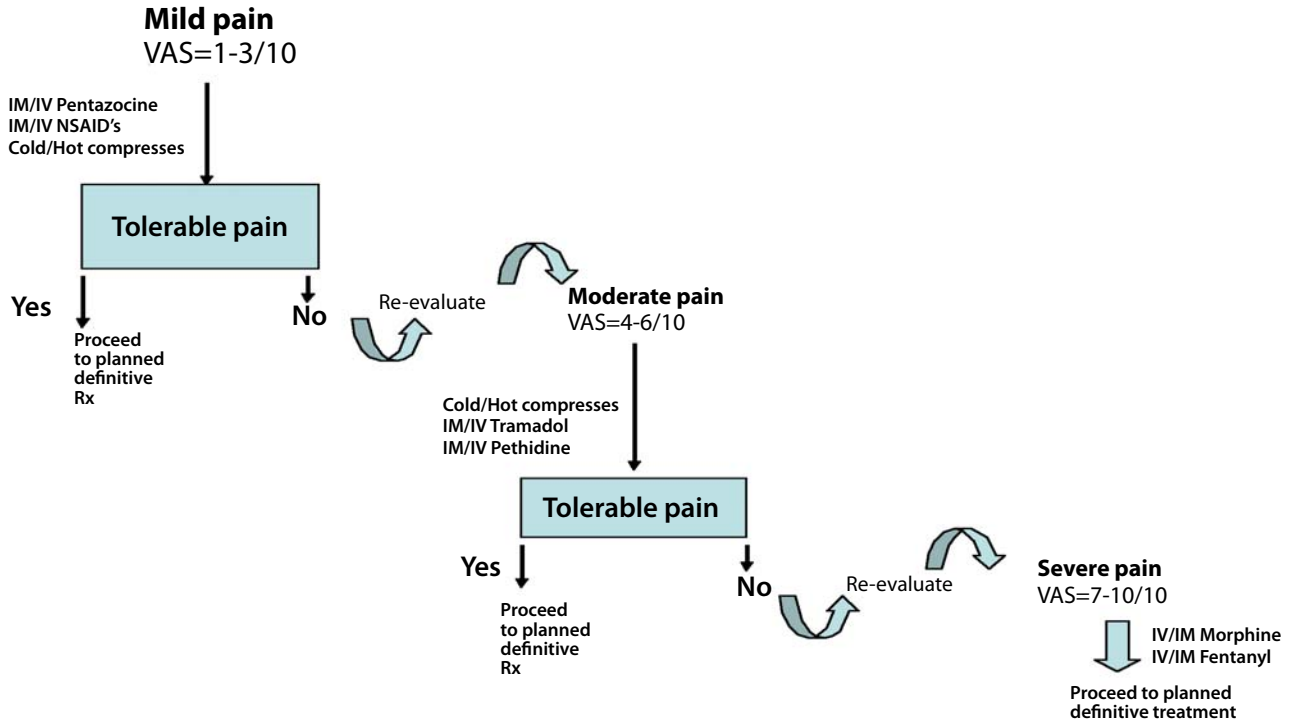

Fig. 1. An algorithm of the management of pain in the acute trauma/perioperative setting.

favor of getting them prepared as quickly as possible for surgery. Adequate analgesia facilitates the evaluation and subsequent treatment of the underlying injury or disease.

What is the attitude of the patient to pain?

Except when the cause is very obvious, as in the case of a fractured limb, the patient does not know the diagnosis, but only knows the symptoms—pain. Often, pain management is poor.

When or how soon should active management of pain be instituted in the acute trauma/preoperative setting?

Immediately after diagnosis, the principles of effective management of acute pain should be adopted and pain control instituted immediately (Fig. 1). The goals of treatment are to relieve pain as quickly as possible and prevent any adverse physical and psychological responses to acute pain.

The general principles of acute pain relief include the following:

- Analgesic selection is based on the pathophysiological mechanism of pain and its severity.
- Both opioid and nonopioid analgesics are highly effective for nociceptive pain.
- Nonopioid agents are preferred for mild pain.
- Opioids may be required for moderate to severe pain.
- Combined treatment with opioids and nonopioids is often appropriate, and nonopioids may be employed to reduce the opioid dose requirement.
- Nonpharmacological treatments may be helpful but should not preclude drug treatment.

What are the principles of effective acute pain management ?

- Unrelieved pain may have negative physical and psychological consequences.
- Aggressive pain prevention and control before, during, and after surgery and medical procedures does result in both short- and long-term benefits.
- Successful evaluation and management of pain is partly dependent on a positive relationship between the patient and his or her relatives on the one hand, and the doctor and nurses on the other.
- Patients should be actively involved in pain evaluation and control.
- Pain control must be evaluated and reevaluated at specific regular intervals.
- Attending physicians and nurses must have a high index of suspicion for pain.
- Total elimination of all pain is not practically attainable.

What specific roles should the doctors and nurses play in ensuring that patients in this scenario are pain-free?

The clinicians should proceed to quantify the patient's degree of pain using the following methodical approaches:

- A brief oral pain history documented at the time of admission.
- A measurement of the patient's pain using a self-reporting instrument, e.g., VAS or VRS.
- The use of behavioral observation as an adjunct to the self-report instruments.
- Monitoring of the patient's vital signs (although this is not a specific or sensitive test for pain).

These procedures should be repeated at periodic intervals by the attending health professional with a view to assessing the efficacy of the analgesic regimen. Further measures include ensuring good patient positioning with the use of pillows and blankets in addition to the application of hot or cold compresses as needed.

Pearls of wisdom

- Avoid misconceptions and recognize culturally determined beliefs about pain.
- Always remember that pain cannot be ignored.
- Don't believe that the ability to tolerate pain is a measure of "manhood."
- The truth is that pain is not meant to be tolerated.
- It may not be practical to expect patients in the acute trauma/preoperative setting to be absolutely pain-free.
- However, pain can be reduced to tolerable levels by using widely available techniques.
- Develop an algorithm for the management of pain in the acute trauma/perioperative setting, as shown in Fig. 1.

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Chapter 16
Pain Management in Ambulatory/Day Surgery

Andrew Amata

Case report

John, a 5-year-old boy, had an orchidopexy done under general anesthesia. The perioperative period was uneventful, and the child (accompanied by his mother) was discharged home, fully awake and comfortable about 5 hours after the procedure with a prescription of oral paracetamol (acetaminophen). Problems began later that night when the child woke up complaining of significant pain around the operation site. The mother gave him the prescribed analgesic, but the pain persisted, and the child had now become inconsolable and unable to go back to sleep, keeping the parents and the other siblings awake.

This sort of scenario is unfortunately very common and causes unnecessary pain, distress, and suffering, not only to the patient but often to the whole household. The good news is that this type of situation is easily preventable or at least effectively treatable in most cases by applying simple and safe methods of pain relief.

For our illustrative case above, an example of a typical pharmacological analgesia therapy can be as follows. Paracetamol and/or a nonsteroidal anti-inflammatory drug (NSAID) is given orally as a premedication about 1 hour before surgery or as a suppository after induction of anesthesia. A caudal block or a field block or local infiltration with bupivacaine or ropivacaine local anesthetic is administered after induction of anesthesia. Postoperatively, oral paracetamol and/or an NSAID should be given at regular intervals for the first 48 hours, and oral tramadol or codeine ordered as required (rescue analgesia) for unrelieved moderate to severe pain.

Why is analgesia for minor surgical procedures a topic worth reading about ?

In this section, I will explain why pain may be a common and significant problem in seemingly minor surgical procedures and how such pain can be effectively managed. Postoperative pain should be considered a complication of surgery with significant adverse effects, and every effort should therefore be made to avoid or minimize it. It is obvious that there are various options for providing effective and safe analgesia after minor surgical procedures. Satisfactory analgesia should be feasible for every patient, irrespective of geographical location or level of resources.

What is minor surgery?

Surgery is commonly classified as major or minor depending on the seriousness of the illness, the parts of the body affected, the complexity of the operation, and the expected recovery time. Minor surgical procedures now constitute the majority of procedures carried out in health care facilities because of greater awareness and

earlier presentation of patients, and the increasing availability and accessibility of health care resources. Generally, more than half or even two-thirds of all surgical cases in health care facilities are usually considered minor and are often done as "same-day" or "day-case" or as "outpatient" or "ambulatory" surgery, where the patient comes into the health care facility, has the procedure done, and goes home the same day. This trend has been increasing recently and is mainly driven by economic factors, patients' preferences, improved anesthetic and surgical techniques, and the increasing availability of minimally invasive surgical procedures.

What is the prevalence of pain after minor surgery?

The general assumption is that minor surgery is associated with less pain than major surgery. One of the criteria for selection for outpatient surgery is that pain should be minimal or easily treatable. However, it may be difficult to accurately predict pain intensity in a particular individual as some seemingly minor surgery may elicit moderate to severe pain for various reasons, including interindividual variability in pain perception and response. For the same type of surgical procedure, two similar individuals may perceive and experience pain very differently, and even for the same individual, the intensity of pain of a procedure may vary with time and activity. Several studies have shown that more than 50% of children and a similar proportion of adults who undergo outpatient surgery experience clinically significant pain after discharge.

What factors lead to poor pain control after minor surgery?

Contributory factors to poor postoperative pain control in minor surgery include:

- The assumption that minor surgery is associated with little or no pain, so that little or no analgesics are given in the postoperative period.
- The pressures of current ambulatory surgical practices, which emphasize rapid recovery and return to "street fitness" and early discharge, resulting in anesthesia care givers and surgeons avoiding or minimizing the perioperative use of potent and longer-lasting analgesics and sedatives that may delay recovery and discharge.
- The fear among health care providers of the respiratory depressant and sedative effects of opioid drugs outside of immediate supervised medical care.
- The presumption that patients or guardians may be ignorant of the risks of medications and may abuse them, with significant consequences at home.
- Legislative and restrictive policies in some regions that make it difficult to have access to potent analgesics.

Strategies for ensuring effective postoperative analgesia

Be proactive

Effective postoperative pain management begins preoperatively. Patients are often very anxious and distressed by the hospital and procedure experience, and this distress may exacerbate pain postoperatively. Preoperative information and education regarding pain control has been shown to significantly reduce patients' and guardians' anxiety and analgesic consumption. Education improves understanding and compliance with the analgesic administration regimen. Important information may need to be repeated or provided in written form as patients or their guardians may not remember everything they had been told during the perioperative period.

Most patients recovering from anesthesia in the recovery room are comfortable because of the proactive and aggressive pain management by the anesthesia care provider. Unfortunately, when the patient is discharged, the intensity or continuity of pain care is disrupted. The pain of surgery often outlasts the pain medication or local anesthetic administered in the perioperative period. To avoid this problem, administer the first postoperative analgesic dose before the effects of the intraoperative analgesics wear off completely.

Use preemptive or preventive analgesia

Preemptive analgesia implies that giving analgesia *before* the noxious stimulus is more effective than giving the same analgesia *after* the stimulus. While this concept has not been convincingly proven in all clinical studies, what is clear is that more analgesia is often required to treat pain that is already established than to prevent or attenuate pain that is still developing. One

should therefore aim to preempt or prevent pain if possible or proactively treat pain as early as possible.

Avoid analgesic gaps

Analgesic gaps subject the patient to recurring pain and unsatisfactory analgesia. Such gaps tend to occur when the effect of a prior analgesic dose or technique is allowed to wear off before the subsequent dose is given. An appropriate dosing interval based on knowledge of the pharmacology of the agent is important to minimize this gap.

Apply a multimodal analgesia strategy

Multimodal analgesia implies the use of several analgesics or modalities that act by different mechanisms in combination to maximize analgesic efficacy and minimize side effects. This strategy allows the total doses and side effects of analgesics to be reduced.

Paracetamol, a nonsteroidal anti-inflammatory drug (NSAID), and local analgesia should be routinely used as components of a multimodal analgesic strategy, unless there is a specific reason not to use one of these agents, as they are synergistic or additive. In other words, the combination provides better analgesia than one of the individual drugs alone. Potent opioids, especially the long-acting ones like morphine and methadone, should preferably be avoided or used sparingly as postoperative analgesics for minor surgery because of their associated side effects, especially nausea and vomiting, respiratory depression, and sedation. Postoperative nausea and vomiting (PONV) can be quite distressing, and some patients may prefer to tolerate the pain rather than use opioids. PONV and pain are the two most common causes of delayed discharge and also for unanticipated admission in day-case surgery. However, if the severity of pain warrants the use of opioids, the shorter-acting agents such as fentanyl should preferably be used by careful titration to effect in the immediate postoperative period.

Alternatively, the "weaker" opioids such as tramadol or codeine should be used. The "weaker" opioids have the advantages of minimal sedative and respiratory depressant effects, a low potential for abuse, and not being subject to stringent opioid restrictions, and thus they may be more easily dispensed to appropriate patients. They therefore fill an important gap in the analgesic ladder between the mild non-opioid analgesics and the more potent opioids, especially for day-cases.

An often forgotten or neglected part of the multimodal approach is the use of nonpharmacological therapies. Psychological and physical therapies complement medications and should be used whenever possible. Physical therapies include splinting and immobilizing painful areas, application of cold or hot compresses, acupuncture, massage, and transcutaneous electrical nerve stimulation (TENS). Psychological therapies include behavioral and cognitive coping strategies such as psychological support and reassurance, guided imagery, relaxation techniques, biofeedback, procedural and sensory information, and music therapy. Studies suggest that these nonpharmacological therapies improve pain scores and reduce analgesic consumption.

Pearls of wisdom

- Discuss the options and plan the method of postoperative pain management with the patient and/or guardian preoperatively.
- Be proactive; begin postoperative pain management preoperatively. This strategy will reduce intraoperative anesthetic requirements and facilitate earlier recovery and discharge.
- Give preemptive or preventive analgesia. Prevention is better than cure. Much larger amounts of an analgesic are required to treat established pain than to prevent it.
- Use a multimodal approach to pain management, incorporating both pharmacological and nonpharmacological methods.
- Provide a supply of effective analgesics and information on their use before discharge.
- Give appropriate and effective analgesics regularly (around-the-clock) rather than p.r.n. or "as required" for the first 24 to 48 hours postoperatively, when the pain intensity is likely to be highest. Make provision for management of breakthrough pain (rescue analgesics).
- Always provide a contact number that a patient or guardian can call if necessary.

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Chapter 17
Pharmacological Management of Pain in Obstetrics

Katarina Jankovic

Case report

Charity, a 28-year-old office worker living in Nyeri, arrives late one evening at Consolata Hospital. She is in her first pregnancy and is accompanied by her mother Jane, an experienced mother who thought it would be about the right time to see the obstetrician, since Charity's contractions had become more and more regular. On admission, Charity says she would like to try to go through the labor without pain killers, but as contractions become stronger, she starts screaming for help. What could you do to relieve the pain?

Do all women in labor have pain that requires analgesic treatment?

The pain of labor and delivery varies among women, and even for an individual woman, each childbirth may be quite different. As an example, an abnormal fetal presentation, such as occiput posterior, is associated with more severe pain and may be present in one pregnancy, but not the next. It may be estimated that one in four women in labor require analgesia.

What are the application routes for analgesia if needed?

Pharmacological approaches to manage childbirth pain can be broadly classified as either systemic or regional. Systemic administration includes the intravenous, intramuscular, and inhalation routes. Regional techniques are comprised of spinal and epidural anesthesia. Epidural anesthesia has gained popularity in the last decade and has almost replaced systemic analgesia in many obstetric departments, mostly in developed countries. Regional techniques are widely acknowledged to be the only consistently effective means of relieving the pain of labor and delivery, with significantly better analgesia compared to systemic opioids.

What are the advantages of systemic analgesics?

Systemic analgesics may be administered by individuals who are not qualified to perform epidural or spinal blocks, and so they are often used in situations when an anesthesiologist is not available. They also are useful for patients in whom regional techniques are contraindicated. The most popular agents are opioids (e.g., morphine, fentanyl, butorphanol, pethidine [meperidine], and tramadol). While the sedative side effects of opioids are generally unwanted and irritating for the patient, in the laboring woman sedation induces relief and general relaxation. Analgesic effects sometimes appear to be secondary.

A systematic review of randomized trials of parenteral opioids for labor pain relief was able to show that satisfaction with pain relief provided by opioids during labor was low, and the analgesia from

opioids only slightly better than placebo. Interestingly, midwifes have rated pethidine much better than parturients, probably because sedation was confused with analgesia.

Which route of administration for systemic analgesia should be preferred, and why?

If an anesthesiologist is not available, pethidine (meperidine) is usually the drug of choice. It remains the best investigated and most often used opioid in labor. The dose of pethidine commonly prescribed is 1 mg/kg i.m. up to the maximum dose of 150 mg/kg. The intramuscular route is not recommended because it is not dependable—the rate of drug-absorption may vary. Intravenous administration is more reliable, and the maximum total dose of 200 mg is reported to produce significantly lower pain scores and no difference in maternal or neonatal complications. Higher doses have to be strictly avoided, since pethidine may provoke seizures. This is due to the drug's unique pharmacological structure, which gives it a special place among the opioids.

What is the clinical relevance of opioids passing the placenta barrier?

Opioids cross the placenta and may affect the fetus. This is manifested in utero by changes in fetal heart rate patterns (e.g., decreased heart rate variability 25 minutes after i.v. administration and 40 minutes after i.m. administration of pethidine) and in the neonate by central nervous system depression (e.g., slowing of respiratory rate and changes in muscle tone).

The adverse effects of pethidine and its active metabolite norpethidine on the fetus may—in rare instances—need to be reversed by an opioid antagonist. The appropriate i.m. dose of naloxone would be 10 μg/kg body weight. But ideally, naloxone—as most drugs in pain management, should be titrated intravenously to its effect (the cumulative dose would be, as for i.m. application, 10 μg/kg).

If I have various opioids available, which one I would choose, and why?

Onset time and context-sensitive half-life of all available opioids are comparable, and so the potential to induce respiratory depression in the neonate is the primary reason for selecting a particular opioid. Regarding this potential, pethidine (meperidine) may be preferred over others, as long as maximum daily doses (500 mg) are respected. Pethidine remains the only opioid with dose-dependent neurotoxicity. There is no evidence in the scientific literature that any other opioid is significantly more effective than pethidine. Also, pethidine is widely available and affordable. If available, nalbuphine, butorphanol, or tramadol may be also be used. These opioids are not "pure" agonists of the mu-receptor, but mixed agonists and antagonists, which is the reason for their unique safety regarding respiratory depression.

However, as with other opioids, respiratory depression may be avoided with pethidine. To achieve that outcome in the neonate, it is recommended to observe a certain time corridor for the application of pethidine to the parturient. Side effects are more likely to occur if delivery is between 1 and 4 hours after administration of pethidine. As a result, the classic teaching is that the neonate should be delivered within 1 hour or more than 4 hours after the last pethidine application. Timing of delivery, however, is difficult to predict with precision. In addition, the metabolite norpethidine is pharmacologically active, with a prolonged half-life in the neonate of up to 2½ days. Thus, neonatal behavior might be affected, and difficulties with breastfeeding are possible, regardless of the timing of maternal administration.

Pentazocine should not be used because of its potential to cause dysphoria and sympathetic stimulation. Theoretically, the opioid best suited for providing systemic labor analgesia would be remifentanil, which is metabolized by nonspecific plasma and tissue esterases. Therefore, although remifentanil rapidly transfers across the placenta, fetal esterases will inactivate this new opioid. Data regarding the use of remifentanil in parturients are limited, however, and so the drug cannot yet be recommended widely.

It must be noted, though, that only a few drugs are considered "safe" regarding placental passage and breastfeeding, but lack of data makes it advisable to rely on individual judgment, if only a limited number of drugs are available.

Breast-feeding during maternal treatment with paracetamol (acetaminophen) should be regarded as safe. Short-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) seems to be compatible with breastfeeding. For long term-treatment, short-acting agents

Table 1
Relative infant dose and clinical significance of selected analgesic agents

Drug	Relative Infant Dose (%)	Clinical Significance	AAP* Approval
Ibuprofen	0.6	None detected in infants; no adverse effects.	Yes
Ketorolac	0.16 to 0.4	Milk concentrations are very low; no untoward effects reported.	Yes
Naproxen	3.0	Long half-life; may accumulate in infant. Bleeding, diarrhea reported in one infant. Short-term use acceptable; avoid chronic use.	Yes
Indomethacin	0.4	Milk concentrations low; plasma concentrations low-to-undetectable in infants; caution with chronic administration.	Yes
Morphine	5.8	Oral bioavailability poor; milk concentrations generally low; considered safe; observe for sedation.	Yes
Methadone	2.6, 5.6, 2.4, 1.0	Milk concentrations low; approved for use in breastfeeding mothers; will not prevent neonatal abstinence syndrome.	Yes
Meperidine (pethidine)	1	Neurobehavioral delay, sedation noted from long half-life metabolite; avoid.	Yes
Fentanyl	<3	Milk concentrations low; no untoward effects from exposure in milk.	Yes

*American Academy of Pediatrics. Transfer of drugs and other chemicals into human milk. *Pediatrics* 2001.

without active metabolites, such as ibuprofen, should perhaps be preferred.

The use of aspirin (acetylsalicylic acid) in single doses should not pose any significant risks to the suckling infant. Aspirin, due to its causal association with Reye syndrome, generally is not recommended in breastfeeding mothers. However, the absolute transfer of aspirin into milk is negligible (< 2.4%), about 1 mg/L of milk, when following clinical doses. It is unlikely that there is enough aspirin in milk after the mother's use of an 82-mg tablet to predispose the infant to Reye syndrome, but this is not certain.

The use of pethidine (meperidine) in the perinatal period is increasingly controversial. Although the drug is used commonly in obstetrics, such use is gaining disfavor as more sedation is reported in newborns. When administered to mothers, the drug has been found to produce neonatal respiratory depression, decreased Apgar scores, lower oxygen saturation, respiratory acidosis, and abnormal neurobehavioral scores. Pethidine is metabolized to norpethidine, which is active and has a half-life of approximately 62 to 73 hours in newborns. Because of this prolonged half-life, neonatal depression after exposure to pethidine may be profound and prolonged. The transfer of fentanyl into human milk is low. In women receiving doses varying from 50 to 400 μg intravenously during labor, the amount found in milk was generally below the limit of detection (<0.05 μg/L).

Postpartum anesthesia

Nonopioid analgesics

Non-opioid analgesics generally should be the first choice for pain management in breastfeeding postpartum women, as they do not affect maternal or infant alertness.

- Acetaminophen and ibuprofen are safe and effective for analgesia in postpartum mothers.
- Parenteral ketorolac may be used in mothers who are not subject to hemorrhage and have no history of gastritis, aspirin allergy, or renal insufficiency.
- Diclofenac suppositories are available in some countries and are commonly used for postpartum analgesia. Levels in breast milk are extremely low.
- COX-2 inhibitors such as celecoxib may have some theoretic advantages if maternal bleeding is a concern. The possible advantages must be balanced against higher cost and possible cardiovascular risks, which should be minimal with short-term use in healthy young women.

Both pain and opioid analgesia can have a negative impact on breastfeeding outcomes; thus, mothers should be encouraged to control their pain with the lowest medication dose that is fully effective. Opioid analgesia postpartum may affect babies' alertness and suckling vigor. However, when maternal pain

is adequately treated, breastfeeding outcomes improve. Especially after cesarean birth or severe perineal trauma requiring repair, mothers should be encouraged to adequately control their pain.

Intravenous medications

- Pethidine should be avoided because of reported neonatal sedation when given to breastfeeding mothers postpartum, in addition to the concerns of cyanosis, bradycardia, and risk of apnea, which have been noted with intrapartum administration.
- The administration of moderate to low doses of intravenous (i.v.) or intramuscular (i.m.) morphine is preferred because transfer to breast milk and oral bioavailability in the infant are lowest with this agent.
- When patient-controlled i.v. analgesia (PCA) is chosen after cesarean section, morphine or fentanyl is preferred to meperidine.
- Although there are no data on the transfer of nalbuphine, butorphanol, or pentazocine into milk, there have been numerous anecdotal reports of a psychotomimetic effect when these agents are used in labor. They may be suitable in individuals with certain opioid allergies or other conditions described in the preceding section on labor.
- Hydromorphone (approximately 7 to 11 times as potent as morphine) is sometimes used for extreme pain in a PCA, i.m., i.v., or orally. Following a 2-mg intranasal dose, levels in milk were quite low, with a relative infant dose of about 0.67%. This correlates with about 2.2 μg/day via milk. This dose is probably too low to affect a breastfeeding infant, but this drug is a strong opioid, and some caution is recommended.

Oral medications

- Hydrocodone and codeine have been used worldwide in millions of breastfeeding mothers. This history suggests that they are suitable choices, even though there are no data reporting their transfer into milk. Higher doses (10 mg hydrocodone) and frequent use may lead to some sedation in the infant.

Epidural/spinal medications

- Single-dose opioid medications (e.g., neuraxial morphine) should have minimal effects on breastfeeding because of negligible maternal plasma levels achieved. Extremely low doses of morphine are effective.
- Continuous postcesarean epidural infusion may be an effective form of pain relief that minimizes opioid exposure. A randomized study that compared spinal anesthesia for elective cesarean with or without the use of postoperative extradural continuous bupivacaine found that the continuous group had lower pain scores and a higher volume of milk fed to their infants.

In general, if treatment of a lactating mother with an analgesic drug is considered necessary, the lowest effective maternal dose should be given. Moreover, infant exposure can be further reduced if breastfeeding is avoided at times of peak drug concentration in milk. As breast milk has considerable nutritional, immunological, and other advantages over formula milk, the possible risks to the infant should always be carefully weighed on an individual basis against the benefits of continuing breastfeeding.

If I have no opioids available, do I have any pharmacological options to relieve the discomfort of childbirth in my patients?

A variety of different drug classes are used in obstetrics when regional techniques and opioids are not available. While neuroleptics (promethazine) and antihistamines (hydroxyzine) are specifically indicated in nausea and vomiting, other drug classes have a direct effect on the distress of childbirth through their anxiolytic, sedative, and dissociative activity. Above all, a single small dose of benzodiazepines may be used (mainly midazolam or diazepam). In prodromal and early stages of childbirth, barbiturates (secobarbital or pentobarbital) may be a choice, and in experienced hands ketamine or S-ketamine may be helpful. With "analgesic doses," which are only a fraction of the anesthetic dose, cholinergic and central nervous system effects are usually absent. Tramadol, which has some opioid-like effects but acts mostly by a unique mechanism, would be another alternative choice for analgesia. Tramadol is recommended at a dose of 50–100 mg i.m. or i.v.; with efficacy similar to that of pethidine or morphine, it has fewer maternal side effects and no neonatal depression. All of these drugs pass the placental barrier and may induce sedation ("sloppy child")

in the neonate. Therefore, if the use of these drugs is unavoidable, postpartum observation of the neonate (for approximately 8–12 hours) is required.

What is the oldest analgesia method still in use, and can it still be recommended?

On Queen Victoria's request, Dr. John Snow provided for her eighth childbirth (Prince Leopold) the newly developed chloroform anesthesia with an open-drop method. "Her Majesty is a model patient," declared Dr Snow. He refused to disclose any more details, despite many importunate inquiries from the Queen's loyal subjects. The social elite in London soon followed the Queen's lead, adding further credibility to the use of anesthesia. *The Lancet* deplored the use of this "unnatural novelty for natural labor"; however, royal sanction helped make anesthesia respectable in midwifery as well as surgery. Chloroform is no longer in use, but the method has withstood the test of time. The inhalation method of analgesia in labor now uses 50% nitrous

Table 2
Use of analgesics in pregnancy

Medication	Risk	Comments
Opioids and Opioid Agonists		
Meperidine	1	
Morphine	1	Neonatal narcotic withdrawal is seen in women using long-term opioids
Fentanyl	2	
Hydrocodone	1	Almost all cause respiratory depression in the neonate when used near delivery
Oxycodone	2	Used for treatment of acute pain: nephrolithiasis, cholelithiasis, appendicitis, injury, postoperative pain
Propoxyphene	2	
Codeine	1	
Hydromorphone	2	
Methadone	3	
Nonsteroidals		
Diclofenac	4	Associated with third-trimester (after 32 weeks) pregnancy complications: oligohydramnios, premature closure of ductus arteriosus
Etodolac	4	
Ibuprofen	2/4	Both ibuprofen and indomethacin have been used for short courses before 32 weeks of gestation without harm; indomethacin is often used to arrest preterm labor
Indomethacin	2/4	
Ketoprofen	4	
Ketorolac	4	
Naproxen	4	
Sulindac	4	
Aspirin		
Full-strength aspirin	4	Full-strength aspirin can cause constriction of the ductus arteriosus
Low-dose (baby) aspirin	1	Low-dose (baby) aspirin is safe throughout pregnancy
Salicylates		
Acetaminophen	1	Widely used
Salicylate-Opioid Combinations		
Acetaminophen-codeine	1	Widely used for treatment of acute pain
Acetaminophen-hydrocodone	1	
Acetaminophen-oxycodone	1	
Acetaminophen-propoxyphene	2	

1 = Primary recommended agent
2 = Recommended if currently using or if their primary agent is contraindicated
3 = Limited data to support or prescribe use
4 = Not recommended.

oxide in oxygen. It was introduced in clinical practice more than 100 years ago, and it remains a standard analgesia method in obstetrics departments ("anaesthesia de la reine"). Later on, other inhalation ("volatile") agents such as halothane also came into use. The parturient self-administers the anesthetic gas using a hand-held face mask. The safety of this technique is that the parturient will be unable to hold the mask if she becomes too drowsy, and thus will cease to inhale the anesthetic. It is easy to administer and safe for both mother and fetus. The analgesia is considered to be superior to opioids, but less effective than epidural analgesia. Although there are data on maternal desaturation, recent studies have not demonstrated any adverse effects on mothers or neonates. Inhalation agents such as 0.25–1% enflurane and 0.2–0.25% isoflurane in nitrous oxide have given better analgesia in labor than nitrous oxide alone. Desflurane has been used as 1–4.5% in oxygen for the second stage of labor, but 23% of women reported unwanted amnesia during the period of usage.

What is a simple and effective regional anesthesia method for the second stage of labor that is easy to learn and may be applied by the non-anesthetist?

The pudendal nerve block is useful for alleviating pain arising from vaginal and perineal distension during the second stage of labor. It may be used as a supplement for epidural analgesia if the sacral nerves are not sufficiently anesthetized, and as a supplement for systemic analgesia. Pudendal nerve blocks may also be performed to provide analgesia for low-forceps delivery, but they are inadequate for mid-forceps delivery (see paragraph on "pudendal and paracervical block").

If epidural analgesia is available, which patients will benefit most?

Indications for epidural analgesia include maternal request, anticipated difficulty with intubation for surgical delivery, a history of malignant hyperthermia, some cardiovascular and respiratory disorders, AV malformations, brain tumors, and morbid obesity, as well as preeclampsia and HELLP syndrome (hemolytic anemia, elevated liver enzymes, and low platelet count).

Absolute contraindications include patient refusal, allergy (although "true" allergy to local anesthetics is rare), coagulopathy (to avoid spinal/epidural hematoma; negative history is considered sufficiently effective to identify patients at risk), skin infections at the site of needle entry (to avoid epidural abscess formation), hypovolemia (to avoid profound hypotension from the sympathetic block that comes with epidural analgesia of the lumbar and sacral segments), and increased intracranial pressure (herniation of the cerebral contents through the foramen magnum with distal pressure loss after dural puncture).

If epidural analgesia is used, could it be a single-shot technique? Which drugs should be selected, and where should the catheter should be placed?

For labor analgesia, epidural catheters are usually inserted at the level of L2–3 or L3–4. The main drugs used for this method are local anesthetics and opioids.

Table 3
Chemical characteristics of commonly used local anesthetics in labor

	Lidocaine	Ropivacaine	Bupivacaine	L-Bupivacaine
Molecular weight	234	274	288	325
pKa	7.7	8.0	8.2	8.1
Lipid solubility	2.9	3	28	25
Mean tissue uptake ratio	1	1.8	3.3	?
Uv/Mvtot ratio*	0.6	0.28	0.3	0.3
Protein binding (%)	65	98	95	98

* Uv/Mvtot ratio represents fetal/maternal concentration ratio of the total drug plasma concentration (protein bound + unbound) of maternal and umbilical venous plasma.

Table 4
Characteristics of commonly used opioids in labor

	Morphine	Fentanyl	Sufentanil	Pethidine	Diamorphine
Lipid solubility	816	1727	39	1.4	280
Normal epidural doses	50–100 μg	5–10 μg	25–50 mg	3–5 mg	2.5–5 mg
Onset time (min)	5–10	5–10	5–10	30–60	9–15
Duration (h)	1–2	1–3	2–4	4–12	6–12

Epidural requirements differ in pregnancy, and injection of a dose of local anesthetic results in a 35% increase in segmental spread compared to the nonpregnant state. Bupivacaine is the most popular local anesthetic in use. Care has to be taken to avoid high blood levels by overdosing or accidental i.v. or intraarterial injection (high blood concentrations may produce arrhythmias of the reentry type). Whether other local anesthetics (e.g., levobupivacaine or ropivacaine) have less toxicity or less motor-fiber-blocking potential, or both, is under discussion.

The most commonly used epidural opioids are fentanyl and sufentanil. They are sometimes effective in early labor, but they usually need supplementation with a local anesthetic as labor progresses. The main advantage of epidural opioids is that they improve the quality of analgesia and reduce the dose of local anesthetic needed. This reduction is considered an advantage, since local anesthetics can produce unwanted motor block. Therefore, most obstetric anesthesiologists combine a diluted mixture of a local anesthetic with a small opioid dose to achieve what is called a "walking epidural."

The most commonly used combination is a low-dose mixture of fentanyl (2–2.5 μg/mL) and bupivacaine (0.0625–0.1%). Continuous infusions or intermittent boluses or both of these agents can be given throughout labor, but the initial loading dose of 10–30 mL of the same mixture has to be given initially in divided doses.

Epidural solutions for labor may be continuously given for 12 hours or more. Drugs can be administered via a catheter, and the analgesia can be maintained by varying the infusion rate to provide an upper sensory level to T10. Low-dose local anesthetic/opioid mixtures are commonly started at 8–15 mL/h with the rate increased or top-ups of 5–10 mL given for breakthrough pain (minimum time between boluses: 45–60 min). Alternatively, a mixture of 0.0625% bupivacaine and sufentanil 0.25 μg/mL can be used at the same dose.

Midwives can be trained to give low-dose intermittent top-ups as the mother requires. The resulting analgesia is excellent, and there is no need for expensive devices. The main benefit of the intermittent technique—compared to continuous infusion—is the reduction in the use of bupivacaine and fentanyl throughout labor, along with reduced side effects, especially motor block.

Patient-controlled analgesia is a choice for the technically sophisticated obstetrics department. The patient can receive self-administered boluses by pressing a button. An electronic pump is required, and the patient must be thoroughly educated about using the device. For a background infusion, usually a dose of 10 mL/h is used, with a preset lockout interval of about 15–30 minutes. Mothers have welcomed the reduction in motor block with this method and some of them decide to get up to use the toilet and to sit in a comfortable chair by the bedside. Although not necessary in most cases, someone should be at the patient's side to support her whenever she wants to get in case orthostatic hypotension develops. Mobilization is safe if the mother can perform a bilateral straight leg raise while sitting in bed and a deep knee bend while standing, provided she feels steady on her feet. Unfortunately, there is no evidence that active mobilization reduces the risk of assisted delivery. Cardiotocography (CTG) (monitoring of fetal heartbeat and uterine contractions) can be performed intermittently. If continuous monitoring is indicated for obstetric reasons, the mother can be seated in a chair or standing by the bedside.

Complications of labor analgesia include hypotension (with much lower incidence nowadays with low concentration of local anesthetic), accidental i.v. injection, unexpected high block (total spinal/subdural blockade), urinary retention, pruritus, accidental dural puncture (the more troublesome and common problem), catheter migration, unilateral/partial blockade, and shivering.

Accidental intravascular injection usually occurs as a result of accidental placement of the epidural catheter into an epidural vein. Thus, even a small dose can produce central nervous system effects. Care should be taken to avoid accidental placement in the first place with repeated aspiration tests and applying only smaller doses of local anesthetics at any one time (avoiding large volumes of bolus applications). Unexpected high block is often the result of the catheter being placed advertently into the subarachnoid space. Low-dose local anesthetic/opioid mixtures, if given accidently intrathecally, will not produce total spinal block with respiratory depression, but can cause motor block and dysesthesias and will frighten the patient (and the physician). For intrathecal ("spinal") application of local anesthetics, the total *dose* of drug injected is more important than the total *volume* in which it is given. A high block can also, very rarely, be the result of a subdural block. The subdural space is located between the dura and the arachnoidea. While the epidural space extends only up to the foramen magnum, the subdural space extends all the way upward. This space can be entered unintentionally at any stage of labor. Subdural block should be recognized by an unexpected increase in anesthesia level and presentation with slow onset, patchy blockade, minimal sacral analgesia, cranial nerve palsies, and a relative lack of sympathetic blockade. Subsequent injection of large volumes of local anesthetic into the subdural space may rupture the arachnoidal mater and exert intrathecal effects.

Is there a "best time" for initiating epidural analgesia?

Occasionally, a parturient reaches the second stage of labor before neuraxial analgesia is requested. The patient may not have wanted an epidural catheter earlier, or the fetal heart rate tracing or position may necessitate assisted delivery (e.g., using forceps or vacuum extractor). Initiation of epidural analgesia is still possible at this point, but the prolonged latency between catheter placement and start of adequate analgesia may make this choice less desirable than a spinal technique. On the other hand, the initiation of an epidural catheter cannot be done be too early. The argument that early catheter placement may prolong the first stage of labor has not be confirmed in studies. If an epidural is used, ultra-low concentrations of local anesthetics may not be adequate to relieve the intense pain of the second stage. Adding 3 mL 0.25% bupivacaine to the standard high-volume (20 mL), low-concentration formulation of bupivacaine/fentanyl will initiate good analgesia. Additional 3-mL doses are given if pain persists after 15 minutes. Another reasonable option for providing second-stage analgesia is to perform a spinal or combined spinal and epidural (CSE) using a local anesthetic-opioid combination (e.g., 2 mg isobaric bupivacaine intrathecally). This method has a rapid onset, so that the patient is comfortable and can even be ready for cesarian section within 5 minutes.

If vaginal delivery is unsuccessful and caesarian section is necessary, how should one proceed with intra- and postoperative analgesia?

Our patient from the beginning of the chapter has been monitored for fetal heart rate, and the obstetrician is indicating urgent cesarian section due to fetal distress. Then you might think about using spinal instead of general anesthesia, since it is easy, cheap, safe, and provides prolonged analgesia.

Over the past 15 years, there has been a large increase in the number of cesarian sections done under regional anesthesia. It is therefore tempting to advocate that general anesthesia is no longer indicated, but certain factors must be taken into account when changing the standard anesthesia technique from general to spinal anesthesia. It is important to remember that when spinal anesthesia is used, the standard of care cannot be lower than for general anesthesia.

The work-up for the mother having an elective or emergency cesarian section is the same regardless of the anesthesia plan. This must include preoperative fasting, if possible, and preparation of gastric content with appropriate antacids. The anesthetist must have access to all the equipment (including difficult airways equipment) and recovery facilities required for both techniques.

Spinal anesthesia is probably safer (one study calculated 16 times safer) than general anesthesia, provided it is performed carefully with good knowledge of maternal physiology. Difficult airways and obesity-related edema become less of an issue, but remember that a pregnant woman lying supine can become hypotensive, even without augmenting the problem by giving local anesthetics intrathecally. Poor management of this problem can cause severe hypotension, vomiting, and loss of consciousness, which can lead to aspiration of gastric contents.

Fundamental differences in the spread of local anesthetic between a pregnant and nonpregnant woman must be respected, and an unacceptably high block can result in spinal (or epidural) anesthesia. Some medical conditions can cause additional problems, all related to poor compensatory response to rapid change in afterload in low cardiac output states, e.g., aortic stenosis, cyanotic congenital heart disease, and worsening of venous shunting.

What are the other pros and cons for regional anesthesia in caesarian section?

Regarding the risk of hemorrhage, it appears that there is less bleeding to be expected in cesarian section under regional blocks. In contrast, general anesthesia, when using inhalation agents, carries the risk of uterine relaxation and increased venous bleeding from pelvic venous plexuses. Although there is a traditionally held view that regional anesthesia should be avoided whenever hemorrhage is expected in gestosis, the favorable influence of regional blocks on this disease may on the contrary be an argument for regional anesthesia.

Postoperative pain is better managed after regional anesthesia in both obstetric and nonobstetric patients, perhaps due to a reduction in centrally transmitted pain, as suggested in laboratory work. Postoperative recovery is improved, and mothers are able to bond with their babies sooner. The lack of drug effects in the newborn, seen when regional anesthesia is used, means less intervention for the baby. Poor condition of the newborn after a regional technique is related to a prolonged time from uterine incision to delivery and to maternal hypotension, fetal acidosis, and asphyxia, unlike after general anesthesia, where the baby's low APGAR score will probably be due to sedation.

Whenever the newborn is already distressed and acidotic, attention must be paid to avoiding aorto-caval compression and maternal hypotension. The full lateral position must be adopted in all mothers expected to develop severe hypotension. Traditionally used i.v. crystalloid infusion preload has been shown to be unreliable in eliminating hypotension. Rapid infusion of a large volume of fluid can cause a sudden rise in central venous pressure and lead to pulmonary edema in predisposed parturients. Intravenous crystalloid preload will not reduce the need for vasopressors, and the infusion must consist of a very large quantity, e.g., 40–59 mL/kg, and must significantly affect maternal packed cell volume. Minimal preload of 200–500 mL is good enough in most situations in combination with a vasopressor. There is some evidence that a combination of colloid and crystalloid i.v. infusion can decrease the incidence of hypotension. Vasopressin agents commonly used to correct hypotension are ephedrine (6–10 mg i.v. bolus or as an infusion) and phenylephrine (25–100 μg i.v. intermittent boluses). Phenylephrine is a drug of choice when tachycardia is undesirable.

There are certain situations when a general anesthetic will be more appropriate than a regional one. These situations include maternal refusal of regional blockade, coagulopathy, low platelet count, anticipated or actual severe bleeding, local infection of the site of insertion of the spinal or epidural needle, anatomical problems, and certain medical conditions. Lack of time is the most common reason to choose general anesthesia, although for a skilled clinician, time is not an issue. If there is an epidural catheter in place, assessment and top-up should not take more than 10 minutes, which is usually more than enough time for the majority of circumstances.

Maternal hypotension is a common complication of blockade of sympathetic nerves, most characteristically cardiac sympathetic nerves. This complication can lead to a sudden drop in heart rate with low cardiac output, and if aorto-caval compression is not avoided there will be persistent hypotension that can compromise the baby. The height of a sympathetic block can be a few dermatomes higher than the measured sensory level. This complication is seen more in women who come for elective sections more often than in those who are already in labor, because the reduced amount of fluids after the rupture of the membranes causes less aorto-caval compression, and because maternal physiological adjustments have already taken place.

Supplementation of intraoperative analgesia can be used, when performed with vigilance for sedation. Fifty percent nitrous oxide in oxygen, i.v. ketamine 0.25 mg/kg, and fentanyl 1 μg/kg have been shown to be safe and effective. Intravenous sedatives such as diazepam can help a very anxious mother.

Is there a "cookbook" approach to spinal anesthesia for cesarian section?

With the smaller needles, with their atraumatic pencil-point tips, the rate of headache is less than 1% unless the mother is very short or very tall. Factors like patient

positioning and the size of pregnancy can influence the spread and extent of the block. Reducing the dose of local anesthetic to less than 10 mg hyperbaric or plain 0.5% bupivacaine without any opioid added can give an inadequate block. Fentanyl can be added at a dose range of 12.5–15 μg. Increasing the dose beyond this recommended dose does not seem to provide better analgesia intra- or postoperatively. Patient positioning does not seem to influence the final level or height of the block, but it interferes with the rate of onset and spread of the local anesthetic. The sitting position is commonly used by many anesthesiologists, but a lateral position can be used too.

The block extended to T5 to light touch is an effective level for this type of surgery, using either the epidural or spinal technique. The only difference may be that a more profound block is achieved more easily with the intrathecal block.

How to test the block

It has been found that absence of sensation to cold is two dermatomes higher than sensation of pinprick, which in turn is two dermatomes higher than sensation to light touch. That means that light touch is the best method to test the level of the block. If sensation to light touch is lost at the level of S1 to T8–6 (the level of the nipples is around T5), there is adequate anesthesia for the surgery. The extent of the motor block mirrors the block of light touch (with the corner of a tissue or a nylon filament) and is mostly adequate with complete absence of hip flexion and ankle dorsiflexion. The anesthetist should always use the same technique to assess the block, and it is important to do so bilaterally. Measuring the thoracic dermatomes must be done about 5 cm lateral to the midline.

If an epidural is already in use for a vaginal delivery, but cesarean section is necessary, how should one proceed?

The volume of epidural top-up to convert epidural analgesia for labor into epidural anesthesia for cesarian section is variable. If surgery is urgent, a large initial bolus of local anesthetic is required for fast and reliable onset of anesthesia. Initially, the existing block must be assessed, and the anesthesiologist must be involved early on, if surgery seems likely. The epidural must be topped up as soon as possible, unless a very recent top-up has been given during labor, and then 20 mL of plain 0.5% bupivacaine seems to be the best choice. Once the top-up has been given, the anesthesiologist must stay with the patient all the time, check her blood pressure, and have diluted ephedrine at hand. The safest position for the mother during transport to the operating room is the full lateral position. If there is any inequality in the spread of the block on initial assessment, put the mother in the full lateral position on the side of the poor block and give the top-up. The average time for this block to take effect is about 15 minutes.

Pearls of wisdom

There are a variety of pharmacological options for managing the pain of parturition. Opioids administered systemically act primarily by inducing somnolence, rather than by producing analgesia. Moreover, placental transfer of opioids to the fetus may produce neonatal respiratory depression. The advantage of systemic analgesia is its simplicity. Fancy techniques such as intravenous patient-controlled analgesia (PCA) are nice but not necessary to achieve good analgesia. An adequately trained midwife or obstetrician is able to provide excellent nurse- or physician-controlled analgesia in locations where an anesthesiologist is not available or if regional analgesia (epidural and/or spinal) is contraindicated.

Regional analgesic techniques are the most reliable means of relieving the pain of labor and delivery. Furthermore, by blocking the maternal stress response, epidural and spinal analgesia may reverse the untoward physiological consequences of labor pain. Another advantage of the epidural technique is that an in situ epidural catheter may be used to administer anesthetics to provide pain relief for instrumental or cesarean delivery, if required. If no epidural catheter is in place already, spinal anesthesia—a safe and easy technique—may be a good and perhaps even preferable alternative for general anesthesia.

For cesarean delivery under neuraxial anesthesia, the primary drug used is a local anesthetic. If an epidural approach is used, 2% lidocaine with epinephrine, 5 μg/mL, is a reasonable choice, because systemic cardiotoxic effects are relatively unlikely to occur. Alternatively, 0.5% bupivacaine or ropivacaine may also

be used. If a spinal approach is used, 10 to 15 mg of hyperbaric bupivacaine provides reliable anesthesia. Hyperbaric lidocaine has fallen into disfavor because of a high incidence of neurotoxic effects, even though these effects have been reported primarily in nonpregnant patients.

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British Pain Society

Management of Cancer Pain

International Association for the Study of Pain
IASP
Working together for pain relief

Chapter 18
Abdominal Cancer, Constipation, and Anorexia

Andreas Kopf

Case report

Yohannes Kassete, 52 years old, and married with four children (12, 15, 21, and 23 years old), is a cook born in Addis Ababa, who has found work in the railway restaurant of Nazret. About four times a year he travels on the Djibouti-Addis Ababa railway to see his family at home.

When he first experienced stomach pain, he suspected that he did not tolerate food as well as when he was younger. Also, he attributed it to his increasing sorrows because business was deteriorating. Common aids such as aspirin and an occasional smoke of "bhanghi" did relieve some of the symptoms, but not all. The next time he was traveling to Addis Ababa he felt almost restored, but when he was with his family, he was struck with the most intense pain he had ever felt in his life. When the pain did not go away the next day, his brother, who works at the Ambassador Bar, which caters lunch for the doctors of the Tikur Ambessa Hospital across Churchill Avenue, made an "unofficial" appointment with a doctor of internal medicine.

Although Yohannes was reluctant to see the doctor, his brother pushed him until he agreed. On physical examination, the doctor suspected a "mass" in the upper left abdomen and scheduled an abdominal sonography. The results were devastating; cancer of the head of the pancreas was most likely. The doctor did not dare to reveal the diagnosis to Mr. Kassete and talked of "some inflammation," said he just needed some rest, and gave him diclofenac (75 mg t.i.d.) as a painkiller.

Taking diclofenac regularly in an adequate dose instead of irregular 500-mg doses of aspirin actually relieved most of the pain for some time, so that Mr. Kassete could resume his job in Nazret. Being a cook, he was a little overweight, so he did not mind that he was losing weight over the next 3 months, since he did not feel like eating. When he started to have some nausea, he also reduced his fluid intake. Unfortunately, he then started to experience increasing difficulty relieving himself. Papaya seeds, he knew, would help, but that did not relieve him of the abdominal pain, which he attributed solely to constipation. With decreasing weight, increasing upper abdominal pain, and recurrent nausea, he was seen at the local health station. Since the pain was radiating to his back, they suspected some spinal problem due to his constant standing and bending in the kitchen, and a x-ray of the spine was taken, which showed no spinal problem. Nevertheless, codeine 50 mg p.r.n. was prescribed. Mr. Kassete felt weaker and weaker, and when the pain increased, he increased his dose of codeine. Since he was worried, he used his next trip to his family in Addis Ababa for another visit to the doctor his brother knew.

When this doctor was not available, he was seen by another colleague from the internal medicine department, who admitted him immediately when seeing him: he had a maximally extended abdomen, with no bowel movements on auscultation. Rectal examination revealed

a solid fecal mass in the rectum, which had to be manually removed for three consecutive days. After that enemas, bisacodyl, and senna were able to regulate the consistency of Mr. Kassete's stool. He was advised to take senna daily and add a tablespoon of vegetable oil or liquid margarine to his daily diet. Since it was assumed that the constipation was at least in part codeine-induced, the doctor advised him to take senna on a regular base with lots of fluids. Also, since the daily codeine dose was already 100 mg q.i.d., the doctor changed the opioid from codeine to morphine for better effectiveness. According to the opioid equivalence dose list, he calculated the daily morphine demand to be 10 mg q.i.d., which actually was also cheaper than codeine for Mr. Kassete. But his family was shocked to learn that the oldest son was now "on drugs" and joined him on his next visit to the doctor to complain. It took the doctor a lot of courage to explain why opioids were now inevitable and would have to be used by the patient for a long time to come. He also revealed to the patient and the family for the first time that the diagnosis was pancreatic cancer without surgical options. A Cuban doctor currently present at the department suggested a celiac plexus block, but Mr. Kassete did not trust his words and refused.

The family immediately decided not to let Mr. Kassete travel back to Nazret, and he moved in with his family, which allowed him to use a small room for himself. The hospital dispensary had no slow-release morphine available but handed him morphine syrup in a 0.1% solution (1 mg/mL) to be taken 10 cc q.i.d. This dose proved to be fine for Mr. Kassete. He was in bed most of the time now, and washing and sitting up for a little snack increased his pain unbearably. But he found that a regular smoke of some "bhanghi" helped reduce the nausea, allowing him, at least, a little food intake. His brother was clever enough to propose an extra and higher dose of morphine. In the next few weeks, his general condition deteriorated, but with 15 mg morphine 4 times daily, and sometimes 6 times daily, Mr. Kassete was fine until he again developed a massive abdominal swelling, with nausea and abdominal pain. Since he was now too weak to go to the hospital, a neighbor working as a nurse was called to see him. When she noticed the foul smell of the vomit, it was clear to her that intestinal obstruction was present, and no further efforts could be indicated to restore his bowel function. Through her intervention, a nurse from the Addis Hospice came to see Mr. Kassete and talked to the family. It took some time to convince the family and Mr. Kassete to increase his dose of morphine to 30 mg q.i.d. To improve sleep, the bedtime dose was doubled, too. Seemingly, things changed for the better. Although his abdomen remained considerably distended, Mr. Kassete found some rest, was relieved from the pain and from vomiting twice daily, and was almost free of nausea. The family was advised not to force him to take any food or drink, and Mr. Kassete did not ask for it. After becoming sleepy on the fourth day, he died in the night of the sixth day after the beginning of his deterioration.

Why a chapter on abdominal cancer with constipation and anorexia?

Pain starts early in the course of abdominal cancer. For example, in pancreatic cancer, symptom management and surgery are the only realistic treatment options, even in developed countries, since radiochemotherapy hardly influences the course of the illness. Constipation, although appearing to be a simple health problem, often complicates therapy and further decreases the quality of life of patients. Anorexia, cachexia, malabsorption, and pain may additionally complicate the course of abdominal cancer. Although awareness about the need to control cancer-related symptoms has increased in the last few decades, pain management often remains suboptimal.

What special issues apply to patients with gastrointestinal cancer?

The average incidence of pain in cancer is 33% in the early stage and around 70% in the late stage of disease. In gastrointestinal cancer, these numbers are considerable higher, e.g., in pancreatic cancer almost all patients develop pain in the advanced stages of disease. With regard to pain intensity, about half of patients report moderate or major pain, with the incidence of major pain tending to be highest in cancer of the pancreas, esophagus, and stomach.

Typical causes of pain in gastrointestinal cancer include stenosis in the small intestines and colon, capsula distension in metastatic liver disease, and obstructions of the bile duct and ureter due to infiltration by cancer tissue. Such visceral pain is difficult to localize by the patient due to the specific innervation of the abdominal organs, and it may appear as referred pain, e.g.,

as pain felt in the spinal column, due to the distribution of intercostal or other spinal nerves.

Why it is so difficult for the patient with visceral pain to identify exactly the spot that hurts?

Visceral afferent fibers (pain-conducting C fibers) converge on the spinal level at the dorsal horn. Therefore, discrimination of pain and exact localization of the source of pain is impossible for the patient. A patient with pancreatic cancer would never tell the doctor that his pancreas hurts, but instead will report "pain in the upper part of the belly" radiating around to his back in a bandlike fashion. This radiation of pain is called "referred pain."

Why is it interesting to know how the nociceptive fibers from the visceral organs travel?

The nociceptive pain conducting afferent nerve fibers of some of the visceral organs meet sympathetic efferent fibers before reaching the spinal cord in knots called nerve plexuses. From here, the pain-conducting fibers continue via the preganglionic splanchnic nerves to the spinal cord (T5–T12). This situation allows an interesting therapeutic option: interruption of the nociceptive pathway with a neurolytic block at the site of the celiac plexus. This is one of the few remaining "neurodestructive" therapeutic options still considered useful today. Nerve destruction at other locations has been shown to cause more disadvantages than benefits to the patient, such as anesthesia dolorosa (pain in the location of nerve deafferentation).

How does the patient typically describe his intra-abdominal pain?

Generally, pain of the intra-abdominal organs originates from the stimulation of terminal nerve endings, and is referred to as visceral-somatic pain, as opposed to pain from nerve lesions, which is called neuropathic pain. The pain characteristic most often reported by the patient is that it is not well localized. Patients typically describe the pain as generally "dull" or "pressing," but sometimes "colicky." Pain intensity is assessed as in all other pain etiologies, with the visual or numeric analogue scale.

What are the expected success rates with "simple" analgesia methods?

Pain management in patients with gastrointestinal cancer is fairly easy. From the literature, we know that in more than 90% of patients, the pain may be controlled with simple pain management algorithms. Observational studies from palliative care institutions, such as the Nairobi Hospice, Kenya, report an almost 100% success rate with a simple pain algorithm. As with all cancer pain, the pain management protocol follows the WHO recommendations, and is based on a combination of opioids and nonopioid analgesics, such as paracetamol, dipyrone, or nonsteroidal antiinflammatory drugs (NSAIDs). Coanalgesics and invasive therapy options are rarely indicated (see other chapters on general rules for cancer pain management and on opioids). If fluoroscopy is available, along with adequately trained clinicians, neurolysis of the celiac plexus may be used to reduce the amount of opioids and augment pain control in hepatic and pancreatic cancer.

Why are some people reluctant to use morphine or other opioids in patients with gastrointestinal cancer?

From early studies, we know that one of the undesired effects of morphine is the induction of spasticity at the sphincter of Oddi and bile duct. This opioid side effect is mediated through the cholinergic action of opioids as well as through direct interaction of the opioids with mu-opioid receptors. Consequently, in the past there was some reluctance to use morphine. Instead pethidine (meperidine) was preferred. Recent studies have not confirmed these findings, and so morphine can be used without reservations.

Where and how should neurodestructive techniques be used?

For upper abdominal cancer, the target structure would be the celiac plexus. For colon and pelvic organ cancers, the target is the myenteric plexus, and for bladder and rectosigmoid cancers, the hypogastric plexus is the target. Usually these structures are easy to identify using landmarks and fluoroscopy. If available, a computed tomography (CT) scan would be the gold standard

for identifying the targets. However, these techniques should only be used by experienced therapists—book knowledge is definitely insufficient.

The indication for a neurolytic block in pancreatic cancer is well recognized because of the rapid progression of the disease and its insufficient sensitivity to radiotherapy and chemotherapy. From the literature, we know that up to 85% of patients do benefit from a neurolytic block. Some patients can even be taken off opioids. Although serious side effects from neurolysis of the celiac plexus are rare, the facts have to be explained to the patient, and an informed consent form should be signed.

In gastrointestinal cancer, pain is frequent, but what other symptoms cause the patient suffering?

Pain is not the only problem for cancer patients. Actually, the complaint with the highest prevalence is fatigue, followed by anorexia. Discomfort due to constipation is also a frequent complaint. Unfortunately, constipation may often be considered unimportant by the therapist, and therefore overlooked or ignored. In fact, constipation may be a frequent cause of anorexia, nausea, and abdominal pain. Therefore, constipation must be checked for on a regular basis, and attempts should be made to relieve or at least reduce it.

Everybody seems to know what constipation is, but most people would not agree on when to make the diagnosis, so what is the definition?

Constipation is precisely defined: delayed bowel movements with a frequency of less than twice weekly, combined with painful discharge, abdominal swelling, and irregularity. Nausea and vomiting, disorientation, colics, and paradoxical diarrhea may be also present. The "Rome criteria for the diagnosis of constipation" are used to define constipation. Unfortunately, the patient may not agree and may feel constipated with less or other symptoms. The diagnosis is made solely by taking a patient history.

What are the "Rome criteria"?

According to the "Rome criteria," at least two of the following symptoms must be fulfilled for a minimum of 3 months in the past year:

- Two or fewer discharges weekly.
- Physical effort to discharge with major pressing.
- Hard and bulbous feces.
- Feeling of incomplete discharge.
- Manual maneuvers for discharge.

Are patient complaints about constipation similar around the world?

It is estimated that worldwide 1 in 8 individuals suffer, at least from time to time, from constipation. Regional differences in prevalence have been described in North and Latin America as well as in the Pacific region, where the prevalence is approximately double compared to the rest of the world. Higher age and female sex may increase the prevalence to 20–30%. In advanced stages of abdominal cancer, especially in palliative treatment situations, incidences are higher than 60%.

Which tests are indicated?

Basically, the diagnosis of constipation is made by taking the history of the patient. If constipation is diagnosed according to the criteria listed above and abdominal cancer is present, the etiology of constipation may be obvious. For safety, a digital examination of the anal canal and—if available—a proctoscopy are indicated. Rectal examination should be carried out—with the consent of the patient—during initial examination in most patients. In special cases manometric testing and evaluation of the oral-anal transit time may be done to differentiate between a functional or a morphological problem of the terminal intestines or more proximal structures.

What may be the conclusions from rectal examination?

When the rectum is found to be filled by hard fecal masses it would not be advised to give fecal expanders since they would make the problem even more difficult to resolve—manual removal is indicated. In terminal illness, when recurrent hard fecal masses will be expected, the family should be instructed to perform this procedure. When the rectum is found empty, but "ballooned," laxatives with "softening" and "pushing" effects are indicated. After descent of the feces into the rectum,

enemas will help to evacuate the feces. If the rectum is found to be empty and collapsed, fecal impaction is not probable, then oral fecal expanders (combined with peristaltic stimulants) should be used.

Which etiologies apart from the cancer must be considered?

Certain factors influence the motility of the colon. The most important "extrinsic" factor is pharmacotherapy (e.g., opioids and all anticholinergic drugs such as antidepressants, calcium, and aluminum-containing antacids), and the most important "intrinsic" factor are plexopathies (e.g., with autonomous neuropathy in diabetes or Parkinson disease). Dehydration, immobilization, hypokalemia (e.g., as a result of diuretic therapy), and physical weakness are additional factors. The latter conditions are the main reasons for constipation in gastroenterological cancer patients in addition to the direct effects of the cancer tissue growth (obstruction and inflammation). Sometimes overlooked, depression and anxiety disorders, which have a higher incidence in cancer patients, may be another predisposing factor.

What are the specific risk factors for cancer patients to get constipated?

- Dehydration, e.g., following repeated vomiting
- Reduced nutritional intake due to cancer-related anorexia
- Multiple surgical or diagnostic manipulations (e.g., barium use for radiology is a potent constipating agent)
- Gastrointestinal metastasis
- Continuous opioid medication
- Coanalgesics with anticholinergic effects (e.g., tricyclic antidepressants and anticonvulsants)
- Chemotherapeutics (e.g., vinca alkaloids)
- Hypercalcemia (frequent with osseous metastasis)
- Immobilization in inpatient treatment (plus loss of privacy, causing a "psychological inhibition" of normal defecation)
- Uncontrolled pain (from surgery or the cancer itself), depressive disorders, and anxiety (causing "arousal" of sympathetic stimulation with consequent reduction of bowel motility)

Why do opioids induce constipation?

To understand opioid-induced constipation, we have to remember that peristaltic movement is the consequence of longitudinal contractions of the smooth muscles proximal to descending food and intestinal compliance. The excitatory motoneurons in the intestines responsible for longitudinal contractions have cholinergic innervation. Since opioids have anticholinergic effects, they inhibit peristaltic movements. Additionally, opioids enhance local concentrations of 5-HT and norepinephrine, thereby reducing the secretions of the intestinal wall, which further impedes movement of the feces. A central peristalsis-reducing effect from the opioids may add to the problem. Although opioid use is one of the most frequent causes of constipation, there is no evidence-based treatment protocol or prophylaxis protocol for this therapeutic situation, but it is advisable to always use a prophylaxis to prevent opioid-induced constipation, whether constipation is already present or not.

Do all patients with constipation require special laxative therapy, and what would be the most simple treatment algorithm?

As usual, simple solutions are the best. Specific laxative therapy is only indicated in special situations, one of the most important one being the prophylactic treatment of opioid-induced constipation.

"Unspecific" techniques to reduce constipation may be effective if used in combination, e.g., fiber-rich nutrition, regular daily activities, colonic massage, and sufficient oral hydration. Unfortunately, the effectiveness of this prophylactic regimen is limited if opioids or other constipation-causing medications are used. Additionally, in most cases it will be not appropriate in patients who will be unable to follow such a diet and activities most of the time. Therefore, constipating drugs should be limited to those that are absolutely necessary. If therapy cannot be done without these drugs, specific regimens should be instituted in every patient, starting with a stepwise approach. The first step would be locally available laxatives, e.g., dried and crushed pawpaw seeds (1–5 teaspoons daily, at bedtime) combined with vegetable oil (1 teaspoon daily) or alternative remedies

patients have found to be helpful in their personal experience. If these laxatives are insufficient, the second step is to combine them with either senna or bisacodyl tablets. These tablets also should be taken at bedtime and increased by one tablet daily until there are successful bowel movements. The permanent dose would be the result of careful up-and-down titration at the beginning of laxative therapy. At step three, the laxatives have to be combined with local therapy, either suppositories with bisacodyl or glycerine. If suppositories are unavailable, custom-made petroleum jelly will do as well (a lump of it has to be held inside by the patient, preferably for about 20 minutes). Always try to avoid bedpans and allow the patient to sit or squat to have more effective abdominal muscle contractions.

If laxatives are indicated, what would be the most "advanced" treatment algorithm?

Always consider local herbal laxatives and foods that the patient has found useful previously, such as crushed papaya seeds or crushed coffee beans from the coffee senna tree. Therefore, always listen to the patient and change therapy according to the needs of your patient.

For patients on permanent opioid medication, prophylactic laxatives have to be prescribed simultaneously at all times. An exception to this rule are patients with chronic diarrhea, including many patients with advanced HIV/AIDS who are receiving opioids to control neuropathic pain and who may even benefit from the constipating effects of opioids.

Some laxatives are not recommended for extended use, especially antiresorptive and secretory laxatives, because they may cause considerable potassium and fluid loss, which increases constipation in the long term. Patients with advanced cancer and/or permanent opioid therapy should not use these substances but instead should be treated stepwise with:

1) Macrogol or lactulose
2) Macrogol plus sodium picosulfate or senna ("softener")
3) Macrogol plus senna + bisacodyl ("pusher")
4) Senna plus bisacodyl and paraffin
4) Suppositories (glycerine or bisacodyl)
5) Enemas (soap and water)
6) Manual removal of feces
7) In "emergencies": castor oil, radiocontrast agent, or naloxone/methylnaltrexone

What are the mechanisms of action of typical laxatives?

The simplest mechanism is the "softening of stool," which usually is sufficient to allow stool regulation in non-cancer patients who have normal daily activities and a normal daily fluid intake. The cheap and available polysaccharide lactulose is non-resorbable and attracts water into the intraluminal space of the intestines. By increasing intraluminal volume and dilating the intestinal wall, a propulsive effect is triggered. Unfortunately, fermentation is a side effect of lactulose, resulting in gas formation.

The artificial polyethylene glycol macrogol has a similar osmotic effect but does not need as much fluid intake and therefore may be better suited for the abdominal cancer patient, whose daily fluid intake is often reduced. Macrogol has saline effects and is not metabolized, therefore there is no fermentation or increased gas production. Lactulose and macrogol have a dose-dependent laxative effect and do suffer from tolerance effects.

Another class of laxatives are the nonresorbable oils (paraffins), which have both softening and lubricant effects. Since they may irritate the intestinal wall, cause serious pulmonary damage when aspirated, and interact with the absorption of lipophilic vitamins, they should only be used for a short time in complicated constipation.

A third class of laxatives has mainly stimulating (propulsive) effects on the intestinal wall, causing inhibition of the reabsorption of fluids in the colon and increasing the secretion of fluids and electrolytes into the intraluminal cavity. Laxatives belonging to this class include the anthraquinone glycosides (aloe, senna leaves), diphenols (bisacodyl und sodium picosulfate), as well as fatty acids (castor oil). In some patients the "stimulating" effects—especially from castor oil—may cause considerable discomfort through colicky abdominal pains.

The fourth class of laxatives are the "prokinetic" ones, which are rarely used. These include the 5-HT_4-receptor-agonist tegaserod, the macrolide antibiotic erythromycin, and the prostaglandin analogue misoprostol.

Is there a way to antagonize the intestinal effects of opioids directly?

Using selective opioid antagonists to block the intestinal side effects of opioids would be an "intelligent" approach to constipation therapy in patients with an

indication for permanent or long-term opioid therapy. In fact, this approach is based on an interesting hepatic mechanism: morphine is metabolized in the liver into its active products, while the opioid antagonist naloxone is completely metabolized in its first pass through the liver into inactive forms. Therefore, the antagonist would only be active at the intestinal opioid receptors, specifically antagonizing the constipation side effects of morphine or other opioids.

Some opioids are now available that are a combination of agonist and antagonist. Unfortunately, they are available in only a handful of countries, and due to patent protection, they are rather expensive. A cheap alternative is to provide the patient with oral naloxone, which—if available—is a low-cost substance and has anticonstipation effects in a dose range of 2–4 mg q.i.d. A recent development is methylnaltrexone, which is a selective opioid antagonist. It is administered subcutaneously and has a predictable effect within 120 minutes for more than 80% of treated patients. Due to its route of application and high costs, its use is limited to "emergency situations," when intestinal paralysis, not merely obstruction, is imminent.

If my patient complains about fatigue and loss of appetite, what do I tell him?

Patients must be educated about the fact that the cancer induces certain changes in the central regulation of appetite. In abdominal cancer, about three-quarters of patients experience weight loss of more than 5% monthly in the advanced stage of cancer (breast cancer and prostate cancer are exceptions to the rule, causing only moderate weight loss). We know now that cytokines, which play a prominent role in infections, are released from cancer cells and are involved in changes in appetite. They influence the melanocortin system in the central nervous system (the hypothalamus), thereby reducing the patient's appetite. Even high caloric intake cannot prevent weight loss. Therefore, patients should be instructed to continue eating what they like best, but they should not be encouraged to force their nutritional intake. The patient's family should be instructed likewise, because they might feel that they have to "feed" the patient more since they see the continuous reduction in body weight.

Can we do something about the weight loss?

Although it would be tempting to give the patient parenteral nutrition, if available, it is well known that this method does not influence the course of the weight loss and even poses a risk for the patient (e.g., refeeding syndrome, infections from catheters). The exception to this rule is the special situation when the patient requires surgery, when perioperative parenteral nutrition is indicated to reduce further weight loss. In general, our main target is to educate patients and help them, if possible, with some symptomatic treatment to increase appetite. This support may be very helpful for the patient, since eating is one of our main "social" activities. Although there will be no relevant weight gain, the increased appetite will have a positive effect on the patient's general well-being. Two substances have been shown to have a positive effect on appetite and may be tried if they are locally available. First, the patient should be encouraged to smoke or eat cannabis, if available. An artificial cannabis product is available on the pharmaceutical market (delta-9-tetrahydrocannabinol), but it is unaffordable for most people if it is not covered by insurance, as is the case in most countries of the world. The second option would be the use of steroids. A low dose of dexamethasone (2–4 mg once daily), prednisolone (20 mg once daily), or another steroid at an equipotent dose may improve anorexia.

Is there also a good recommendation for my patient complaining of fatigue?

Fatigue is a term describing major exhaustion and should not be confused with depression or sedation. Depression usually goes along with difficulties in falling asleep, constant "thinking in circles," lacking drive, especially in the morning hours, and general loss of interest, while sedation means falling asleep again and again for short periods (maybe the opioid dose is too high?). If fatigue is diagnosed, we have to admit to the patient that it can hardly be influenced and is a "protective" function of the body to save energy because of the cancer. While pharmacological options such as methylphenidate have been very disappointing, some patients have reported having less fatigue with a high

intake of coffee, or from chewing coca leaves (in the Andean mountains in Latin America) or khat (in the Arab Peninsula and East Africa).

Pearls of wisdom

- Morphine is still the opioid of first choice.
- The preferred route of application is oral.
- In patients needing long-term parenteral opioids, subcutaneous administration should be preferred.
- Opioids should be used early on and not as the last resort of therapy.
- There is no advantage to using "weak" opioids like codeine or tramadol; therefore—if only morphine is available—morphine or other "strong" opioids may be used first.
- Opioids should be combined with NSAIDs, dipyrone, or paracetamol (acetaminophen) to reduce the dose and side effects of opioids.
- If neuropathic pain is the leading symptom, coanalgesics such as amitriptyline or gabapentin should be added where available.
- All opioid medication should consist of a fixed-dose regimen and an on-demand dose. If available, the fixed dose should be a slow-release opioid and the on-demand dose an immediate-release opioid.
- The on-demand dose should be calculated from the fixed-dose regimen (around 10% of the cumulative daily dose of opioid).
- The on-demand dose may be used by patients as often as they need it, with a 30–45 minute minimum wait before the next on-demand dose.
- If more than four on-demand doses are used daily on average, the fixed daily dose should be increased by 75% of the cumulative daily on-demand dose.
- If the sedating and nauseating side effects of the first opioid used last longer than 2 weeks and the daily dose cannot be reduced due to the patient's analgesic requirement, the opioid should be rotated to another opioid, which might have a more favorable individual side-effect profile for the patient.
- Alternative routes of application for opioids (e.g., parenteral or intrathecal) are never required in the normal course of cancer and are seldom required in patients undergoing sophisticated radiochemotherapy and those who are at advanced stages of disease.
- Opioids should only be prescribed by one person.
- Patients and their relatives should—before starting the opioid medication—receive an education on the pros (nontoxic, long-term use) and cons (no stopping therapy without consulting the prescriber, no change of doses without consultation of the prescriber) of opioids.
- When initial pain readings are high, intravenous titration of morphine may be used to estimate the (additional) daily opioid requirements of the patient (this only applies to cancer patients!). The cumulative dose of i.v. morphine that is necessary to achieve acute pain control multiplied by 12 will roughly give the daily oral dose of morphine the patient will need in the days to come. The next consultation should be within the next few days to reevaluate the patient.
- When pain readings are high, but pain is not excruciating, a dose increase of roughly 25–50% will be adequate, and the next consultation should be within a few days to reevaluate the patient.
- Opioid-naive patients should expect sedation and nausea. Nausea should be treated prophylactically for about one week (e.g., with metoclopramide, when available).
- Always educate patients about the constipating effects of opioids and advise them to take laxatives.
- Transdermal opioid patches—if available—are only indicated in patients with stable dose requirements of opioids and have to be combined with on-demand doses.

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Websites

www.cancercare.ns.ca: a provincial educational cancer program (from Nova Scotia in Canada) with a lot of useful information on different cancer types and their management

http://aspi.wisc.edu (Alliance of State Pain Initiatives with downloadable educational material on cancer pain)

Appendix

Profiles of laxatives (in alphabetic order)
Bisacodyl (phenolphthalein): antiresorptive and hydragogue, 5–10 mg for prophylaxis, 10–20 mg for therapy
Gastrographin (dye): propulsive, only in acute danger of ileus, 50–100 cc
Lactulose (osmotic sugar): for prophylaxis when oral fluid intake is not impaired, 10–40 g
Macrogol 3350 (polyethylene glycol): osmotic, prophylaxis for cancer patients, 13–40 g
Magnesium sulfate and sodium sulfate (saline and osmotic): short term-treatment, 10–20 g
Naloxone (opioid antagonist): prophylaxis with chronic sub-ileus, 4 × 3–5 mg orally
Sodium-picosulfate (phenolphthalein): antiresorptive and hydragogue, for cancer patients, 5–10 mg
Paraffin: improves “gliding” of stools, short-term therapy without risk of aspiration, daily 10–30 mL
Senna (anthraquinone glycoside): antiresorptive und hydragogue for prophylaxis and long-term therapy, 10–20 mL
Sorbitol: saline and osmotic for refractory constipation, suppository in the morning (fast-acting)

Chapter 19
Osseous Metastasis with Incident Pain

M. Omar Tawfik

What is incident pain? Is it different from breakthrough pain?

Incident pain is an episodic increase in pain intensity. Some include incident pain as a subtype of breakthrough pain (BTP), while others define BTP as one of the subtypes of incident pain. BTP is defined as "a transient increase in pain to greater than moderate intensity, which occurred on a baseline pain of moderate intensity or less."

The term BTP can only be used when baseline pain is controlled by analgesics. However, there is no general agreement on the definition of BTP. In the United Kingdom the term is often used synonymously with end-of-dose failure. However, there is a general agreement that BTP in cancer patients may occur spontaneously. When it is precipitated by an event, it can be defined as incident pain. Precipitating events may be volitional and related to movements, walking, coughing, sitting, standing, or even touching. BTP usually occurs at the same site as the background pain, while incident pain may occur at the site or in a different place when there is widespread osseous metastasis.

The onset, duration, and frequency of BTP differ. The duration may vary from minutes to hours It has been estimated to be 15–30 minutes on average, with a frequency of 4–7 pain episodes per day.

How common is osseous metastasis?

Bone metastasis in cancer patients is seen frequently. It is the third most common metastatic site after the lung and liver. Myeloma is the hematological malignancy most frequently associated with lytic bone lesions. Bone metastases are more often seen with cancer of the lung and the prostate in males and cancer of the breast in females; up to 85% of patients dying from breast, prostate, or lung cancer demonstrate bone involvement at autopsy. The most common cancer that produces pain metastasis is breast cancer, and the most common site is vertebral bodies, as seen in Table 2. Twenty-five percent of patients have multiple sites of pain, and 10% of patients with spine pain have been found to have epidural cord compression.

Are all osseous metastases similar?

Osteolytic bone disease is the major source of pain. It causes difficulty in ambulation or immobility, neurological deficits, and pathological fractures. Pathological fractures due to increased bone fragility have been reported to occur in 8–30% of patients with bone metastases. Fracture is common in patients with a myeloma and breast cancer, and long bones are more frequently involved.

Table 1
Differences between breakthrough and incident pain

Breakthrough Pain	Incident Pain
Occurs in the same site as background pain	Occurs at any site
Is spontaneous, without any volitional act	Should be related to a volitional act
Has a duration and frequency	Occurs with an incident and needs a specific interventional treatment

Prostate cancer cells produce osteoblast-stimulating factors, probably specific growth factors or acid phosphatase. In this case, new bone is laid down directly on the trabecular bone surface before osteoclastic resorption. The resulting sclerotic metastases are less prone to fracture because of the locally increased bony mass.

Table 2
Bone metastatic lesions and sites

Primary sites in this study:	Pain sites of these metastases:
Breast cancer (24%)	Lumbar spine (34%)
Prostate cancer (19%)	Thoracic spine (33%
Unknown primary (22%)	Pelvis (27%)
Renal cancer (13%).	Hip (27%)
Malignant melanoma (7%)	Sacrum (17%)
Lung cancer (6%)	Humerus (19%)
Other (8%)	Femur (14%)

Breast cancer cell metastasis to bone promotes osteoclastic activity. However, the normal balance of bone resorption and new formation is upset. It exhibits a mixed picture of both lytic and sclerotic areas, with fractures usually occurring through the lytic areas. These different mechanisms correspond to typical radiological features showing mixed lytic and sclerotic metastases, osteolytic metastases, or sclerotic metastases (see Table 3).

Table 3
Characteristics of skeletal assessment in the most common tumors associated with bone metastases

	Myeloma	Breast	Prostate
Hypercalcemia	30%	30%	Rare
Bone scans	-	+	++
Alkaline phosphatase	-	+	++
Histology	Osteoclastic	Mixed	Osteoblastic
X-ray	Osteolytic	Mixed	Sclerotic

How does bone destruction occur?

Bone destruction results from interactions between tumor cells and bone cells that are normally responsible for the maintenance of skeletal integrity. The enhanced osteoclastic bone resorption, stimulated by bone-resorbing factors, is a major factor in the development of bone metastases. Moreover, immobilization and secondary effects of osteolysis may be the reasons for depressed osteoblast function.

Osteoclasts can be activated by tumor products or indirectly through an influence on other cells. Tumor cells frequently produce factors that can activate immune cells, which release powerful osteoclast-stimulating substances, such as tumor necrosis factor and interleukins 1 and 6. Tumor products could also act directly on bone cells. In the late stages of a metastatic disease, malignant cells appear to directly cause the destruction of bone.

In bone metastases, reactive osteoblastic activity can occur and is detected by bone scans and serum alkaline phosphatase. Osteoclastic activity leads to collagen fragments such as pyridinoline and deoxypyridinoline that can be measured in urine. Patients have localized sharp pain, often worsened by movement or weight bearing.

Can all osseous metastases produce pain?

Not all bone metastases are painful. However, a study at a multidisciplinary bone metastasis clinic found that 57% of patients reported severe (7–10) pain, and 22% had experienced intolerable pain. The pathophysiological mechanism of pain in patients with bone metastases without fracture is poorly understood. The presence of pain is not correlated with the type of tumor, location, number and size of metastases, or gender or age of patients. While about 80% of patients with breast cancer will develop osteolytic or osteoblastic metastases, about

two-thirds of all demonstrated sites of bone metastases are painless. Many nerves are found in the periosteum, and others enter bones via the blood vessels.

Microfractures occur in bony trabeculae at the site of metastases, resulting in bone distortion. The stretching of periosteum by tumor expansion, mechanical stress on the weakened bone, nerve entrapment by the tumor, or direct destruction of the bone with a consequent collapse are possible associated mechanisms. The weakening of bone trabeculate and the release of cytokines, which mediate osteoclastic bone destruction, may activate pain receptors.

The release of algesic chemicals within the marrow probably accounts for the observation that pain produced by tumors is often disproportionate to their size or degree of bone involvement. A secondary pain may be caused by reactive muscle spasm. Nerve root infiltration and the compression of nerves by the collapse of osteolytic vertebrae are other sources of pain.

Clinical presentation

Case study

A female patient, aged 63 years, came to the pain clinic with vague aching pain in the lower back, which she has had for 3 months, accompanied by gnawing pain in the middle of her right thigh, particularly on standing up or walking. Pain scoring by the patient defined the pain at rest as 4, and pain on walking as 6, on a 10-cm line. The back pain has been steadily increasing during this time, and now she lies in bed all the time to prevent her pain from increasing further. Her back pain was greatly reduced by NSAIDs. The patient has had radical left breast surgery due to breast cancer, followed up by radiotherapy. On examination, there was clear tenderness on the lumbar spine, at the second lumbar vertebra, and on the medial part of the lower third of the right thigh.

Pain may be vague or absent because osseous metastasis may be painless. However, any vague pain in a patient with a history of treated cancer should be taken seriously and thoroughly investigated. Bone pain usually results from osteolytic bone metastases. Pain as a symptom is present in about 50% of patients. The five most frequently involved sites are the vertebrae, pelvis, ribs, femur, and skull. Pain develops gradually during a period of weeks or months, becoming progressively more severe. The pain usually is localized in a particular area, such as the back and the lower third of the femur, and is often felt at night or on weight bearing. Pain is characteristically described as dull in character, constant in presentation, and gradually progressive in intensity. Pain increases with pressure on the area of involvement. These characteristics are fully described by the patient, so the condition should be investigated as probable osseous metastasis with bone pain.

The gnawing pain described by the patient is characteristic sign suggesting neuropathic elements. It is radicular in distribution (L2/3) and unilateral, suggesting an origin from the lumbosacral spine. Pain is usually bilateral when originating in the thoracic spine and is exacerbated in certain positions that the patient usually tries to avoid. Straight leg raising, coughing, and local pressure can exaggerate the pain, while pain may be relieved by sitting up or lying absolutely still. Weakness, sphincter impairment, and sensory loss are uncommon at presentation, but they develop when the disease progresses in the compressive phase, and should be prevented.

In osseous metastasis, hypercalcemia, i.e., elevated plasma levels of ionized calcium, is inevitable. As half of the calcium is albumin-bound, the total calcium value should be adjusted for the albumin level to correctly evaluate the calcemic status. Renal function, including urea and electrolytes, should be checked. Symptoms occur with calcium values exceeding 3 mmol/L, and their severity is correlated with higher values. In elderly and very ill patients, very slight increases of ionized calcium plasma levels may be symptomatic.

- A shortened QT interval on the electrocardiogram may be evidenced. Increases in urinary calcium levels are caused by the release of calcium into the circulation secondary to an increased bone resorption.
- Urinary excretion of hydroxyproline, a major constituent of type I collagen, is an indirect measure of increased bone turnover. Both urinary hydroxyproline/creatinine and calcium/creatinine ratio have been used to monitor the effects of bisphosphonate treatment.
- Hypercalcemia is associated with pain, nausea, vomiting, anorexia, constipation, weakness, dehydration, polyuria, mental disturbances, and confusion. Symptoms can mimic those associated with diseases or conditions. Gastrointestinal symptoms are often mistaken for opioid effects or are potentiated by opioid-related symptoms, and neurological symptoms are often attributed to cerebral metastases. Hypercalcemia complicates the

clinical course of 10–20% of patients with lung and breast tumors.

- Serum levels of alkaline phosphatase and osteocalcin reflect osteoblast activity. Patients with a myeloma presenting low values of serum osteocalcin, a sensitive and specific marker of osteoblastic activity, have advanced disease, extensive lytic bone lesions, frequent hypercalcemia, and a poor survival rate.

Case study (cont.)

In questioning the patient, some specific symptoms about the presence of hypercalcemia should be assessed. Symptoms related to hypercalcemia are nausea, vomiting, anorexia, stomach pain, constipation, excessive thirst, dry mouth or throat, fatigue or lethargy, extreme muscle weakness, moodiness, irritability, confusion, irregular heartbeat, and frequent urination. Hypercalcemia can be a life-threatening condition. Investigations related to hypercalcemia should test for free serum calcium level corrected for albumin level, ECG, urinary hydroxyproline/creatinine, and serum alkaline phosphatase. Radiological investigations are of course needed, such as radiography, scintigraphy, CT scan, and MRI, which were ordered for this patient, particularly for the back and right thigh.

How can we choose between radiographic investigations?

Bone metastases may be diagnosed by a variety of methods, including radiography, scintigraphy, computed tomography (CT) scan, and magnetic resonance imaging (MRI). With conventional radiography a change of about 40% in bone density is required before bone metastases may be identified, and small lesions may remain undetected. A change of 5–10% is sufficient when using bone scintigraphy. Bone scintigraphy is positive in 14–34% of patients who have no radiographic evidence of bone metastases. However, the method is less sensitive for the detection of purely osteolytic metastases. Bone scan abnormalities are not specific, and several benign conditions give rise to false-positive results. Scans may appear negative when lesions are predominantly osteolytic, after radiotherapy, and when surrounding bone is diffusely involved with tumor. CT scans allow the identification of the type of metastases and yield more sensitive results than the previous methods.

A magnetic resonance scan delineates the whole spine, identifies multiple sites of cord and vertebral involvement, shows the paravertebral epidural extension and integrity of the spinal cord, and allows differentiation between traumatic, osteoporotic, or pathological fractures and compression without the need of invasive techniques, such as myelography. However, MRI is expensive. All the data deriving from these radiological studies should be interpreted in the context of the clinical findings.

How can we make a plan for treatment?

The treatment plan should contain:

- Management of osseous metastasis.
- Management of pain.
- Treatment of hypercalcemia.
- Prevention of incidental fracture or vertebral collapse.

Case study (cont.)

The investigations reveal osseous metastasis in the lower medial end of the femur as well as in the lumbar spine, particularly L2, by bone scintigraphy and ordinary radiography. Some thoracic vertebrae show early signs on single photon emission computed tomography/CT (SPECT/CT). Hypercalcemia was proven by serum level.

How is osseous metastasis treated?

Once bone cancer is discovered, attempts to treat the cancer should be the primary concern, as all other complications including pain and hypercalcemia can then be alleviated. The most important is radiation therapy, or the use of radionuclides.

Radiation therapy

In 60–90% of patients, radiotherapy has been effective using a standard treatment regime delivering 60 Gy in 30 fractions over 6 weeks with daily treatment sessions. Radiotherapy should be the first step in the management of metastatic bone pain. Radiotherapy is used as an adjunct to orthopedic surgery to decrease the risk of skeletal complications. An actual or impending bone fracture may require a short fractioned course of 20–40 Gy over 1 week. Radiotherapy is used for bone metastases to relieve pain, prevent impending pathological fractures, and promote healing of pathological fractures.

Radiotherapy is successful in relieving pain in 60–70% of patients, but it takes up to 3 weeks for the full effect to be seen.

Potential complications of radiation include systemic side effects not confined to the area of irradiation, such as nausea and vomiting, anorexia, and fatigue, as well as effects specifically related to the irradiation field, including skin lesions, gastrointestinal symptoms, myelosuppression, and alopecia. The best treatment for hypercalcemia due to cancer is treatment of the cancer itself. However, since hypercalcemia often occurs in patients whose cancer is advanced or has not responded to treatment, management of hypercalcemia is sometimes necessary.

Radionuclides

Radionuclides that are absorbed at areas of high bone turnover have been assessed as potential therapies for metastatic bone pain. Strontium-89 chloride and samarium-153 are available in the United States.

How is osseous pain treated?

Analgesic drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are promising as anticancer drugs because they inhibit tumor angiogenesis and induce tumor cell apoptosis. NSAIDs play a key role in the first step of the WHO guidelines for management of cancer pain. Nearly 90% of patients with bone metastasis present with pain. NSAIDs are the most effective agents for treatment of patients with this condition because prostaglandins appear to play an important role. They are comparable in safety profile and effectiveness. Comparison of opioid combination preparations with NSAIDs alone showed no or at most only a slight difference.

Continuous bone pain shows a good response to opioids. Most terminally ill patients with incident pain found that pain was a major limiting factor to activity. The difficulty with incident pain is not a lack of response to systemic opioids, but rather that the doses required to control the incident pain produce unacceptable side effects when the patient is at rest. Oral morphine is the primary opioid used in the United States for treatment of patients with severe pain in advanced stages of cancer. In the United Kingdom, diamorphine (heroin) is used secondarily because of its greater solubility, but it has no clinical advantage over morphine. Methadone hydrochloride, a drug commonly prescribed to prevent withdrawal in recovering drug users, is used in hospices in the United Kingdom and Canada. It is also used in the United States for the treatment of patients with refractory or neuropathy-associated pain.

Numerous opioid preparations are now available. Currently, immediate-release forms of morphine, oxycodone, and hydromorphone are available for a fairly rapid onset of drug action. Sustained-release (SR) preparations (morphine, oxycodone, or hydromorphone) are effective in dosing every 12 or 24 hours, or sometimes every 8 hours. They are usually used after dose titration to define the effective daily dose for baseline continuous pain. Fentanyl is now also available in two forms of immediate-release preparations—the transmucosal formula and sustained-release transdermal patches.

Long-term use of opioids is associated with physical dependence and (rarely) tolerance. Tolerance is defined as a physiological phenomenon of progressive decline in the potency of an opioid with continued use, manifested by the requirement of increasing opioid doses to achieve the same therapeutic effect. Increased doses can continue to provide adequate analgesia because there appears to be no ceiling effect, but escalating doses can increase side effects (nausea, vomiting, constipation, abdominal pain, and pruritus) that may limit their use. At this point, opioid rotation is needed.

Coanalgesics

Steroids, including corticosteroids, have beneficial effects in reducing metastatic bone pain, due to their anti-inflammatory properties in blocking the synthesis of cytokines, which can contribute to both inflammation and nociception. The duration of pain relief is generally short. Special consideration should be given to these drugs in cases of spinal cord and brain compression, in which their role in reducing peritumoral edema is very advantageous. They are effective and can sometimes temporarily stabilize or improve neurological dysfunction. Although corticosteroids are part of the treatment in advanced cancer patients for their benefits regarding improved appetite, reduced fatigue, and a sensation of well-being, prolonged use should be weighed against the adverse effects. Serious complications of prolonged administration of corticosteroids include immunosuppression, pathological fractures, swelling, and delirium.

Calcitonin, a hypocalcemic agent, may be useful as an adjuvant analgesic. Calcitonin inhibits sodium and calcium resorption by the renal tubules and reduces osteoclastic bone resorption. However, despite its rapid

effect, the role of calcitonin appears to be limited by its short duration of action and poor efficacy due to the rapid development of tachyphylaxis (a rapid decrease in the body's response to a drug after repeated doses over a short period of time). Calcitonin is usually administered subcutaneously and intranasally. The initial dose is 200 IU in one nostril a day, alternating nostrils every day. Apart from infrequent hypersensitivity reactions associated with subcutaneous injections, the main side effect is nausea.

Bisphosphonates can delay the onset of skeletal fractures, reduce the need for radiation therapy to treat bone metastasis, reduce hypercalcemia (high blood levels of calcium), and reduce the need for orthopedic surgery. Bisphosphonates available in the clinical field are alendronate, etidronate, ibandronate, pamidronate, risedronate, or tiludronate. Bisphosphonate drugs include zoledronic acid and pamidronate. Of these two drugs, the first appears to demonstrate the strongest activity and is more convenient due to reduced administration time.

Antidepressants are by far the most commonly used coanalgesics when neuropathic pain accompanies osseous bone pain, such as after radiation damage. Tricyclic antidepressants, such as amitriptyline, are used with a daily starting dose of 10–25 mg, which may be titrated to effect, to potentiate analgesia and increase central norepinephrine and serotonin, and for their sodium-channel blocking effect (as local analgesics). They can also promote natural sleep.

Anticonvulsants such as carbamazepine or clonazepam are particularly useful in neuralgias, such as in situations with nerve root compression due to malignant vertebral body collapse. The dose is between 600–1200 mg daily and 0.5 mg, respectively. Although it is successful in trigeminal neuralgia, carbamazepine's effect on secondary neuralgias is less convincing. Gabapentin maybe an alternative for patients with impaired liver function or who have intolerable side effects with carbamazepine.

How is hypercalcemia treated?

Treatment for hypercalcemia is based on a number of factors, including the condition of the patient and the severity of the hypercalcemia. Increasing fluid intake and the use of diuretics have been standard practice. Most recently, bisphosphonate drugs have become an effective approach. Bisphosphonates can effectively prevent loss of bone that occurs from metastatic lesions, reduce the risk of fractures, and decrease pain.

One of the primary treatments for hypercalcemia of malignancy is hydration, which may consist of increasing oral fluid intake or intravenous (i.v.) administration of fluids. Hydration helps decrease the calcium level through dilution and causes the body to eliminate excess calcium through the urine. For mild-to-moderate elevations of calcium, patients are usually directed to increase oral fluid intake. For acute hypercalcemia, hydration with saline is immediately administered intravenously. The rate of hydration is based on the severity of the hypercalcemia, the severity of dehydration, and the ability of the patient to tolerate rehydration.

Sometimes, hypercalcemia related to malignancy is treated with a diuretic. The most commonly used diuretic is furosemide, which causes loss of calcium, sodium, and potassium. Furosemide is well tolerated, but it is not free of side effects, which may include dehydration and low blood potassium and sodium levels. Furosemide is available by i.v. administration, as well as oral tablets. The intravenous method of administration is used to achieve an urgent effect. Oral tablets are used for maintenance (once or twice a day).

Is it possible to prevent incidental fracture or vertebral collapse?

Prediction of impending fracture and prophylactic treatment is very important, although prediction itself remains controversial, with roles advocated both for radiographic and functional predictors. The Healy and Brown system of predictions includes:

- Painful lesions with involvement of more than 50% of the thickness of the cortex.
- A lytic lesion greater than the cross-sectional diameter of the bone.
- A cortical lesion more than 2.5 cm long.
- A lesion producing functional pain after radiation therapy.

Case study (cont.)

Based on previous data, the plan of treatment included referring the patient to the radiotherapy unit to start radiation therapy. Pain management was started according to the WHO ladder system and included an NSAID, celecoxib, 200 mg twice daily. When this proved insufficient,

sustained-release tramadol was added at a dose of 100 mg twice daily.

Bisphosphonates (zoledronic acid) at a dose of 4 mg monthly in a drip was prescribed, together with hydration and advice for the patient to take lots of fluids, along with furosemide (one tablet daily with a potassium supplement to guard against hypercalcemia).

Percutaneous vertebroplasty was done for both L2 and T12, and this procedure was followed by a rapid relief of back pain.

The right lower-limb neuropathic pain was treated with gabapentin, starting with 100 mg three times daily. This dose was gradually increased until a 1200-mg daily dose was achieved and maintained. After vertebroplasty, the neuropathic element disappeared, and the gabapentin was gradually withdrawn.

The patient was satisfied with this treatment for 9 months, during which tramadol was changed to sustained-release morphine (90 mg daily dose).

After 9 months, the patient accidentally fell. She developed severe incidental pain in the right lower third of the thigh. Plain X-ray demonstrated a fracture at the site of the previous femur metastasis.

What options would we have in this case?

Guidelines have been developed using radiographic-series criteria, although the reliability of a radiographic evaluation has been questioned because a bone metastasis becomes apparent only after major bone loss, and some cancers, such as prostate cancer, are not characterized by evident bone destruction. Moreover, bone pain unresponsive to radiation has not been found to be correlated with fracture risk.

The approach to treatment for bone pain may require different modalities depending upon the initial assessment. Surgery should be considered if an impending fracture is diagnosed, and radiation therapy should be considered for painful bone metastases. Pharmacological therapy with NSAIDs and opioids, along with medications for breakthrough pain, form the main symptomatic treatment. In addition, many adjuvant approaches have been recommended, such as calcitonin, bisphosphonates, or radionuclides. In vertebral metastasis with collapse, vertebroplasty may be an important procedure, as well as cementoplasty for other bone metastasis, particularly with weight-bearing pain, depending on availability.

Case study (cont.)

The patient was put on patient-controlled analgesia, using morphine to give her relief from severe pain. She has been transferred to an orthopedic unit for fixation procedures to help relieve her pain and help her to be able to move around.

What can be done by a dedicated orthopedic specialist?

About 10–30% of patients with bone metastases develop fractures of the long bones requiring orthopedic treatment. The femur is the most common site. Extensive bone loss due to the local effects of chemotherapy and radiation should be supported during recovery. Protection with orthotic devices, such as lightweight functional bracing, may be useful during upper-extremity lesions. The lower extremities are not very amenable to this method because of the high degree of load. As a consequence, conservative treatment for fractures or symptomatic impending fractures of the extremities is rarely successful.

Prophylactic pinning is indicated and may prevent a long period of immobility. Conservative treatment of bone fractures in the axial skeleton is more likely to be successful because such bones have a better blood supply and tend to heal more readily. Bracing in combination with radiotherapy may be a successful treatment for pathological vertebral fractures.

It is important to ensure that pathological fractures are stabilized to prevent pain and to facilitate physiotherapy and radiotherapy. Different surgical solutions may be proposed according to the kind of fracture, the clinical situation, and the patient's life expectancy. Orthopedic management includes internal fixation and osteosynthesis, resection of joint and joint replacement, segmental resection of a large tract of bone and prosthetic replacement, and arthroplasty. Surgical treatment should be undertaken when a fracture occurs. The potential benefits of surgical intervention have to be tempered with patient survival.

Surgical stabilization of the spine and extremities may dramatically improve the quality of life, decrease the pain and suffering of these patients, and prevent complications associated with immobility, allowing many patients to be cared for at home. Recovery from prophylactic fixation surgery is quicker and requires less aggressive procedures.

Pearls of wisdom

Osseous metastasis should be expected when vague pain starts to develop in patients with a history of treated or untreated cancer.

Bone scans can detect osseous metastasis earlier than ordinary radiographs.

Attempts to detect hypercalcemia should be done in every case. Early efficient treatment should start, and bisphosphonates are the best remedy.

A high success rate after surgical intervention has been reported, leading to improved patient survival. More than 60% of patients benefit from surgical decompression and obtain adequate neurological recovery, although patients with rapid neurological compromise have a worse prognosis.

If only symptomatic treatment is available, NSAIDs and opioids, and in some cases coanalgesics, may improve pain at rest, but pain on movement will be hard to control sufficiently without mechanical stabilization.

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Chapter 20
Lung Cancer with Plexopathy

Rainer Sabatowski and HansJ. Gerbershagen

Case study

Ruben Perez is a 52-year-old farmer living in the province of Yucatan in Mexico. He had lost his job at a farm some years before and has worked as a laborer ever since. He and his wife, his children, and two grandchildren live in a small hut in the village of Yaxcopil. Mr. Perez has smoked cigarettes his whole life. During the last year, he noticed some health problems, feeling exhaustion and noticing his cough getting worse. When he experienced lancinating pain in his left arm associated with continuous weakness of his arm, he and his family decided to visit the doctor at a large municipal hospital in Mérida. At the initial presentation, Mr. Perez reported his lancinating pain, involving predominantly the lower segments of the brachial plexus. Weakness and sensory loss as well as Horner's syndrome could be confirmed. The pain was severe, and pretreatment with acetaminophen, as needed, and codeine, which had been prescribed by a local doctor, was not able to relieve the pain. Mr. Perez also reported dramatic weight loss, severe coughing with red spots in the sputum, as well as breathlessness.

An initial CT scan, which could be performed at the hospital, showed a tumorous mass in the apical region of the left lung. Invasion and partial destruction of the upper thoracic and lower cervical vertebral bodies could be confirmed. Due to the progress of the disease and the comorbidity, the physicians at the hospital did not see an indication for further palliative treatment such as surgery, radiotherapy, or even chemotherapy. Therefore, they started morphine therapy with a starting dose of 2.5 mg immediate-release morphine every 4 hours. They instructed Mr. Perez to use 2.5 mg additionally in case of pain recurrence, such as breakthrough pain episodes. He was advised to increase his daily fluid intake to a minimum of 1.5 L of water a day to prevent opioid-induced constipation. Additionally, the physicians prescribed gabapentin to improve morphine efficacy in the presence of neuropathic pain. Mr. Perez was told to start with a dose of 100 mg and to increase the dose at day 4 to 100 mg t.i.d. If pain was still not adequately alleviated, he was asked to consult his local physician again.

In the following weeks, the pain was alleviated sufficiently, even though it was not absent. But with this improvement and the support of his family, Mr. Perez could cope with his situation. Several weeks later, he had to go back to the hospital in Mérida because his pain increased dramatically. Even though the morphine dose was increased to a daily dose of 120 mg and gabapentin had been increased to 900 mg, the pain intensity worsened, and Mr. Perez reported a new pain sensation. Light touch on his left arm led to severe pain. Dr. Rodriguez decided to switch from morphine to methadone. Morphine treatment was stopped immediately, and methadone was started with a dose of 5 mg every 4 hours. For breakthrough pain episodes or inadequate pain relief or both, 5 mg methadone could be administered within

a minimum time interval of 1 hour. Additionally, dexamethasone, 16 mg/d, was started to improve pain as well as to stimulate appetite. (Mr. Perez had reported that he could no longer eat Elotes con Rajashe, which his wife used to prepare as his favorite dish.) The dose of methadone had do be increased on day 2 up to 7.5 mg every 4 hours. On day 4, application times could be prolonged to 8-hour intervals (t.i.d.), the breakthrough medication interval was prolonged to 3 hours, and dexamethasone was tapered down to 2 mg/day. It became a major problem to convince his family and his local doctor that methadone, even though it is often used in patients with narcotic drug dependency, was the best drug in his situation. Constipation was satisfactorily controlled by drinking more water and eating some dried fruits. The prescription of laxatives was not necessary. A developing paresis of the left arm was treated with elastic bandages to hold his arm in a comfortable position.

For the doctors caring for Mr. Perez, there were two options for pain management. In option 1, they could start with carbamazepine in a dose of 3 × 100 mg. If pain relief is not sufficient, the dose should be titrated up slowly to a maximum of 1000–1200 mg/d. Morphine should be added, if carbamazepine monotherapy is insufficient or if a dose limit is reached due to intolerable side effects. Morphine should be titrated in 5-mg steps with immediate-release tablets or a solution. Dosing intervals should be every 4–6 hours. In case of stable dose requirements, immediate-release morphine should be switched to a sustained-release formulation, if available. For management of breakthrough pain episodes, a single dose of about 1/6 of the daily morphine dose should be administered.

Option 2 would be to start with an anticonvulsant such as gabapentin or carbamazepine. Slow uptitration is required to prevent severe side effects (e.g., sedation, drowsiness). The maximum dose of gabapentin should not exceed 2100 mg (or for carbamazepine, 1200 mg). In cases of severe pain, an opioid should be added immediately. The opioid can be either tramadol (maximum dose 400 mg/d) or morphine. Be aware that patients should have access to the use of immediate formulations, not only in the titration period but for the management of breakthrough pain as well. If the pain is described as a burning sensation, treatment with an antidepressant such as amitriptyline should be added. Start with 25 mg in the evening; the maximum dose should be 75 mg. When this combination is unsatisfactory (and in case of tumor infiltration of the plexus), dexamethasone in a dose of 16–24 mg/d should be added. After stabilizing the pain, the dose might be reduced slowly down to 4–8 mg/d. In treatment-refractory situations, morphine might be switched to methadone (details are described in the section above).

What is the scope of the problem?

Lung cancer is the most common malignancy worldwide. Despite progress in diagnosis and treatment, 80–90% of patients die within 1 year after having been diagnosed. Lung cancer is associated with a major burden for the patients and their relatives. Among the symptoms associated with lung cancer, pain is one of the most feared, as well as very common. Approximately 40–90% of patients who suffer from a malignant disease experience cancer-related pain. Palliation of symptoms and especially of pain due to lung cancer is crucial to improve the patient's situation and the quality of life for both patients and their relatives.

Are there factors associated with pain in lung cancer?

There is no clear evidence for a relationship between the histological subtype of lung cancer and pain prevalence. The most important factor associated with pain is the stage of the disease, which is often advanced—even at the time of the first diagnosis—because patients with lung cancer often present late, and pain is often the first symptom that prompts patients to visit their physician.

What types of pain have to be expected in lung cancer?

Pain in lung cancer is usually of mixed pathophysiology. The majority of patients experience nociceptive pain, but approximately one-third of patients present with neuropathic pain.

What is neuropathic pain, and what are possible reasons it may occur in lung cancer?

The IASP defines neuropathic pain as pain initiated or caused by a primary lesion or dysfunction in the nervous system (e.g., compression or infiltration of the tumor into the brachial plexus, or compression of a nerve

root). However, neuropathic pain might also be generated by processing abnormalities in nociceptors.

Common reasons for neuropathic pain in lung cancer are:

- Compression or infiltration of neurological structures, such as the brachial plexus, the chest wall, or intercostal nerves. Even though Pancoast tumors are associated with only 3% of lung cancers, more than 30% of all cancer-related pain syndromes in lung cancer are attributed to Pancoast tumors. Usually the pain of brachial plexopathy is felt as a burning sensation in the ulnar side of the hand, due to the involvement of C7–T1 nerve roots. Another typical sign of brachial plexopathy is the occurrence of Horner's syndrome (miosis, ptosis, and enophthalmos), and pain is more intense as compared to pain due to radiation therapy.
- Treatment-related neuropathic pain syndromes may be the consequence of (major) surgery (e.g., thoracotomy, installation of a therapeutic chest drain) and might cause a post-thoracotomy syndrome or intercostal neuralgia. Chemotherapy, especially after treatment with vinca alkaloids such as vincristine, is another common reason for treatment-associated neuropathic pain. Radiation-induced plexopathy might be considered as well. However, usually symptoms due to irradiation occur with a latency of approximately 6 months or even later.
- Paraneoplastic syndromes might present with subacute or chronic sensory-motor neuropathy. These syndromes are rare. Subacute sensory neuropathy compromising all sensory modalities preceding the diagnosis of cancer is often associated with small-cell lung cancer. Symptoms of paraneoplastic syndromes develop over days or weeks and might affect all four limbs, the trunk, and sometimes even the face.

How can neuropathic pain be diagnosed?

A thorough medical history and examination are essential. The patient's description of the pain quality often provides a first indication of the presence of neuropathic pain. Common verbal sensory pain descriptors are throbbing, pricking, aching, tender, numb, and nagging. However, descriptors such as burning, lancinating, or hot might be used as well. Other characteristics are pain projection and pain radiation along a course of nerves with either segmental or peripheral distribution, when the pain has a glove-like distribution, or is attributed to a dermatome. Increasing pain when lying down, localized in the midline of the back with or without radiation, and midscapular or bilateral shoulder pain might be associated with neuropathic pain as well. Paresis or muscular weakness and pain of an upper extremity are strong evidence of a plexopathy.

Screening tools such as painDETECT, an easy-to-use self-report questionnaire with nine items that do not require a clinical examination, might be used as well. Patients have to answer seven questions related to the presence of burning sensations, tingling or prickling sensations, light touch being painful, the presence of sudden pain attacks or electric shocks, cold or heat pain, numbness, and slight pressure being painful. The scope of answers ranges from never, hardly noticed, slightly, moderately, strongly, to very strongly and will be attributed a score of 0–5 each. Additionally persistent pain with pain attacks will reduce the total score (minus 1 point), pain attacks without pain in between will add 1 point, pain attacks with pain between them will add 1 point, and finally the presence of radiation pain adds 2 more points. A final sum score of 19 or above strongly suggests the presence of neuropathic pain. PainDETECT has a specificity and sensitivity of more than 80%. Alternatively the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) tool might be used. This screening tool contains 5 symptom items and 2 clinical examination items (clinical examination for allodynia and pinprick threshold is necessary). The sensitivity and specificity is over 80% as well. This tool might also be used to show treatment effects.

These first signs of the presence of neuropathic pain should be followed by a careful neurological examination. Physicians should attend to somatosensory abnormalities, such as dysesthesias, hyperalgesia, hypesthesia, and allodynia. Most of these features can be diagnosed with simple bedside tests. Dysesthesia is an abnormal painful sensation (e.g., burning, lancinating pain). Using a stub-point needle, hyperalgesia—increased perception of painful stimuli—can be diagnosed. Hypoesthesia describes a reduced feeling or an increased pain threshold (anesthesia stands for the nonperception of a stimulus). Allodynia is defined as pain induced by a normally nonpainful stimulus.

Thermal allodynia (pain caused by moderate heat or cold; a warm or cold fork or knife might be used) and dynamic allodynia (e.g., pain induced through contact with clothing; for the examination a cotton-wool tip might be used) are distinguished. A tuning fork can be used to look for abnormalities in the perception of vibration. Elaborate tests such as neurography or quantitative sensory testing (QST) might be used, but often they are not available or in the case of QST, the impact on diagnosis and/or treatment is not yet clear. Radiographic examination such as magnetic resonance tomography might be added in cases when further invasive treatments are considered.

How can pain due to plexopathy in lung cancer be treated?

The initial treatment approach for painful plexopathy should follow the guidelines of the World Health Organization (WHO). However, adjuvants (e.g., anticonvulsants, antidepressants, and corticosteroids) are of particular importance. These adjuvants are recommended at every step of the WHO ladder and sometimes might even be a first-line medication before starting with non-opioid analgesics or opioids.

What are barriers to effective pain management?

From the physician's perspective, common barriers include:

- Lack of familiarity with diagnosing neuropathic pain.
- Reliance on nonopioid analgesics such as diclofenac or acetaminophen (paracetamol) alone (these analgesics are not recommended in the algorithms for treating neuropathic pain).
- Avoidance of opioids due to misconceptions and myths about opioids (e.g., fear of addiction and beliefs that neuropathic pain is not responsive, that opioids should only be used for dying patients, and that respiratory depression is a common side effect of opioids). There is evidence that opioids do relieve neuropathic pain, and they are included into the treatment algorithms for neuropathic pain.
- Unavailability of opioids.
- Fear of legal consequences when prescribing "illicit drugs."
- No knowledge of the use and indication of non-analgesic drugs (e.g., anticonvulsants) in the presence of neuropathic pain.

From the patient's perspective, common barriers include:

- No satisfactory information about the pain and the drugs being used (e.g., an antidepressant was prescribed, or no information was given about the rationale for using opioids).
- Fear or prior experience of side effects (e.g., addiction, dry mouth, erectile dysfunction, and drowsiness).
- No treatment of side effects was provided.
- Drugs are often not available in rural sites, or the drugs being prescribed by a medical center are too expensive.

What strategies should be followed when treating a painful plexopathy?

Primarily cancer-reducing strategies such as chemotherapy or radiotherapy should be considered, to reduce or minimize the direct impact of the tumor on the plexus. However, if this approach is not possible, palliative pharmacological strategies should be started. Palliative treatment approaches include several pharmacological and nonpharmacological options.

Anticonvulsants

These drugs were primarily used in treating trigeminal neuralgia, but current studies give evidence of efficacy in various neuropathic pain conditions. Carbamazepine acts via blockade of voltage-dependent sodium channels. The starting dose is 100 mg twice a day up to a maximum of 1200–1600 mg/day. Side effects such as sedation are common, especially when the initial dose is too high or titration is too rapid. Nowadays, the use in cancer pain is limited due to potential risks such as bone marrow suppression, leucopenia, hyponatremia, and interaction with liver metabolism and therefore multiple drug interactions. Gabapentin, if available, should be used as first-line medication. Gabapentin is a chemical analogue of γ-aminobutyric acid (GABA) that does not act as a GABA-receptor agonist, but binds to the $\alpha_2\delta$-subunit of the voltage-dependent calcium channel in the spinal cord. The binding to these receptors inhibits the release of excitatory neurotransmitters. Gabapentin is administered three to four times a day. The starting dose is 3 × 100 mg, and the maximum dose

around 2400 mg/day. Due to the drug's common side effects such as drowsiness and sedation, a slow titration is necessary.

Antidepressants

Among the antidepressants, the tricyclic antidepressants (TCAs) such as amitriptyline are most frequently applied in neuropathic pain. TCAs have been studied extensively in noncancer pain patients. They enhance the endogenous inhibitory pathways by inhibiting the presynaptic reuptake of serotonin and norepinephrine in spinal pain pathways. TCAs also have agonistic effects on histamine and muscarinic receptors, which contributes to side effects such as sedation and dry mouth. Additionally, there may be binding to sodium channels as well as inhibition of voltage-dependent calcium channels. Due to its sedative effects, amitriptyline should be administered during the evening and should be slowly titrated. Particularly in older patients, the initial dose should not exceed 25 mg. The maximum dose for cancer pain is approximately 75–100 mg/day. Contraindications might arise from preexisting cardiac diseases such as arrhythmias or conduction defects. Secondary antidepressants such as nortriptyline or desipramine are as effective as TCAs but are often better tolerated due to less side effects. Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine are better tolerated as well, but they are also less effective in relieving neuropathic pain. New antidepressants with a mixed mechanism of action such as venlafaxine, paroxetine, or duloxetine seem to be effective as well, but for cancer pain management the evidence is sparse, and they are not available in many countries.

Opioids

Common fallacies about opioids include a lack of efficacy in neuropathic pain conditions. This belief has been proven not to be true. There is abundant evidence demonstrating the efficacy of these drugs. However, neuropathic pain may be less responsive to opioids compared to nociceptive pain. Opioids should be titrated individually and carefully to find out the optimal balance between benefit and side effects. By combining opioids with adjuvants such as gabapentin, the dose of each drug can be reduced and the effect on pain relief is usually greater than using only one of those drugs. Therefore, a combined therapy should be considered in neuropathic pain.

Among opioids, *morphine* is the best studied drug. It is a mu-receptor agonist. Morphine is available in immediate-release formulations and (in some countries) in sustained-release formulations. As the duration of action of the immediate-release formulation is approximately 4 hours, frequent administration is necessary. Titration should start with 5–10 mg every 4 hours. On occurrence of breakthrough pain, an additional 1/6 to 1/10 of the total daily morphine dose should be applied as an initial step. Later, the adequate dose to treat episodes of breakthrough pain must be adjusted according to the individual patient's needs and responses. In the case of painful procedures, immediate-release morphine might be administered approximately half an hour before the procedure (such as wound management) will be performed. The most common side effects include sedation, constipation, nausea, and vomiting. It is essential to take care of side effects (for constipation, prescribe laxatives and advise the patient about fluid intake; for nausea, prescribe antiemetics and inform the patient that nausea is often self-limiting). In cases of hepatic dysfunction (e.g., liver cirrhosis), the duration of action might be prolonged, so dosing intervals should be extended. In renal impairment, dose reduction is recommended while maintaining the application intervals.

Other opioids to be used include *tramadol,* which is a synthetic opioid not only stimulating mu-receptors but also inhibiting the presynaptic reuptake of serotonin and norepinephrine. Dosage is every 4 hours for immediate-release formulations and three times a day for sustained-release formulations. When switching from tramadol, which is sometimes classified as a "weak opioid," to morphine, the conversion ratio has to be considered (e.g., 100 mg oral tramadol is equivalent to approximately 10 mg of oral morphine). The maximum dose of tramadol should not exceed 400–600 mg/day. Among the side effects, there is a high prevalence of nausea and vomiting. In renal failure, intervals between doses should be increased. The recommended dose in the case of liver cirrhosis amounts to 50 mg every 12 hours.

Oxycodone is a semisynthetic opioid that activates the mu-receptor as well as the kappa receptor. Duration of action is 4 hours. Due to the better oral bioavailability the conversion ratio to morphine is 1:2 (e.g., 5 mg oral oxycodone equals 10 mg oral morphine). Oxycodone should be used very carefully in situations of renal or hepatic dysfunction, due to the increased elimination half-life.

Transdermal fentanyl, a synthetic mu-receptor agonist, delivers fentanyl via a self-adhesive patch with a rate-limiting membrane. Due to the slow delivery, the patches have to be changed every 72 hours (in 20% of patients a new patch has to be applied every 48 hours due to end-of-dose failure). The conversion ratio to morphine is 100:1 (e.g., 120 mg morphine/day equals 50 µg fentanyl/hour). Advantages over morphine are the absence of active metabolites. However, in the presence of renal dysfunction, sensitivity to the drug's effect is increased. Liver cirrhosis does not seem to affect the pharmacology of fentanyl, but impaired liver blood flow or liver failure does so. Constipation is less pronounced as compared to morphine. Disadvantages include adhesive problems and the slow onset of action (when the patch is applied for the first time, a 12-hour gap before the onset of action has to be taken into account).

Methadone might be considered an important alternative and, in cases of severe plexopathy, even as a first-line opioid. Methadone is a synthetic opioid acting as a µ-receptor agonist, an NMDA-receptor blocker, and a presynaptic serotonin reuptake inhibitor. Due to its long elimination half-life of 24 hours (up to 130 hours), titration is sometimes difficult, but methadone can also be regarded as a long-acting opioid, which necessitates only three to four daily dosages. The usual dose begin with 5 mg q.i.d. for 2–3 days. For inadequate pain relief or breakthrough pain, an additional 5 mg might be administered. Switching to or starting with methadone might be difficult. For this reason an algorithm is recommended. On day 1 treatment with preexisting opioids should be stopped. Oral methadone 2.5–5 mg should be administered every 4 hours. For breakthrough pain 2.5–5 mg methadone might be used additionally (with a dosage interval of 1 hour). On days 2–3, a dose maximal increment of 30% might be necessary, if pain relief on day 1 was not sufficient. On day 4, 72 hours after initiating methadone therapy, the dosing interval should be changed to t.i.d. (every 8 hours), and the intervals for breakthrough medication should be prolonged to 3 hours as well. If pain relief is still not adequate or if pain increases due to cancer progression, dose adjustments might be performed. Patients on very high oral morphine doses (>1000 mg/day) should start on day 1 with 50 mg methadone q.i.d. Over the following days, dose adjustments should be performed as described above. Due to its metabolism via cytochrome P-450, precautions have to be taken to prevent drug interactions. Ketoconazole, HIV protease inhibitors, and grapefruit juice are responsible for magnified methadone effects, whereas corticosteroids, St. John's wort, carbamazepine, and rifampin might lower the effect. Methadone might cause prolongation of the QT-interval and may cause torsades de pointes ventricular tachycardia. Therefore in patients at risk of hypokalemia, cardiac diseases, or cocaine abuse, methadone should be used carefully, and an electrocardiogram should be performed, if available.

Corticosteroids

Corticosteroids, especially dexamethasone, are helpful when there is clinical evidence of nerve structure compression or pain due to edema surrounding the metastases. In cases of severe pain, doses of 16–24 mg a day should be prescribed initially. In cases of an emergency (spinal cord compression) initial intravenous doses of up to 100 mg, followed by 60 mg in three divided doses should be used. Steroids should be continued until other treatment approaches (radiotherapy, drug therapy) are initiated, after which dexamethasone can be tapered off gradually. Dexamethasone has two other "side effects" that might be helpful for palliative treatment. It has an antiemetic effect and might increase the appetite. To increase appetite, dexamethasone can be prescribed continuously in a daily dose of 2 mg.

NMDA-receptor antagonists

Excitatory neurotransmitters, such as glutamate, play a major role in pain transmission at the spinal cord level. Glutamate activates the NMDA receptor, which is associated with phenomenon such as central sensitization. *Ketamine,* an NMDA-receptor antagonist and a drug used extensively in anesthesia, should be considered, especially in situations when opioid analgesia is not effective enough. The addition of oral ketamine approximately 10–25 mg t.i.d. should be combined with diazepam in low doses (e.g., 5 mg) to avoid psychotic symptoms associated with the use of ketamine.

Cannabinoids

Newer classes of drugs to treat neuropathic pain are cannabinoids. There is evidence that oral delta-9-tetrahydrocannabinol (THC) and other cannabinoids might provide relief from neuropathic pain, improve appetite, and reduce nausea and vomiting. However, these drugs cannot be recommended in general, due to the lack of well-designed studies in the area of cancer-related neuropathic pain.

Nonpharmacological Approaches

Nonpharmacological treatment approaches include epidural opioid application and continuous infusion of local anesthetics via a brachial plexus catheter. However, catheter dislocation and infection might be regarded as a major obstacle in applying this form of therapy, especially in rural areas where anesthesiologists are not available.

Cordotomy is a neurodestructive procedure in which the anterolateral spinothalamic tract is destroyed to produce contralateral analgesia. The pain has to be strictly unilateral and due to the frequent recurrence of pain, the life expectancy of the patient should be limited. Important neurological complications include paresis, ataxia, phrenic nerve paralysis, and in long-term survivors a delayed onset of dysesthetic pain.

Pearls of wisdom

- In the clinical evaluation certain pain descriptors (e.g., burning or lancinating pain) reported by patients in combination with neurological signs (e.g., hypoesthesia, allodynia, or pathological cold/warm thresholds) by bedside testing with simple tools (e.g., a cotton-wool tip, needle, or cold spoon) give strong evidence of a neuropathic pain syndrome.
- In cases of neuropathic pain, a combination of anticonvulsants, antidepressants, and opioids is usually more effective compared to an opioid monotherapy.
- Consider the use of methadone in cases of "intractable" neuropathic pain syndromes.

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International Association for the Study of Pain
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Chapter 21
Lung Cancer with Breathing Problems

Thomas Jehser

Why is important to know about pain in lung cancer?

Lung cancer is the most common lung tumor and the most common malignant disease. The incidence in Europe is estimated by the World Health Organization (WHO) to be 38/100,000 inhabitants (in Africa 9/100,000). It causes about 1.2 million deaths per year worldwide. Since 1953 it has been the most common cause of death by cancer within the male population, and since 1985 within the female population.

Case report—part one

Mr. Tarik Al-Khater is a 65-year-old man with an athletic constitution. He used to work as a postman in Barbar, Northern Sudan, and remained active doing fitness exercises until a year ago. Twenty years ago, he had quit smoking, having accumulated 10 "pack years" (one "pack year" means smoking 20 cigarettes per day throughout one year). Up to 2 years ago, he had never been ill, though he had undergone an appendectomy and osteosynthetic surgery for a tibial fracture. Then at the age of 63, he received a diagnosis of pulmonary emphysema and diabetes mellitus. Nine months ago, he suffered a herniated lumbar disk and underwent surgery because of muscle weakness of the right thighs. Furthermore, there remained a mixed pain syndrome of the lower back, right hip, and right knee, with a dominating neuropathic component (burning pain). Mr. K. sought consultation with his doctor, who established a successful medication regimen with a combination of tramadol and carbamazepine. Being able to move a lot better, Mr. K. became more aware of his dyspnea and exhaustion following relatively short distances of walking. His wife also noticed that he had significant weight loss and a constant cough during the last couple of months. An X-ray of the thorax showed a prominence of the right hilum of the lung. He was sent to Atbara for further examination. Unfortunately, the CT detected a central tumor of the right bronchial system, which by bronchoscopy was histologically classified as a non-small-cell lung cancer. Furthermore, scintigraphic and X-ray examinations reveal scattered bone metastases, such as in the lumbar spine and the right knee.

What are the causes and risk factors for lung cancer?

There are endogenous factors for the onset of lung cancer (genetic disposition, active HIV infection, pulmonary fibrosis, and scarring following parenchyma injury or tuberculosis). Exogenous conditions considered as risk factors are smoking in the first place (partly responsible in 90% of lung cancer deaths) as well as exposure to dust and particles such as asbestos, chromates, and polycyclic aromatics or to radiation from uranium, radon, or even medical radiation therapy.

How does lung cancer start?

Bronchial carcinomas mostly start in the central airway region and less often in the more peripheral smaller bronchi. The first and most noticeable symptom is a nonproductive persistent cough (suspicious when lasting longer than 6 weeks). Other primary symptoms are hemoptysis, dyspnea or chest pain, and rarer symptoms are hoarseness, anxiety, fever, and mucoid expectoration or paraneoplastic syndromes or signs following any kind of early metastasis (Box 1). The histological analysis differentiates small-cell (13%) from non-small-cell (81%) carcinomas. Six percent of analyses deliver no distinct result (anaplastic carcinoma). Other malignancies or space-consuming processes of the thorax are pleural mesotheliomas, thymomas, metastases of extrathoracic tumors, or infectious diseases (Box 2). An accurate differential diagnosis of thoracic discomfort therefore has to consider tumorous illnesses.

Case report—part two

Unfortunately, tumor metastasis was detected at the moment of initial diagnosis, and the primary growth was located in a very central position. Breathing capacity—when tested—was limited to a FEV_1 of 1.1 L. Therefore it was decided that a surgical resection would be impossible. For symptomatic treatment, Mr. K. was treated by radiotherapy at the tumor region (cumulative dose of 46 Gy) following radiation of the bone metastasis at the spine (36 Gy) and the knee (8 Gy). In the course of treatment, blood testing revealed elevated hepatic transaminases. Since no hepatic metastasis was found, the carbamazepine component of the pain medication was suspected to be responsible. After the completion of radiotherapy, Mr. K. experienced much better breathing and almost no pain, although the medication had been reduced to metamizol q.i.d. and tramadol p.r.n.

What are the disease trajectory and treatment options?

Tumor diseases may cause local, regional, and systemic functional disorders, symptoms, and complications. The local effects of lung cancer are airway obstruction and infiltration of neighboring tissues. This may lead to mucoid impaction, retrostenotic pneumonia, hemorrhage, or pleural effusion. The regional spreading of the tumor follows continuous infiltration of the mediastinum, the pleura, or the axilla or spreads via local lymph vessels.

Symptoms of regional spreading are weakness; loss of appetite and weight; congestion of head and neck vessels; infiltration into the mediastinum, axilla, and chest wall with mixed pain in the arm, shoulder, chest and upper back; dysphagia; or neurological disorders (palsy of the arm, Horner syndrome, or paraplegia). The systemic dissemination of primary lung tumors via the bloodstream or lymphatic pathways causes symptoms and disorders according to the quantity and location of the metastases. Patients may now suffer from neurological, metabolic, cardiovascular or gastrointestinal disorders (Box 3). Common locations of dissemination of lung cancer are thoracic and cervical lymph nodes, bone, pleura, the brain and its linings, the liver, and the adrenal glands. Very seldom are the spleen, heart, skin, eye (choroid coat), kidney, or pancreas afflicted.

Box 1. Common symptoms of beginning lung cancer	**Box 2.** Common extrathoracic diseases and infections with pulmonary manifestation
Persistent cough	Breast cancer
Hemoptysis	Rectal cancer
Dyspnea	Renal cancer
Chest pain	Malignant melanoma
Hoarseness	Sarcomas
Fever, mucoid impaction	Aspergillosis
Other pain locations	Tuberculosis
Loss of appetite, weight, and strength	Helminthiasis
Paraneoplastic syndromes	
Cushing syndrome	
Herpes zoster	
Peripheral neuropathy	
Venous thrombosis	

Case report—part three

Mr. K. has been ill with lung cancer for 7 months now. Four weeks ago, he lost his appetite, and he feels sick quite often. He has lost weight continuously (about 30% of his initial body weight within one and a half years). Although carbamazepine has been stopped, the blood tests show high values for liver transaminases, accompanied by upper abdominal pain. A physical examination reveals an upper abdominal mass, and ultrasonography detects multiple metastases in the liver and also in both adrenal glands.

The oncologist recommends chemotherapy, which would have to be conducted in the regional hospital. Mr. K. is reluctant to return to the hospital in Atbara, the capital, and asks his friends and relatives for information on traditional treatment options they might have heard of.

What are the treatment options in advanced lung cancer?

Treatment options include:

- Surgical therapy (curative or palliative)
- Radiotherapy (neoadjuvant, palliative, or symptom-targeted)
- Chemotherapy and other pharmacological therapy (palliative)
- Naturopathy (palliative)
- Palliative care (adjuvant)

Of course, the very best therapy would be the prevention of risk factors, but primary prevention procedures are not established. Diagnostic evaluation at the earliest time is crucial for the course of the illness.

Curative surgery needs the diagnosis of a low stage of disease (0–IIIa) in order to make eradication of the tumor possible by resection. Potential techniques include lobe resection, (pleuro-) pneumonectomy, or bronchial reconstruction. Additional options are dissections of lymph nodes and reconstruction of pericardium and blood vessels. The degree of ventilatory restriction depends on the magnitude of resection. Surgical treatment needs to be conducted in a specialized clinical department. Postoperative rehabilitation is possible in the outpatient setting and must not be disregarded. Palliative surgery is done to remove metastases of extrathoracic tumors or local relapse as well as for draining of secondary infection such as empyema. Endoscopic or vascular interventions help with the reopening of airways and vessels by stenting or by laser or cryoextraction.

Radiotherapy alone cannot be used with a curative intention. In combination with chemotherapy, it may reduce the size of the tumor (downstaging), which might open the route to successful surgery (neoadjuvant strategy) and to an extension of survival time. Palliative radiotherapy intends to reduce the activity of metastases, which may result in reduction of pain (bones, liver, CNS, and pleura), blood congestion (superior vena cava syndrome caused by lymph node metastases of the mediastinum), or neurological disorders (CNS).

Systemic pharmacological therapies (chemotherapeutic, antihormone therapy, and others) work in a palliative way to reduce the bulk mass or the tumor growth rate, allowing prolongation of survival. Their application usually weakens the general condition of the patient. It is therefore necessary to consider the quality of life of individual patients from their personal perspective.

Are there therapeutic alternatives to surgery, chemotherapy, and radiotherapy?

Alternative (or complimentary) treatment strategies are based on traditional and empirical concepts. They may be looked at as palliative and should not replace scientific medical efforts. Using a palliative perspective, these strategies may very well be of great meaning and effectiveness within the individual disease trajectory. It

Box 3. Common general disorders in lung cancer patients

Neurological: Limb palsy, hemiparesis, paraparesis, pain, delirium, epileptic seizures
Metabolic: Diabetes mellitus, SIADH (syndrome of inappropriate antidiuretic hormone hypersecretion), anemia, thrombocytosis, thrombopenia, hypercalcemia
Cardiovascular: Hypotension, thrombosis, superior (or inferior) vena cava congestion
Gastrointestinal: Nausea, vomiting, bowel obstruction, liver failure

is often quite astonishing how they help the patient and their relatives face the illness with more understanding and to deal better with feelings of helplessness, which again might help to direct the path of disease to a certain extent.

According to the WHO, "Palliative care is an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual." The founder of modern palliative care, Dame Cicely Saunders (1918–2005), developed her fundamental ideas when she was trying to ease and diminish cancer pain by looking at it from more than a "physical" perspective. So she inaugurated treatment strategies for the psychological, social, and spiritual needs of the patients besides taking care of their physical condition, according to the concept of "total pain." Palliative care, therefore, eases physical suffering and provides information and understanding within the social context of the patient. In the same way, it delivers consolation and assistance to help with anxiety and emotional pain caused by the threatened loss of one's relations and life.

Case report—part four

Mr. K. finally agrees to have chemotherapy. After finding transportation, he visits the district hospital in Atbara routinely for the treatments and the necessary examinations and feels somehow safe and stabilized, although he has to take antibiotics for a short term of pyogenic bronchitis. He meets other patients—many of them much younger than himself—who tell him about side effects, which he finds to be irrelevant to himself at this point. He gets a lot of relief when he finds a group supervised by a health care worker in his home town where they practice breathing and relaxation techniques. With the help of his family and friends he also gets advice from a traditional healer, who recommends an additional composite medication consisting of herbal and mineral substances. In personal meetings with his spiritual adviser Sheikh Farshi, he learns to talk to his wife and three children about the possible consequences of a fatal disease for the family and their financial affairs.

After the next course of chemotherapy, he suffers from vomiting and weakness for the first time following such a treatment. Again he feels abdominal and back pain, as well as some dyspnea at rest. Shortly afterwards, a scleral icterus begins, and Mr. K. shows periods of disorientation and depression. His family takes him again to the Atbara district hospital for examination. It turns out there that he has developed a serious bone marrow insufficiency so that no further chemotherapy can be given. He is now sent home to talk with his family doctor about further action that might be taken.

What are the consequences of dyspnea, and how is it treated?

Dyspnea is defined as a subjective experience of breathing discomfort, consisting of different conditions that all lead to an increased breathing effort, either needing more strength or a higher respiratory rate. This experience is also influenced by interactions among physical and emotional conditions. Dyspnea may be caused by, but is not at all identical to, respiratory insufficiency. While dyspnea is a subjective sensation of the patient, respiratory insufficiency is a "physiological" phenomenon that can be exactly quantified by testing. There are multiple causes for respiratory insufficiency originating in the pulmonary, cardiac, vascular, bony, muscular, and nervous systems. The amount of resulting dyspnea depends heavily on the course of development of respiratory insufficiency and its profoundness. Therefore, some patients may be able to live with a greatly decreased respiratory capacity without feeling any dyspnea at rest, while others with minor respiratory insufficiency may suffer intense shortness of breath. Feeling dyspnea easily causes anxiety, and vice versa. The differentiation of shortness of breath therefore requires the clinician to evaluate not only vital capacity and FEV_1, but also the general condition of the patient, so as to avoid underestimation of the problem.

For therapy for dyspnea to be effective, knowledge of its physiology is helpful. In case of a possible treatment of underlying causes, such as bronchospasm or anemia, priority is given to this type of therapy. As one symptom of dyspnea deals with some sort of agitation, sedative treatment allows successful symptom control, which might even help the breathing system to run more efficiently.

Besides sedative drugs such as benzodiazepines, morphine is probably the most important remedy available for this important clinical situation. Morphine reduces the subjective "air hunger" significantly, regardless of the actual physiological need for O_2 and CO_2 transport

and exchange. Other drugs such as haloperidol, cannabinol, and doxepin help to reduce the psychological distress and agitation. Besides pharmacotherapy, the treatment of cutaneous trigger zones by massage, cognitive and behavioral distraction, and even simply directing fresh air toward the face stimulating trigeminal receptors, with a direct influence on breathing frequency, are means that lead to reproducible relief of suffering. The availability of morphine, oxygen, and a fan may therefore be the most important means and, most of the time, are sufficient to control even advanced stages of dyspnea.

Besides dyspnea, what else should be considered in the treatment of lung cancer?

Most often lung cancer is a progressive disease accompanied by complications caused by tumor metastases and general physical exhaustion. These complications often go along with pain and dyspnea and lead to enormous psychological suffering, which needs to be addressed by appropriate treatment and honest information about the therapeutic options. In this way it is possible to influence the patient's perspective regarding his or her personal quality of life.

- The wide range of treatments targeting the different possible complications include:
- Medication (e.g., analgetics, antibiotics, bronchodilators, corticosteroids).
- Substitution of albumin, erythrocytes, electrolytes, fluids, and caloric agents.
- Radiotherapy (to treat lytic bone lesions, tumor obstruction of central airways, superior vena cava syndrome, or intracranial pressure).
- Surgical, endoscopic, and intravascular interventions.

Complementary treatment offers exercise (physiotherapy), psychological or spiritual support, as well as receptive and imaginative therapies (massage, musical therapy, and active relaxation techniques). A great number of patients carrying progressive lung cancers die from the complications of their illness rather than from the lung cancer itself. During the final period of life, supporting and comforting the patient by lowering anxiety, agitation, weakness, pain, and dyspnea is most important. When clinicians have provided comprehensive instructions and are available as a backup if needed, this support may be provided by family members at home.

Case report—part five

Mr. K. has returned home and is mostly resting in a comfortable chair in the living room. His wife and two of the three children live with him in the house. Neighbors and some other family members visit quite regularly so that the patient participates in what is going on around him to a certain extent. Mr. K. has started to smoke again (about three cigarettes on a good day), which he claims "does not make any difference" at this point and reminds him of the "good old days" when he was a young postman in his original home town. Smoking also gets him to walk a few steps, because his family insists that smoking is only allowed outside. The family doctor regularly visits the patient twice a week. He has instructed Mrs. K. and one of the sons to administer morphine via a subcutaneous route using titration doses in case of pain or dyspnea, which has been occurring several times during the evenings and nights. One day Mr. K. stumbles on his way back to his chair and is afraid of falling again after this incident. The next day he does not leave his bed and seems to be more disoriented than ever. The visiting community nurse administers a sedative drug to the more and more agitated Mr. K. and calls for the family doctor. When the doctor comes in the next day, the general condition of Mr. K. has worsened. He dreams heavily, is feverish, and shows seizures of his right arm and his face. The doctor decides to leave Mr. K. in Barbar, since he sees no further options for specific treatment, as he explains patiently to the anxious family. Again a sedative is given subcutaneously, and the patient's agitation subsides, which helps the family to remain at his side constantly, though weeping a lot. At the end of this day, Mr. K. dies without regaining consciousness or showing signs of agitation or suffering, especially dyspnea.

Pearls of wisdom

Understand that:

- Lung cancer is a life-threatening disease.
- The character of breathing problems helps you to decide on their treatment.
- Lung cancer causes pain problems, which can be treated.
- Palliative care can be given to patients with lung cancer.
- Morphine and a fan may, in most cases, be sufficient to prevent the patient from suffocating.
- The necessary dose of morphine is not given as milligrams per kilogram of body weight, but

rather by titration in small repetitive doses until an effective dose is achieved.

- The positive effects of morphine far outweigh the risk of respiratory depression by opioids, since titration allows finding the balance between reduction of dyspnea and the typical side effect of respiratory depression.
- Morphine should be given subcutaneously to allow fast onset of action in acute situations of dyspnea, if the intravenous route is not available.
- Patients with dyspnea in end-stage lung cancer not only need pharmacotherapy, but especially require a team of caring family members, health care workers, friends, and spiritual advisors.
- Anything that helps the patient should be used, because in palliative care, reservations about complimentary, alternative, or traditional medicine are not justified.

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Guide to Pain Management in Low-Resource Settings

Chapter 22
Hematologic Cancer with Nausea and Vomiting

Justin Baker, Raul Ribeiro, and Javier Kane

Case report

Michael is a 23-year-old man with recurrent lymphoblastic lymphoma in his bone marrow and central nervous system (CNS) who is receiving end-of-life care with palliative chemotherapy. Five days ago, Michael started on a course of oral cyclophosphamide (see Table 1 for emetogenic properties of chemotherapy) with the intention of prolonging a life of good quality. Michael's chief complaint at this time is severe nausea accompanied by vomiting 2 or 3 times per day. The main concern of Michael's parents is his inability to eat or drink anything considerable. Michael is currently receiving morphine 30 mg orally every 4 hours, mostly to control his headaches. He is on no other medications. Further history reveals that Michael's nausea and vomiting have been increasing in severity over the past 3 days (he started the cyclophosphamide 5 days ago). He has not had a bowel movement for 7 days.

Why is treatment of nausea and vomiting so important?

Nausea is defined as a feeling of sickness in the stomach and is characterized by an urge to vomit. Vomiting is the forceful expulsion of the contents of the stomach and proximal small intestine. Nausea and vomiting (N/V) are common symptoms in dying patients and arise as a result of either treatment-related toxicity (disease-specific treatment or palliative treatment) or complications directly or indirectly related to the disease. More than half of cancer patients who are dying experience significant nausea, and nearly one-third experience vomiting. The clinical picture of N/V is often multifactorial. Regardless of the etiology, the symptoms of N/V can interfere with patients' nutritional status and their enjoyment of eating and drinking and can significantly affect their quality of life and the quality of their death. When not properly managed, N/V interferes with a patient's nutritional status, hydroelectrolytic homeostasis, mental status, clinical performance, and compliance with treatment. Clinicians therefore have an ethical imperative to prevent, screen, assess, treat, and follow up N/V to ensure the best possible care for dying cancer patients.

What are the main pathways involved in the pathophysiology of nausea and vomiting?

The pathophysiology of nausea and vomiting is fairly well characterized. The vomiting center receives afferent input from four neuronal pathways that carry emetogenic signals:

Peripheral pathways from the gastrointestinal (GI) tract through the vagus and splanchnic nerves. The GI tract may elicit nausea through sensations of irritation by medications, tumor infiltration, obstruction, distension, or constipation or fecal impaction.

Neuronal pathways from the chemoreceptor trigger zone (CTZ). The CTZ is located in the floor of the fourth ventricle and lacks a true blood-brain barrier. This allows the zone to sense fluctuations in the concentration of certain substances in the bloodstream. The CTZ may also be stimulated by posterior fossa tumors.

Vestibular pathways from the labyrinth. Vestibular pathways may be stimulated by vestibular disease such as vertigo, middle-ear infections, or motion sickness.

Cortical pathways in response to sensory or psychogenic stimuli. Cortical stimulation may come from a CNS or meningeal tumor, increased intracranial pressure, anxiety, or uncontrolled pain.

How are nausea and vomiting classified?

Nausea and vomiting are usually classified as acute, delayed, refractory, anticipatory, or breakthrough. Acute emesis, which appears to be mediated by serotonin, occurs within 3 to 4 hours after exposure to an emetogen such as chemotherapy (see Table 1). Serotonin is released from the enterochromaffin cells of the small intestine and activates 5-HT_3 receptors on peripheral vagal fibers and central structures. Delayed emesis occurs after the first 24 hours of the exposure to the emetogen and persists up to 4–6 days. In addition to serotonin, substance P, along with other neurotransmitters, appears to have an important role in the maintenance of acute and delayed N/V. Anticipatory N/V is defined as a conditioned "learned" response, usually occurring when episodes of N/V have been inadequately controlled with prior exposures. It occurs before, during, or after the exposure to the emetogen, but not at the time emetogen-related N/V would be expected to occur. In this situation, a variety of stimuli such as odor, sight, or sound provoke emesis.

What is the differential diagnosis of nausea and vomiting?

Michael's case has helped demonstrate that nausea and vomiting is often multifactorial. Fig. 2 details the differential diagnosis and etiologies of nausea and vomiting as well as providing a helpful mnemonic to quickly recall the cartoon:

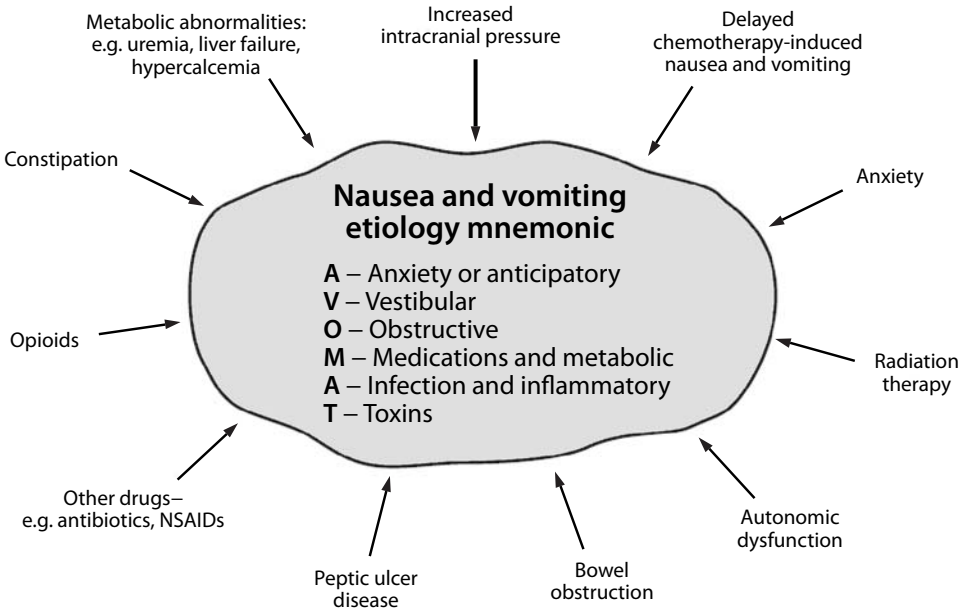

Fig. 1. Differential diagnosis/etiologies of nausea and vomiting (adapted from Dalal et al. [1]) and a quick differential diagnosis mnemonic.

What chemotherapy agents cause the most problems with nausea and vomiting?

Table 1
Risk for emesis in the absence of prophylactic antiemetic treatment with commonly used chemotherapy drugs [adapted from Perry (2001)]

Drug (Dose)		
High Risk (>90%)	Moderate Risk (≥30–90%)	Low Risk (<30%)
Carmustine (>250 mg/m^2)	Carboplatin	Asparaginase
Cisplatin	Carmustine (<250 mg/m^2)	Bleomycin
Cyclophosphamide (1500 mg/m^2)	Cisplatin (<50 mg/m^2)	Cytarabine (<1 g/m^2)
Dacarbazine (>500 mg/m^2)	Cyclophosphamide (<1500 mg/m^2)	Docetaxel
Dactinomycin	Cytarabine (>1 g/m^2)	Doxorubicin (<20 mg/m^2)
Lomustine (>60 mg/m^2)	Doxorubicin	Etoposide (p.o. or i.v.)
Mechlorethamine	Epirubicin	Fluorouracil (<1 g/m^2)
Streptozocin	Idarubicin	Gemcitabine
	Ifosfamide	Interleukin-2
	Irinotecan	Methotrexate (<100 mg/m^2)
	Melphalan	Methotrexate (>100 mg/m^2)
	Mitoxantrone (>12 mg/m^2)	Mitomycin
	Procarbazine	Mitoxantrone (<12 mg/m^2)
		Paclitaxel
		Rituximab
		Temozolomide
		Teniposide
		Thiotepa
		Topotecan
		Trastuzumab
		Vinblastine
		Vincristine

How should I assess for nausea and vomiting?

The assessment should include the history and physical examination of the patient. When taking the history, ask about the characteristics of N/V:

- Onset (to identify a specific trigger)
- Relationship to eating (postprandial N/V may be caused by an obstruction)
- Medication review (a medication change may help)
- Bowel movement history (are there indications for dysfunctional intestines?)
- Vestibular component (antihistamines might be useful)
- Anxiety or unrelieved pain (often overlooked as causes of nausea)

When performing the physical examination, watch out for:

- Cachexia or malnutrition, muscle wasting, decreased skin fold thickness (indicators for malabsorption)
- Abdominal distension, increased bowel sounds, abdominal masses or ascites (indicators for bowel obstruction)
- Abdominal fullness, including rectal examination (constipation due to hypomotility)
- Papilledema (raised intracranial pressure)
- Lying and standing blood pressure and Valsalva's maneuver (autonomic dysfunction)

How can nausea and vomiting be treated pharmacologically?

Pharmacological treatment of N/V is the mainstay of therapy. Table 2 lists frequently used medications to treat N/V. The summary table at the end of this chapter also includes useful treatment algorithms, including pharmacological therapy. As with all symptoms, clinicians need to frequently reassess the efficacy of treatment and anticipate exacerbating factors. Adequate treatment and prevention of recurrent or prolonged nausea and vomiting are critical.

Can you treat nausea and vomiting with nonpharmacological options (complementary and alternative medicine)?

Nonpharmacological modalities have not yet been adopted and incorporated into evidence-based practice guidelines. However, several acupuncture-point stimulation techniques have been examined for treating nausea, vomiting, or both. These techniques include methods that involve needles, electrical stimulation, magnets, or acupressure. Evidence supports the use of

Table 2
Common pharmacological agents used to treat nausea and vomiting (adapted from Policzer and Sobel [3])

Class of Drug	Dose	Comments
Prokinetic Agents		
Metoclopramide	5–15 mg before meals and at bedtime; s.c./i.v. = p.o.	For nausea and gastric stasis from various causes. Use metoclopramide with care; may cause dystonia, which is reversible with 1 mg/kg diphenhydramine. Antiemetic dosage is greater than prokinetic dosage by 0.1–0.2 mg/kg/dose. Well tolerated with s.c. administration.
Domperidone	0.3–0.6 mg/kg dose before meals and at bedtime to a maximum of 80 mg/day.	Use domperidone with care; may cause dystonia, which is reversible with 1 mg/kg diphenhydramine.
Antihistamines (Useful for vestibular and gut receptor nausea and vomiting, but relatively contraindicated by constipation because they slow the bowels further)		
Diphenhydramine	1 mg/kg/dose p.o. every 4 hours to a maximum of 100 mg/dose; s.c./i.v. = p.o.	
Hydroxyzine	0.5–1 mg/kg/dose every 4 hours to a maximum of 600 mg/day; s.c./i.v. = p.o.	
Promethazine	0.25–1 mg/kg every 4 hours; s.c./i.v. = p.o.	Use promethazine with care; can cause dystonia. Risk of respiratory arrest in infants
Dopamine Antagonists (Useful for medication and metabolic-related nausea and vomiting. Can cause dystonia, reversible with 1 mg/kg diphenhydramine or 0.02–0.05 mg/kg/dose benztropine to a maximum of 4 mg i.v. Intravenous use can cause postural hypotension; therefore i.v. should be given slowly.)		
Haloperidol	0.5–5 mg/dose every 8 hours up to 30 mg/day; s.c./i.v. = ½ p.o.	Use with care; only some preparations can be given i.v. Use dextrose 5% in water to dilute. Well tolerated with s.c. administration.
Chlorpromazine	0.5–1 mg/kg every 8 hours; i.v. = p.o.	More sedating. Irritating to tissues with s.c. administration.
Prochlorperazine	0.15 mg/kg/dose every 4 hours to a maximum of 10 mg/dose; i.v. = p.o.	Irritating to tissues with s.c. administration.
Serotonin 5-HT$_3$ Receptor Antagonists (Also useful for postoperative nausea and vomiting and as second- or third-line agents after other types of antiemetics have demonstrated limited utility)		
Ondansetron	0.15 mg/kg/dose every 6 hours to a maximum of 8 mg; i.v. = p.o.	Particularly helpful in chemotherapy-induced nausea and vomiting. High cost may preclude its use.

Class of Drug	Dose	Comments
Benzodiazepines		
Diazepam	0.05–0.2 mg/kg dose every 6 hours; i.v. = p.o.	Helpful for anticipatory nausea and vomiting. Diazepam stings during i.v. administration; use a large vein and dilute solution. For patients younger than 5 years, max. dosage is 5 mg/dose. For patients older than 5 years, max. dosage is 10 mg/dose.
Lorazepam	0.03–0.05 mg/kg dose every 5 hours to a maximum 4 mg/dose; i.v. = p.o./s.l.	
Corticosteroids		
Dexamethasone	6–10 mg loading dose, then 2–4 mg 2–4 times a day for maintenance; i.m./i.v. = p.o.	Helpful for hepatic capsular distention, anorexia, and increased intracranial pressure. Can have long-term side effects. If the patient weighs less than 10 kg, 1 mg/kg loading dose, and then 0.1–0.2 mg/kg 2–4 times a day for maintenance. Agonist effect when used in combination with serotonin antagonists.
Prednisone	1.5 mg dexamethasone = 10 mg prednisone	
Cannabinoids		
Dronabinol	2.5 mg twice a day (for adults only) to a max of 20 mg/day	Can cause dysphoria, drowsiness, or hallucinations. Appetite stimulant.
Other Anticholinergics		
Scopolamine	Transdermal preparation: 0.5 mg changed every 72 hours; i.v./s.c.: 0.006 mg/kg every 6 hours	Helpful for motion- or movement-related nausea and vomiting. Well-tolerated by s.c. tissues. Often causes dry mouth and blurred vision, and sometimes causes confusion.

electroacupuncture by clinicians competent in its administration for chemotherapy-induced nausea. Other modalities have not been well studied, but details are provided for a comprehensive analysis. Table 3 provides details of all nonpharmacological and complementary and alternative modalities and gives examples of potential antiemetic benefits.

Table 3
Nonpharmacologic and complementary and alternative modalities used to treat nausea and vomiting (adapted from the National Comprehensive Cancer Network 2005)

Modality	Definition	Examples with Benefit in Nausea and Vomiting
Massage therapy	Group of systematic and scientific manipulations of body tissues best performed with the hands to affect the nervous and muscular systems and general circulation	Reiki, therapeutic touch
Mind-body, other relaxation techniques	Methods that emphasize mind-body interactions with intended benefits that include relaxation and emotional well-being	Meditation—transcendental and mindfulness, yoga, prayer, guided imagery, relaxation training
Music therapy	The use of music to help treat neurological, mental, and behavioral disorders	Effective in postoperative nausea/vomiting
Acupuncture therapy	Treatment of symptoms by inserting needles along specific pathways	Acupuncture or acupressure at the Nei Guan or P6 point
Dietary supplements	Products in capsule, tablet, liquid, or dried form, including vitamins, proteins, herbs, and other over-the-counter substances intended for decreasing nausea and vomiting	Ginger root, huangqi decoctions, aromatherapy

What are the side effects of therapy?

All medications have a primary effect and side effects. Antiemetics should be chosen mainly on the basis of the etiology of the N/V and the mechanism of the medication. Side effects may hinder the ability to use certain drugs, however. Table 4 lists common side effects of antiemetics by the category of drug.

Table 4
Side effects of medications commonly used to treat nausea and vomiting

Medication	Adverse Effects*
Antihistamines Diphenhydramine Hydroxyzine	Most common: sedation, dry mouth, constipation. Less common: confusion, blurred vision, urinary retention.
Belladonna alkaloid Scopolamine	Most common: dry mouth, drowsiness, impaired eye accommodation. Rare: disorientation, memory disturbances, dizziness, hallucinations.
Benzamides Benzquinamide Metoclopramide Trimethobenzamide	Most common: sedation, restlessness, diarrhoea (metoclopramide), agitation, CNS depression. Less common: extrapyramidal effects (more frequent with higher doses), hypotension, neuroleptic syndrome, supraventricular tachycardia (with i.v. administration).
Benzodiazepines Lorazepam	Most common: sedation, amnesia. Rare: respiratory depression, ataxia, blurred vision, hallucinations, paradoxical reactions (weeping, emotional reactions).
Butyrophenones Droperidol Haloperidol	Most common: sedation, hypotension, tachycardia. Less common: extrapyramidal effects, dizziness, increase in blood pressure, chills, hallucinations.
Cannabinoids Dronabinol	Most common: drowsiness, euphoria, somnolence, vasodilation, vision difficulties, abnormal thinking, dysphoria. Less common: diarrhea, flushing, tremor, myalgia.
Corticosteroids Dexamethasone Methylprednisolone	Most common: gastrointestinal upset, anxiety, insomnia. Less common: hyperglycemia, myopathies, osteonecrosis, facial flushing, mood changes, perineal itching or burning.
Phenothiazines Prochlorperazine Promethazine Chlorpromazine Thiethylperazine	Most common: sedation, lethargy, skin sensitization. Less common: cardiovascular effects, extrapyramidal effects, cholestatic jaundice, hyperprolactinemia. Rare: neuroleptic syndrome, hematological abnormalities.
5-HT_3-receptor antagonists Granisetron Dolasetron Ondansetron	Most common: headache, asymptomatic prolongation of electrocardiographic interval. Less common: constipation, asthenia, somnolence, diarrhea, fever, tremor or twitching, ataxia, lightheadedness, dizziness, nervousness, thirst, muscle pain, warm or flushing sensation on i.v. administration. Rare: transient elevations in serum transaminases.

* Most common; >10%; less common, 1%–10%; rare, <1%. Based on U.S. Food and Drug Administration-approved labeling and generalized to the drug class.

Pearls of wisdom

Treatment algorithms (adapted from Policzer and Sobel [3]) are shown in Table 5.

Table 5
Treatment algorithms

Cause	Symptoms	Treatment Alternatives
Cortical		
CNS tumor/meningeal irritation	Focal neurological signs or mental status changes	Corticosteroids Consider palliative radiation
Increased intracranial pressure	Projectile vomiting and headache	Corticosteroids
Anxiety or psychogenic symptoms	Anticipatory nausea, conditioned responses	Counseling Relaxation techniques Benzodiazepines
Uncontrolled pain	Pain and nausea	Increase pain medications Use adjuvants
Vestibular		
Vestibular disease	Vertigo or vomiting after head motion	Antihistamines (meclizine)
Middle-ear infections	Ear pain or bulging tympanic membrane	Antibiotic therapy and other supportive care
Motion sickness	Travel-related nausea	Anticholinergics (scopolamine)
Chemoreceptor Trigger Zone		
Medications	Nausea worse after medication dosage or exacerbated after increasing dose	Decrease dose or discontinue medication
Metabolic (renal or liver failure)	Increased blood urea nitrogen (BUN), creatinine, bilirubin, etc.	Dopamine antagonist
Hypercalcemia	Somnolence, delirium, high calcium	Hydration Corticosteroids Bisphosphonates
Gastrointestinal Tract		
Irritation from medications	Use of nonsteroidal anti-inflammatory drugs (NSAIDs), iron, alcohol, antibiotics	Discontinue drug if possible Add histamine (H_2) blocker, proton pump inhibitor, or misoprostol
Tumor infiltration or infection	Evidence of abdominal tumor, candida esophagitis, colitis	Antihistamines Treat infection Anticholinergics
Constipation or impaction	Abdominal distension, no bowel movement for many days	Laxatives Manual disimpaction Enema
Obstruction by tumor or poor motility	Constipation unrelieved by treatment	Prokinetic agents
Malignant bowel obstruction	Severe pain, abdominal distension, visible peristalsis	Analgesics (opioids) Anticholinergics Dopamine antagonists Corticosteroids Consider octreotides

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Management of Neuropathic Pain

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Chapter 23
Painful Diabetic Neuropathy

Gaman Mohammed

Case report 1 ("neuroarthropathy")

Zipporah, a 54-year-old woman, who has had type 2 diabetes for 12 years and is on oral hypoglycemic agents, came to the office complaining about a history of leg pains, especially at night. She regularly walks to the local market where she sells vegetables. She has noticed swelling on her legs over the last few months, but has no history of pain or trauma to the feet. Her husband Tom noted blisters on her feet a day after she had worn a new pair of sandals bought at her local market. Zipporah hadn't felt any discomfort while wearing these sandals. The blisters had burst, revealing cuts over the feet, and her husband convinced her to seek medical attention after she unsuccessfully tried using home remedies such as bandaging the wound with an old cloth and cleaning the wound with salt solution.

Tests revealed an elevated random blood sugar of 15 mmol with an HbA of 11%. On visual examination she had bilateral foot edema with a septic lesion over both feet. Her foot pulses were present but feeble, probably as result of the edema. She had reduced vibration perception and pressure sensation in both feet. X-rays were suggestive of destruction of the talus and calcaneus bones in her feet.

On discussion with Zipporah, she was advised that in view of her current poor glycemic control and foot infections, insulin therapy had to be recommended to control the blood sugar. She was started on twice-daily insulin that she could also obtain at her local hospital and was given an antibiotic with a good Gram-positive and -negative effect. She was advised to have her daily dressing done at her local clinic and not use hydrogen peroxide solution on her injury. She was started on simple analgesics (paracetamol/acetaminophen) in combination with a weak opioid, tramadol. During follow-up review, she was started on amitriptyline at a low dose of 25 mg after she complained of burning sensations, especially at night. She was also given crutches and was advised to mobilize, with partial weight bearing, for a month as she mentioned she had to attend to her duties at the market.

Case report 2 (60-year-old diabetic male on oral hypoglycemic medication)

Yusuf, a 60-year-old man from a coastal city, has had diabetes for 6 years. He gave a history of severe burning sensations in his feet at night, which was relieved by placing his feet in a bucket of water. He didn't seek medical treatment for his ailment until he noted a painful swelling of his toes of the right leg, although he did not remember having had an injury to the foot. Examination revealed that the right foot was infected, and the infection had spread to the interdigital spaces. He also had decreased vibration and pressure sensation, as tested by using a 10-g monofilament and a tuning fork.

He was started on insulin, antibiotics, analgesics, and a tricyclic antidepressant and was given a thorough education on the importance of good glucose control and appropriate footwear. Local care was given. Yusuf reported decreased pain at night and improved wound-site healing on his return visit to the office approximately 3 weeks later.

What is the scope of the problem?

Diabetes currently affects 246 million people worldwide and is expected to affect 380 million by 2025. By 2025, the largest increases in diabetes prevalence will take place in developing countries. Unfortunately, these countries have economic burdens and constraints. More than 80% of the expenditure for medical care for diabetes is made in the world's economically richest countries, and less than 20% in the middle- and low-income countries, where 80% of diabetics live. The WHO estimates that diabetes, heart disease, and stroke together will cost billions of dollars, even in a low-resource country like Tanzania.

Why is pain in patients with diabetes an issue?

In diabetic patients, neuropathy is the most common complication and greatest source of morbidity and mortality, with an estimated global prevalence of approximately 20%, with the highest numbers being in African countries: Tanzania (25–32%), Zambia (31%), and South Africa (28–42%). Diabetic neuropathy is implicated in 50–75% of nontraumatic amputations in African countries.

Why do patients with diabetes develop neuropathy?

There are four factors:

- Microvascular disease
- Advanced glycosylated end-products
- Protein kinase C
- Polyol pathway

What is microvascular disease?

Blood vessels depend on normal nerve function, and nerves depend on adequate blood flow. The first pathological change in the microvasculature is vasoconstriction. As the disease progresses, neuronal dysfunction correlates closely with the development of vascular abnormalities, such as capillary basement membrane thickening and endothelial hyperplasia (thickening), which contribute to diminished oxygen supply and hypoxia. Neuronal ischemia is a well-established characteristic of diabetic neuropathy. Vasodilator agents (e.g., angiotensin-converting-enzyme inhibitors) can lead to substantial improvements in neuronal blood flow, with corresponding improvements in nerve conduction velocities. Thus, the microvascular dysfunction that occurs early in diabetes parallels the progression of neural dysfunction and may be sufficient to support the severity of structural, functional, and clinical changes observed in diabetic neuropathy. In addition, elevated intracellular levels of glucose lead to binding of glucose with proteins, thus altering their structure and destroying their function. Certain of these glycosylated proteins are implicated in the pathology of diabetic neuropathy and other long-term complications of diabetes.

Are analgesics the only treatment option in diabetic polyneuropathy?

Just the opposite! Glycemic control has a favorable effect on each of the microvascular complications of diabetes mellitus, both in preventing the onset of new complications and in slowing the progression of established complications. Glycemic control should be an important cornerstone in pain control because pain associated with diabetic neuropathy decreases with improved glycemic control.

Why does it hurt even though the patient does not "feel" anything, as is typical in diabetic neuropathy ?

Neuropathy in diabetics can present as sensory loss (insensate) neuropathy or painful neuropathy. The majority of people have the insensate type. However, approximately 4–7% of patients with diabetes suffer chronic, often distressing symptoms of pain ("pins and needles") or numbness in their feet. Why patients with diabetes may develop painful neuropathy is not fully understood, although it is known that patients with poorly controlled diabetes for a long time are more likely to get chronic painful neuropathy. Painful symptoms can be transient, often lasting less than 12 months. These

symptoms are often associated with periods of high blood glucose levels, or paradoxically, may occur when blood glucose levels rapidly improve. In these acute situations, once the blood glucose has stabilized for a few months, the painful symptoms often spontaneously disappear. Once symptoms have persisted for more than 12 months, they are less likely to disappear on their own.

How did the patients mentioned above describe their pain, and what would be typical?

Pain associated with painful diabetic neuropathy is often described as tingling pain, numbness, or severe pain with stimuli that normally do not cause pain ("allodynia"). It may also be described as stabbing, deep seated, burning, electrical, or stabbing, with paresthesia or hyperesthesia. Typically, the pain develops in the feet and lower legs, but may also involve the hands, and it is normally greater at night. Diabetic neuropathy affects the daily activities of the patient: sleep, independence, ability to work, interpersonal relationships, as well as mood. Although patients with painful diabetic neuropathy typically voice their symptoms, many patients may not report their symptoms until the pain is severe. In Africa and other developing regions in the world, where people often walk barefoot or have poor-fitting and inappropriate footwear, diabetics with neuropathy may often have infected foot lesions, which can be painful. They may have a history of minor injuries or at times they may not be aware of any injuries, despite evidence of trauma to the feet on examination. Approximately 40–60% of all nontraumatic amputations are done on patients with diabetes, and 85% of diabetes-related lower-extremity amputations are preceded by foot ulcers. Four out of five ulcers in diabetics are precipitated by external trauma.

If in doubt after taking the history, what may I do to confirm the diagnosis of diabetic polyneuropathy?

Screening for neuropathy should be done annually for most diabetics. Any diabetic patient with a painless ulcer can be confirmed to have diabetic polyneuropathy. Simple tests, using 128-Hz tuning fork, cotton wool, 10-g monofilaments, and a patellar hammer, can reveal decrease in pressure or vibratory sensation or altered superficial pain and temperature sensation. Sensory loss due to diabetic polyneuropathy can be assessed using the following techniques:

Pressure perception	The risk of future ulceration can be determined with a 10-gram monofilament
Vibration perception	128-Hz tuning fork placed at the hallux
Discrimination	Pinprick (at the dorsum of the foot without penetrating the skin)
Tactile sensation	Cotton wool (at the dorsum of the foot)
Reflexes	Achilles tendon reflexes

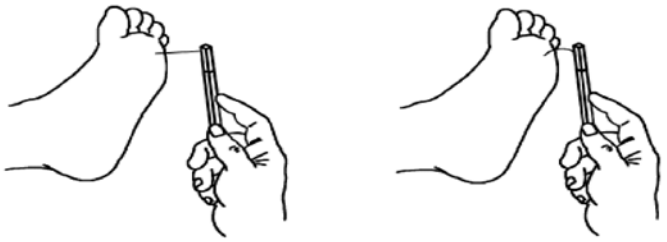
How is the physical examination performed?

- The sensory examination should be done in a quiet and relaxed setting. First apply the tuning fork on the patient's wrists (or elbow, or clavicle) so the patient knows what to expect.
- The patient must not be able to see if and where the examiner applies the tuning fork. The tuning fork is applied on a bony part of the dorsal side of the distal phalanx of the first toe.
- The tuning fork should be applied perpendicularly with a constant pressure.
- Repeat this application twice, but alternate with at least one "sham" application, in which the tuning fork is not vibrating.
- The test is positive if the patient answered correctly for two out of three applications. It is negative ("at risk for ulceration") with two out of three incorrect answers.
- If the patient is unable to sense the vibrations at the big toe, the test is repeated more proximally (malleolus, tibial tuberosity).
- Encourage the patient during testing.

How is touch pressure sensation tested with a monofilament?

A standardized filament is pressed against part of the foot. When the filament bends, its tip is exerting a pressure of 10 grams (therefore this monofilament is often referred to as the 10-gram monofilament). If the patient cannot feel the monofilament at certain specified sites on the foot, he or she has lost enough sensation to be at risk of developing a neuropathic ulcer. The monofilament has the advantage of being cheaper than

a biothesiometer, but to get results that can be compared to others, the monofilament needs to be calibrated to make sure it is exerting a force of 10 grams.



Press until the filament bends.

Advanced testing can be done using a biothesiometer. A probe is applied to a specified part of the foot, usually on the big toe. The probe can be made to vibrate at increasing intensity by turning a dial. The person being tested indicates as soon as he or she can feel the vibration, and the reading on the dial at that point is recorded. The biothesiometer can have a reading from 0 to 50 volts. It is known that the risk of developing a neuropathic ulcer is much higher if a person has a biothesiometer reading greater than 30–40 volts, if the high reading cannot be explained by age.

What are the pharmacological treatment options for painful diabetic neuropathy?

See Chapter 20 on *Management of Postherpetic Neuralgia* for pharmacological analgesic treatment options, since the same principles for treatment of neuropathic pain apply.

What are complimentary approaches in management of painful diabetic neuropathy?

Sometimes the simple things maybe very effective; patients sometimes find out what works for they and may be very inventive. Techniques often reported by patients to be very effective are:

- Immersing the feet in a bucket of cold water
- Placing the feet on a cold cement floor
- Wrapping the feet with a cloth soaked in cold water
- Gentle foot massage
- Electromagnetic nerve stimulation or other local counterirritation (e.g., capsaicin cream)

Pearls of wisdom

- Managing painful diabetic neuropathy continues to be a challenge in developing countries where resources are scarce and access to health care facilities is limited.
- Diabetic patients often have poor follow-up or are seeking treatment at a late stage, when complications associated with neuropathy have already set in.
- On the other hand, primary care physicians may lack adequate knowledge and skills to screen for and treat diabetic neuropathy.
- However, with basic knowledge on diabetic neuropathy and appropriate management of diabetes, and with the help of simple screening tools such as tuning forks and monofilaments, early diagnosis and improved management of diabetic neuropathy are possible.
- Since a diverse range of mechanism cause pain in diabetic neuropathy, treatment principles should include a multifaceted approach aiming at improving glucose control, targeting the underlying pathological factors, and treating the symptoms.
- Painkillers are selected according to the principles of treating neuropathic pain.
- Since pain often has a continuous burning quality, gabapentin or amitriptyline—possibly combined with a weak opioid—are typical choices for pharmacological management of pain.
- The effectiveness of nonpharmacological treatment options should not be underestimated.

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Guide to Pain Management in Low-Resource Settings

Chapter 24
Management of Postherpetic Neuralgia

Maged El-Ansary

Case report

As a general practitioner, you receive a 75-year-old male patient with a history of diabetes mellitus. He has had bronchogenic carcinoma and is currently on chemotherapy. He has pain in the left side of the chest along the distribution of the 5th, 6th, and 7th intercostal nerves. What is your possible diagnosis?

The possibilities are myositis, coronary ischemia, left-sided pleurisy, fractured ribs, itching due to skin allergy or drug eruption or other causes, such as the preeruptive stage of acute herpes zoster.

Why is postherpetic neuralgia difficult to treat?

Postherpetic neuralgia (PHN) is known to be one of the most resistant chronic pain problems. It is classified as a neuropathic pain state. The significance is that the pain is coming from nerve lesions due to viral infections at the site of spinal nerve roots.

Not only pain fibers of the nerve but also sympathetic and tactile fibers, and in rare occasions motor fibers, may be involved in the syndrome. Remember: you can only make a diagnosis if you undress your patient and look at the site of pain.

When is pain after herpes zoster called postherpetic neuralgia?

Most experts agree that pain lasting longer than 3 months after an acute herpes infection ("shingles") should be called postherpetic neuralgia. This has a therapeutic consequence because spontaneous remission of pain becomes more unlikely after this period of time. Therapeutic efforts should be increased if pain lasts longer than a couple of weeks.

Is acute pain a predictor of an outcome of postherpetic neuralgia?

Unfortunately, there are no accepted and validated factors for predicting the severity and duration of pain after herpes infections. Pain may be almost or completely absent in patients who develop PHN. But for the elderly, as pain can start before the skin changes, hemorrhagic efflorescence and a location outside the trunk might indicate a high-risk patient.

Are pain management and antiviral therapy sufficient to treat a patient with herpes zoster?

It is wise to summarize acute herpes zoster as a sign of an alarmingly low level of immunity. It should be known that acute herpes zoster and PHN could indicate a wide range of underlying diseases. In many regions of the world, the first diseases to consider underlying shingles are immune-compromised diseases such as HIV/AIDS and/or malnutrition. Early use of antiviral drugs and pain treatment in the early stages of the acute herpes zoster will have an impact on the course of an acute attack and the possibility of lowering the incidence of

PHN, but there are no evidence-based studies to prove this point.

Diagnosis

Which other conditions must be considered when herpes zoster is diagnosed?

When taking the medical history, the patient's age, sex, and race and certain psychosocial factors will guide you to the proper diagnosis. Different age groups would indicate certain probable causes. One should be aware of other possible causes, which may be present depending on the age group.

Age	Possible Cause
0–18 years	AIDS/HIV, leukemia, Hodgkin's disease, tuberculosis
20–40 years	Steroid therapy, AIDS/HIV, diabetes mellitus, major operations (organ transplant), infection (viral, bacterial, fungal, or parasitic)
60–80 years	Malignant conditions should be the first possibility, and most of the above-mentioned factors could also be present

Sex

Males and females can develop herpes zoster.

Race

Races with darker skin (Indian, African, and Latin American) are more resistant than those with lighter skin (Caucasian). The reason is unknown.

Social and psychological factors

The incidence of shingles is associated with exposure to severe stressful conditions such as war, loss of a job, or the death of close family members.

What symptoms are helpful in diagnosis of shingles and postherpetic neuralgia?

The clinician should know the symptoms of acute herpes zoster and the different stages of disease, which typically are:

- Sharp and jabbing, burning, or deep and aching pain
- Extreme sensitivity to touch and temperature changes (symptoms 1 and 2 could be misdiagnosed as myositis, pleurisy, or ischemic heart disease)
- Itching and numbness (which may be misdiagnosed as skin allergy)
- Headaches (present as a general response to viremia)
- Appearance of red skin areas (2–3 days later)
- The patient cannot tolerate his clothes due to hypersensitivity of the skin (which may be misdiagnosed as urticaria with histamine release)
- Typical painful vesicles (blisters) will appear that are full of serous fluid (3–5 days later)
- Blisters full of pus will break down and start to crust over (2–3 weeks later)
- The crusts will heal and itching stops, but pain persists along the distribution of the nerve (after another 3–4 weeks)

In rare cases the above symptoms will be accompanied by muscle weakness or paralysis if the nerves involved also control muscle movement.

What are the most common nerves affected by herpes zoster?

Trigeminal nerve

Trigeminal neuralgia (all three branches, ophthalmic branch infection: a dendritic ulcer of the cornea may develop as a serious complication, possibly causing corneal opacity).

Cranial nerve VII

With severe tinnitus, the patient complains about hearing loud bells or humming in the head, which may drive some patients to suicide.

Glossopharyngeal nerve

Neuralgia with pain in the throat that increases with swallowing.

Intercostal nerves

Pain starting at the back of the chest wall and shooting along the distribution of the corresponding intercostal nerve, producing a feeling of chest tightness and possibly, if left-sided, confused with myocardial infarction.

Lumbar and sacral plexuses and nerves

Pain in the genital tract (in males and females) may be confused with the diagnosis of genital herpes simplex. However, the fact that PHN is more painful and not usually recurrent like simplex virus should lead to the right diagnosis.

What observations are typically made in the examination of the patient?

Observed signs:

- The skin is discolored, with areas of hyper- and hypopigmentation called "café au lait" skin.

- Severe pain-like electric shock sensations are evoked on gently touching or brushing the affected area of skin with a fine cotton filament or horsehair brush.
- Most of the patients are in a depressed or exhausted state due to lack of sleep.
- The degree of postherpetic scarring of the skin is an indicator of the prognosis of the neuralgia. Severe scarring of the skin is associated with severe nerve destruction (demyelination) and corresponding severe damage of the posterior dorsal horn neurons and nerve root ganglion. Such patients have a higher risk of severe, long-lasting postherpetic neuralgia, which is difficult to treat.

What further investigations could help ensure the correct diagnosis or exclude certain pathologies?

- Full blood screen (screening for signs or evidence of chronic infection, e.g., AIDS/HIV).
- Fasting blood sugar and blood sugar 2 hours after a meal as a screen for diabetes.
- Plain X-ray to screen for bone cancer or fractures.
- CT and MRI if available to screen for soft-tissue malignant masses.
- Coagulation tests, in case invasive therapy is planned.

PHN is a painful condition and may impair the quality of life of affected patients. Can it really become life-threatening?

In the acute stage of herpes zoster, most patients prefer to take off their clothes due to increased touch sensitivity (allodynia) of the skin, which could make them susceptible to pneumonia, especially in the winter season.

A psychological reaction is common in PHN; most patients are elderly and lonely, and they may be suffering from different degrees of depression, which may lead to suicide. Also, the high level of pain might pose a direct threat to the patient due to marked sympathetic stimulation, which can lead to tachycardia or hypertension, or both, and may result in "pain-induced stress." A patient with a comorbidity, such as ischemic heart disease, could be at an increased risk for myocardial or cerebrovascular complications.

Affection of cranial nerve VIII (the vestibulocochlear nerve) may result in severe abnormal sound sensations with subsequent lack of sleep, followed by depression or even suicidal attempts.

Another complication of PHN may be secondary changes of the musculoskeletal system due to the patient's attempts at trying to fix or immobilize the affected body part, such as the shoulder, elbow, wrist, knee joints or fingers. At an older age, long-term immobility of such joints will result in severe painful stiffness. Early and very gentle physiotherapy is highly recommended in such conditions. Another consequence of immobility is disuse atrophy and increased osteoporosis, especially in elderly patients. These patients will be more liable to have bone fractures in response to simple trauma. The highest incidence of bone fractures is to be expected during physiotherapy by an inexperienced physiotherapist.

In conclusion, although herpes zoster and PHN are not considered life-threatening conditions, secondary changes may impair the quality of life, increase morbidity, and may have lethal consequences in some patients. *Therefore the treatment of these pain syndromes involves more than just relieving pain.*

What are the principles of treatment?

The best approach is to prevent herpes zoster infection. A vaccination against herpes zoster was only introduced recently (Zostavax, approved by the U.S. Food and Drug Administration for patients at risk over the age of 60 years) and is not widely available. Therapeutic efforts still have to concentrate on treatment of the acute infection. Unfortunately, even adequate acute treatment does not change the course of PHN, although it does diminish the acute pain and the risk of secondary complications from the herpes zoster infection.

What can be done for patients with herpes zoster infection at an early stage?

With proper and early diagnosis of herpes zoster, antiviral drugs should be used as early as possible, and within 72 hours from appearance of the vesicles, and should be administered to the patient for 5 days. The standard drug is acyclovir at a dose of 200 mg q.i.d. Older patients and those with risk factors but without any indication of generalized infection may additionally receive steroids. Steroids should only be used concomitantly with an antiviral drug to avoid a flare-up of the infection. To avoid dendritic ulcers in ophthalmic

herpes zoster, special ointments of acyclovir should be used locally, if available. In countries with limited resources, acyclovir will be unavailable or unaffordable for most patients, but this does not necessarily mean a worse prognosis regarding PHN compared to patients taking acyclovir.

Antibiotic ointments should be used if secondary infections start to appear. Sometimes, potassium permanganate can be used as topical antiseptic, and calamine lotion for pruritis. A simple and cheap local therapy is the topical application of crushed aspirin tablets mixed either with ether or an antiseptic solution (1000 mg of aspirin mixed in 20 cc of solution).

Another local remedy, which may be repeated, is subcutaneous injection of local anesthetics as a field block in the painful area. All available local anesthetics maybe used, but daily maximum doses have to be observed.

Antiviral, steroids, and topical medications may reduce the symptoms of acute herpes zoster but are often insufficient to control pain. What are the best analgesics to use?

As a general rule in pain management, drugs have to be titrated gradually against pain until effective. Since many of the affected patients are old or have a comorbidity, compromising their general condition, it is advised to "start low and go slow."

Herpes zoster involves inflammation of the tissue around the nerve root. Anti-inflammatory analgesics such as ibuprofen or diclofenac are indicated as drugs of first choice. If there are contraindications, such as steroid medication, dehydration, a history of gastric ulcers, or old age with impaired renal function, paracetamol/acetaminophen (1 g q.i.d.) or dipyrone (at the same dose) is indicated.

If these drugs prove to be inadequate, guidelines for the treatment of neuropathic pain nowadays recommend coanalgesics. If these drugs are not available, opioid analgesics (usually recommended as second-line drugs after the use of coanalgesics) should be used. In herpes zoster pain, it is not necessary to use "strong" opioids, for which there might be governmental restrictions. Tramadol, a weak opioid analgesics, which due to its specific mode of action is not regarded as an opioid in many countries, and is therefore unrestricted, will be sufficient for most patients. Tramadol should be started with 50-mg tablets b.i.d. and may be increased in dose daily by 50–100 mg until sufficient analgesia is achieved. The maximum dose is 150 mg q.i.d., but most patients will do fine with 50–100 mg q.i.d. If slow-release formulations are available, the daily dose has to be divided (b.i.d. to t.i.d.). The typical side effects of nausea and vomiting should be less frequent with the slow-release formulation. Alternatives to tramadol are codeine and dextropropoxyphene.

If I have coanalgesics available, how do I choose the right one for my patient with acute herpes zoster?

Generally speaking, for herpes zoster, coanalgesics should be chosen according to the guidelines published on neuropathic pain, since acute herpes zoster causes mostly neuropathic pain. Therefore, the drug of first choice would be either amitriptyline or gabapentin (or a comparable alternative such as nortriptyline or pregabalin). The decision between a tricyclic antidepressant and an anticonvulsant should be made according to the typical side-effect profile. Patients with liver diseases, reduced general condition, heart arrhythmias, constipation, or glaucoma should receive gabapentin or pregabalin. These are presumably weaker analgesics, but they have the great advantage that no serious side effects are to be expected. Also, no ECG or blood tests have to be performed. Both drug families have their best efficacy against constant burning pain, but they may be insufficient for attacks of shooting or electrical pain. For other drug options, refer to the appropriate chapters in this manual.

I have tried local and systemic therapeutic options, but the patient still has excruciating pain. Are there any other choices?

Unfortunately, there is no "wonder drug" available. If the above therapeutic strategies fail, it might be worthwhile to send the patient to a referral hospital that has dedicated pain therapists. Otherwise, strong opioids would be an alternative, if available. If none of these alternatives apply, guiding the patient with tender loving care and explaining the usual limited time of intense pain are suggested. Never tell a patient that you can't do anything for him.

So, what can an experienced pain therapist or "regular" anesthesiologist offer the patient?

The therapy of choice in such incidences is regional anesthesia using epidural catheters. This technique is usually applied for major surgery or certain surgical

procedures, when no general anesthesia is possible or necessary. These epidural catheters may be inserted at almost all levels (cervical, thoracic, or lumbosacral). If the head or upper neck region is affected, then epidural analgesia will not succeed. There is no evidence that regional anesthesia shortens the course of acute zoster or reduces the chances for PHN. Therefore, such an invasive treatment would only be justified with refractory excruciating pain, in order to control pain for a limited time period until the spontaneous reduction of pain occurs.

Regional sympathetic chain blocks, for example at the stellate ganglion or at the thoracic or lumbar sympathetic chain, are usually only possible as one-time injections, and therefore do not control pain for more than a couple of hours. These techniques have their use in PHN at a specialized pain clinic when there is evidence that the pain is sympathetically maintained.

What to do when the acute herpes zoster has healed and postherpetic neuralgia persists with intolerable pain?

Clinical experience shows that successful treatment of established PHN is difficult. The main reason is the considerable nerve damage present and the unlikelihood that repair mechanisms will restore the nerve roots. Therefore, the patient must be instructed not to have expectations that are too high. The goal of therapy is, therefore not "healing" with complete recovery of the sensory deficit and complete disappearance of pain, but only the reduction of pain, and usually 50% reduction is seen as a "successful treatment."

What drugs should be chosen for postherpetic neuralgia?

In general, the drugs of first choice for PHN are the same as for treatment of pain in acute herpes zoster. Therefore, the first thing to do is to increase the dose of the tricyclic antidepressant (e.g., amitriptyline 25 mg at night) or the anticonvulsant (e.g., gabapentin 100 mg at night) or the weak opioid (e.g., tramadol) in a stepwise fashion, trying to reach the goal of 50% pain reduction. If this is not possible due to side effects, the tricyclic antidepressant or the anticonvulsant should be combined with a weak opioid. The next step would be to try a strong opioid, such as morphine, to replace tramadol, titrating the morphine until pain reduction is achieved. If attacks of pain, such as shooting or electrical pain, occur, gabapentin or pregabalin should be replaced by a sodium-channel-blocking anticonvulsant such as carbamazepine, which often is more successful in this specific type of neuropathic pain.

If the standard drugs are not reducing the pain adequately or cannot be tolerated due to lasting side effects, what options are available, especially with allodynia?

When standard drugs do not reduce the pain adequately, especially with allodynia (pain in response to light touch in the affected dermatome), local topical therapy options should be tried. A very good option would be topical local anesthetics, such as EMLA cream (which might be available from the anesthesia department), which can be very effective if used 3–4 times a day.

Lidocaine patches are small, bandage-like patches that contain the topical pain-relieving medication, lidocaine. The patches, available by prescription, must be applied directly to painful skin to deliver relief for up to 12 hours (preferably at night). Patches containing lidocaine can also be used on the face, taking care to avoid mucus membranes including the eyes, nose, and mouth. The advantage of EMLA cream and lidocaine patches is that the local anesthetic they contain is only absorbed into the bloodstream in very low quantities, therefore avoiding any systemic side effects, but possibly causing local skin irritation.

EMLA cream and lidocaine patches are expensive and are not yet available in most of the developing countries. A cheap and available alternative is the local use of 5% lidocaine jelly. A thin film, spread over the painful area of skin and covered with a fine sheet of polyethylene for 1 hour, effective in most patients. It is important to remove any jelly from the patient's clothes.

What other options would I have, where I have the possibility of referring the patient to a colleague experienced in invasive pain procedures?

Patients with pain unresponsive to systemic drug treatment could receive repeated nerve blocks of the corresponding areas of pain, such as the intercostal nerves. Apart from targeting the peripheral nerves, the epidural or intrathecal space may be used to apply analgesics. Epidural catheters, using, for example, 5 mL bupivacaine 0.125%, morphine 2 mg, and clonidine 35 μg/12 hours, are effective for control of pain. Unfortunately, this catheter technique is not able to reduce pain in the long term. Therefore, after cessation

of the catheter analgesia, the pain usually resumes and remains. Even in major pain management centers, this technique is only used to control acute pain exacerbations, since long-term treatment would imply surgical implantation of a catheter (intrathecally). Implanted catheters need highly specialized care and tend to fail frequently, and therefore they are indicated only in very special circumstances. Most conditions will respond after 3–6 months of treatment.

Another rather simple option is counterirritation of the affected dermatome with transcutaneous electrical nerve stimulation (TENS). With a small and simple device, an electrical current is applied to skin areas with a certain current and frequency, producing a nonpainful dysesthesia. With this treatment, the patient may have short-term or even long-term pain reduction. The mechanism for TENS is the blockade of pain transmission through the nerve fibers responsible for touch (A-beta fibers). Although the mechanism necessary to apply the electrical stimulation is simple, unfortunately TENS devices available on the market are expensive, and therefore should be given to patients on a rental basis. Some patients respond well, and others not, but because TENS is simple and inexpensive, it could be used in developing countries and also by the non-pain specialist, such as a general practitioner. It cannot be used on the head or neck or in pregnant women.

The successful use of TENS helped to develop implantable electrodes for direct stimulation of the spinal cord, for a therapy known as spinal cord stimulation (SCS). Even in high-resource countries this technique is only used in selected patients with PHN. The same applies to cryoanalgesia and radiofrequency. All these techniques are outside the scope of this manual because they are highly sophisticated, very expensive, and require lengthy experience in pain management.

Another simpler option, which might be used by a therapist experienced in block techniques, most likely an anesthesiologist, is ablation of nerves (e.g., the intercostal nerves) by phenol in water (6%) or alcohol (60%). This treatment is effective for prolonged periods of time but is not permanent. Therefore, it is only to be used in cases of PHN associated with cancer where life expectancy is less than 6 months. With careful use of the technique, the complication rate for this patient group can be acceptable. The complication rate depends on the site of ablation.

Pearls of wisdom

- Postherpetic neuralgia is a multifactorial problem.
- Prevention, early diagnosis. and aggressive treatment are of great importance.
- Postherpetic neuralgia is an alarming disease, sometimes hiding a more complicated health problem, and therefore differential diagnosis is crucial. Management of PHN should go hand in hand with a search for other pathology responsible for attenuating the immune-defense system.
- Different modalities are to be used to treat the condition because most of the time no single line of treatment is effective.
- Once PHN is established, it has some complications of its own. These will range from lack of sleep, joint stiffness, secondary infections, and vascular strokes up to suicide attempts. Thus, adequate diagnosis and treatment of acute herpes zoster and postherpetic neuralgia should be expected—and to a certain extent this is possible in most patients—from the caring physician or other health care worker.

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Chapter 25
Central Neuropathic Pain

Maija Haanpää and Aki Hietaharju

Case report 1

Abdul Shamsuddin, a 35-year-old shopkeeper from Gulshan, Dhaka, was found by his wife lying on the floor of his apartment. He was brought into the hospital on a makeshift stretcher carried by four relatives, all saying different things about what had happened. In the emergency room, he was conscious but not able to move his legs or left arm. He was complaining of severe burning pain in his right hand and deep aching pain in both of his upper extremities. The man explained, incoherently, that his house had been entered by a gang of robbers, and the last thing he remembered was a loud gunshot. A lacerated wound 1 cm in diameter was revealed on examination of his neck. Neurological examination showed total loss of sensation below T2. There was severe hyperesthesia, hyperalgesia, and dynamic allodynia as well as impaired cold sensation in the 4th and 5th fingers and on the ulnar side of his right hand. In the left hand, there was mild dynamic allodynia, and hyperalgesia was noticed in the 3rd finger. The patient was able to flex his right arm and lift his hand up against gravity. A radiograph of the cervical spine showed a posterior arch fracture of C7 and a 9-mm bullet lying close to the scapula on the right side. MRI of the cervical spine showed spinal cord contusion extending from the C4 to T2 level. The continuity of the spinal cord was intact, and no signs of hematoma were present.

This case shows that neurological injury and spinal cord pain can occur even if a projectile does not penetrate the spinal canal. Cord contusion was probably the result of the kinetic energy transmitted by the bullet. The patient's pain medication included amitriptyline and gabapentin. Within 4 years, the neuropathic pain started gradually to resolve, and gabapentin was successfully tapered off.

Case report 2

Shabana, an Afghan housewife from Jalalabad in her late thirties, came to a psychiatric outpatient clinic escorted by her husband. She had suffered for more than 2 years from continuous burning pain in her left hand and the right side of her face. She had been referred to the psychiatrist by a general practitioner who, due to Shabana's infertility, had assumed a psychogenic basis as the cause of her pain. History taking revealed that she had had a sudden attack of vertigo, slurred speech, and motor weakness in her left extremities 3 years earlier. She had not consulted her doctor at that time. Most of her symptoms had subsided within 2 days, but the motor weakness had persisted for weeks. She reported that the painful symptoms had appeared about 2 months after this attack. Neurological examination revealed slight clumsiness and ataxia in her left arm, but muscle strength was regarded as normal. A conspicuous decrease in cold and pain sensibility was noticed on her right cheek, and in the lower two-thirds of her left arm as compared to the contralateral side. Cardiac auscultation did not reveal a pathological rhythm or sounds. Due to

lack of resources, brain imaging was not available. Based on the history and clinical findings, a tentative diagnosis of central neuropathic pain due to a low brainstem infarct was made. She was started on amitriptyline and prophylactic acetylsalicylic acid (100 mg/day).

What does "central neuropathic pain" mean?

By definition, neuropathic pain arises as a direct consequence of a lesion or a disease affecting the somatosensory system. In central neuropathic pain, the lesion can be located anywhere in the spinal cord or the brain, affecting the spinothalamocortical pathways (Fig. 1). Therefore, the older concept of "thalamic pain" is incorrect: the lesion may be at any level of the central nervous system (CNS). Musculoskeletal and visceral nociceptive pains are also common in patients with CNS diseases caused by conditions such as spasticity or bladder dysfunction, but these pains are not included in the concept of central neuropathic pain. Acute headaches caused by a stroke or head trauma are not regarded as neuropathic pain, either. They are classified as secondary headaches and are due to distension or irritation of meninges.

What diseases can cause central neuropathic pain?

Possible causes of central neuropathic pain are listed in Table 1.

Table 1
Causes of central neuropathic pain

Spinal Cord	Brain
Trauma	Trauma
Multiple sclerosis	Multiple sclerosis
Vascular lesion (infarction, hemorrhage, arteriovenous malformation)	Vascular lesion (infarction, hemorrhage, arteriovenous malformation)
Infectious diseases (spinal tuberculosis, HIV, syphilitic myelitis, epidural abscesses with spinal cord compression)	Infectious diseases (tuberculomas, cerebral abscesses)
Tumors	Tumors
Subacute combined degeneration of the spinal cord due to vitamin B_{12} deficiency	
Dysraphism	
Syringomyelia	

How common is central neuropathic pain?

The most common brain disease causing central pain is stroke. About 8% of patients who have had a stroke develop central poststroke pain. With an annual incidence of 117–219 per 100,000 in the European population, and 83–329 per 100,000 in the Japanese and Chinese population, stroke represents one of the greatest public health problems worldwide.

The most common cause of spinal cord pain is trauma. About 70% of patients with spinal cord injury are affected with central neuropathic pain. It has been estimated that the annual incidence of spinal cord injury in different countries throughout the world varies from 15 to 40 cases per million.

The prevalence of neuropathic pain is not known in rarer conditions, such as syringomyelia or spinal tuberculosis. Although central neuropathic pain is relatively uncommon, its impact should not be underestimated, because it is difficult to treat and causes disability and suffering to those affected.

What are the clinical characteristics of central neuropathic pain?

A common feature of central neuropathic pain is altered function of the spinothalamic tract, which mediates temperature and pain sensations. Hence, abnormal temperature or pain perception or both is found in sensory testing. Patients usually experience constant spontaneous pain, but they can also have pain paroxysms (brief attacks of pain), evoked pain (pain caused by a stimulus), and allodynia (innocuous stimuli are sensed as painful). Pain may be sensed as deep, superficial, or both. It may be exacerbated by changes in mood, environmental temperature, and physical conditions, and relieved if attention is directed to some interesting issue. Central neuropathic pain is often described as intense, annoying, and exhausting, although it may be mild in some patients. The most common qualities of central pain are burning, pricking, and pressing.

CNS lesions may also cause other neurological symptoms and signs, such as motor paresis, ataxia, abnormal vision, or disturbed bladder function, depending on the location and size. There is no association between pain intensity and the presence or absence of accompanying symptoms, which can be even more disabling than the pain in some patients.

For the diagnosis of central neuropathic pain, the neuroanatomical location of the lesion should be determined (Fig. 1). A lesion in a brain hemisphere causes abnormal findings on the contralateral side of the body. A lesion in the brainstem causes abnormal cranial nerve findings on the ipsilateral side, whereas abnormal findings in the limbs and trunk are due to a contralateral lesion. A lesion in the spinal cord causes abnormal findings below the lesion level.

Central neuropathic pain may be present from the start of the neurological symptoms or appear with a delay of days, months, or even years. In the delayed cases, a repeat neurological examination is mandatory to identify whether it is a new event or a progression of the previous disease (e.g., a new stroke, or syringomyelia with expanding sensory loss after the spinal cord injury). After it appears, central neuropathic pain tends to become chronic, typically continuing for many patients for the rest of their lives.

What is meant by traumatic spinal cord injury?

Various traumas may result in dislocation and fracture of spinal vertebrae and cause spinal cord injury. In advanced countries, road traffic accidents rank highest among the etiological factors for traumatic spinal cord injury. According to an epidemiological study conducted in Haryana, India, the predominant cause of injury was falling from a height (45%), followed by motor vehicle accidents (35%). Other causes of spinal cord trauma include sports injuries and acts of violence, primarily gunshot wounds. In people with asymptomatic cervical spinal stenosis, a fall or a sudden deceleration force can cause a contusion in the cervical cord, even without any bone or joint trauma. Spinal cord injury can be partial, saving some motor or sensory functions or both, or it can be complete, causing paralysis and complete sensory loss below the level of the lesion.

What are the characteristics of central neuropathic pain in spinal cord injury?

Pain following spinal cord injury is divided into below-level pain and at-level pain. The latter is located in a segmental or dermatomal pattern, within two segments above or below the level of spinal cord injury. It may be due to damage of the spinal cord itself or nerve roots. In cases of nerve root damage, the pain may have unilateral predominance. Below-level pain is typically constant, severe, and difficult to treat and represents central deafferentation-type neuropathic pain. If the lesion is partial, the sensory findings may be patchy, whereas in a complete lesion there is total loss of sensation below the level of the injury.

Is all pain neuropathic in patients with spinal cord injury?

Patients with spinal cord injury and central neuropathic pain may often have concomitant nociceptive musculoskeletal pain due to muscle spasms or overuse of the normally functioning parts of the body (e.g., the upper limbs and shoulders in paraparesis). Examples of common visceral nociceptive pains in these patients are pain caused by bowel impaction or distension of the bladder. These symptoms are important to recognize in management of the patient with spinal cord injury.

What is syringomyelia?

Syringomyelia is a cystic cavitation of the central spinal cord, most commonly in the cervical region. It can be developmental, as in Chiari I malformation, or acquired, usually due to traumatic spinal cord injury. It is clinically characterized by segmental sensory loss, which is typically of a dissociated type, in which thermal and pain sensations are lost but tactile and proprioceptive sensations are preserved. Pain in cervical syringomyelia can be located in the hand, shoulder, neck, and thorax, is often predominantly unilateral (ipsilateral to the syrinx), and can be exacerbated by coughing or straining. Autonomic symptoms such as changes in skin temperature or sweating in the painful area can also be present. Pain may be the first symptom, or it may appear after a long delay after the original lesion. Motor weakness may appear with the progression of the disease. Neurosurgical treatment is considered only in cases with recent and quick progression.

What is phantom limb pain?

After traumatic amputation, at least half of patients experience phantom limb pain, which refers to pain experienced in the lost part of the body. It is related

to central reorganization in the cerebrum, which explains the peculiar phenomenon of pain experienced in the missing part of the body. In some patients, phantom limb pain is maintained by stump pain (a peripheral pain at the site of amputation). Phantom limb pain is more likely to occur if the individual has a history of chronic pain before the amputation and is less likely if the amputation is done in childhood.

Phantom pain is often similar to the pain felt before the amputation, and in addition, the patient may experience nonpainful phantom phenomena, such as a twisted leg.

Graded motor imagery and *mirror therapy* are novel and inexpensive approaches that have been shown to reduce pain and disability in patients with phantom limb pain. In graded motor imagery, patients go through three phases. First, they assess images of their limbs in various positions. The second phase consists of imagining moving the limbs in a smooth and painless manner. Finally, patients end up by actually mimicking the movement. In mirror therapy, patients are instructed to use the mirror in such a way that the reflected image of the intact limb seems to appear in the place of the amputated or affected extremity. The mirror image produces an illusion of two "healthy" limbs, and movement of the healthy limb may ameliorate the phantom limb pain. Both of these therapies aim at activation of cortical networks that subserve the affected limb.

What is the definition of central poststroke pain?

All neuropathic pain directly caused by cerebrovascular lesion (i.e. infarct or hemorrhage), independent of where the lesion is located, is called central poststroke pain. It was previously called thalamic pain according to the typical location of the lesion, but it can also be due to cortical (parietal cortex), subcortical, internal capsule (posterior limb), or brainstem lesion.

What are the clinical features of central poststroke pain?

In the majority of patients, central poststroke pain is a contralateral hemi-pain, not always including the face, but it may also be restricted to part of the upper or lower extremity. The most common pain quality is burning pain, but aching, pricking, and lacerating pain is also common. Central poststroke pain is most often constant and spontaneous, but in rare cases it may be paroxysmal and allodynic (i.e., evoked by touch, thermal sensation, or emotions). Hyperesthesia is a common finding in sensory examination. In a hemisphere lesion, there is abnormal sensation on the contralateral side of the face, trunk, and limbs, and accompanying motor paresis if the pyramidal tract is affected. In a low brainstem lesion, there is a crossed pattern in the sensory changes: they are located ipsilaterally in the face and contralaterally in the trunk and limbs due to damage of the ipsilateral trigeminal sensory nucleus and the crossed spinothalamic tract, respectively.

Is all pain neuropathic in patients who have had a stroke?

Nociceptive pain is also very common in patients who have had a cerebrovascular lesion. It most often affects the shoulder and is related to changed dynamics due to motor weakness on the affected side. Possible causes are subluxation of the glenohumeral joint, rotator cuff tear, soft tissue injury due to inappropriate handling of the patient, and spasticity of the shoulder muscles.

What are the characteristics of central pain after traumatic brain injury?

Traumatic brain injury occurs when a sudden, blunt, or penetrating trauma causes brain damage. The prevalence of central pain in patients with traumatic brain injury is not known. Chronic pain in these patients is almost exclusively unilateral, and the most common qualities are pricking, throbbing, and burning. A curious feature is the manifestation of pain in body regions that are not associated with local or spinal injury. These painful regions exhibit very high rates of pathologically evoked pain (allodynia and hyperpathia). The most frequently reported painful body regions are the knee area, shoulders, and feet. Neuronal hyperexcitability has been suggested as a contributing factor to the chronic pain. Treatment of central pain in patients with traumatic brain injury is challenging, because most of these patients are also suffering from cognitive deficits and emotional distress, and neuropathic pain may overlap with pain of psychogenic origin.

How can I diagnose central neuropathic pain?

The cornerstones of the diagnosis are a detailed history of development of symptoms and relieving and aggravating factors, and a careful neurological examination including sensory testing to touch, pinprick, cold, warmth, and vibration. Abnormal sensory findings suggest the possibility of neuropathic pain, and other neurological findings help to localize the site of the lesion. It is important to keep in mind that the region of sensory abnormalities may be larger than the painful region (Case 2). Diagnosing central neuropathic pain is actually identifying symptoms and neurological signs compatible with a lesion in the CNS, and excluding other possible causes of pain. Typical neurological findings referring to a central neurological lesion are a positive Babinski sign, accelerated tendon reflexes, and spasticity. Other possible causes of pain need to be excluded with reasonable certainty. Careful clinical examination is usually sufficient for this process, such as diagnosing musculoskeletal pain or pain due to local infection.

Diagnostic studies, such as neuroimaging and cerebrospinal fluid analysis, may provide useful information in reaching an accurate diagnosis, but they may not be available. In such conditions, recognition of the clinical features of the causative diseases is very useful. The decision as to the use of limited resources and selection of patients for referral is based on the possibilities of treatment of the causative disease, such as with neurosurgery. Spinal and cerebral abscesses, spinal traumas with partial cord lesion, and spinal tumors are examples of conditions with radically improved prognosis with active surgical treatment. Cerebral abscess should be suspected if a patient has fever and progressive neurological symptoms (in cerebral abscess contralateral symptoms, and in spinal abscess sensory and motor deterioration below the level of the abscess).

History of trauma before the onset of weakness of the limbs and sensory changes, including central pain, is suggestive of partial cord lesion. If there is an unstable lesion of the vertebral column, quick stabilizing surgery may prevent complete paralysis, and the same is true with laminectomies in spinal contusion with partial paresis. Slowly progressive paraparesis and sensory changes may be caused by a spinal tumor. Removal of the tumor may prevent paralysis. The final prognosis depends on the histology of the tumour and the severity of the symptoms before surgery. Treatable intracranial hematomas usually present with headache and progressive neurological symptoms, but central neuropathic pain is an uncommon symptom in these cases.

How should the patient be treated?

Treatment consists of:

- Treatment of the causative disease, when possible (e.g., medical and surgical treatment of epidural abscesses causing spinal cord compression).
- Secondary prevention (e.g., commencing acetylsalicylic acid prophylaxis for atherothrombotic cerebral infarct, or treating endocarditis in a patient with embolus from an infected cardiac valve).
- Symptomatic relief of the neuropathic pain.
- Treatment of other concomitant sources of pain such as spasticity, which may exacerbate central neuropathic pain.

The first line of therapy, after a thorough assessment, is information and education, for both the patient and the family. For example, phantom limb pain is difficult to understand for a layman. The doctor's explanation in this situation may be very helpful ("your father is not crazy having pain where he has lost a limb"). The character of the pain, the disease causing it, and the possibilities for pain relief need to be explained to the patient and the family. As symptomatic treatment of central neuropathic pain is less successful than treatment of peripheral neuropathic pain, giving thorough information may be the best way to help the patient.

Similarly to peripheral neuropathic pain, antidepressants and anticonvulsants are used for symptomatic treatment of central neuropathic pain. Amitriptyline is the drug of choice for central poststroke pain. It is started with 10–25 mg in the evening, and the dose is escalated by 10–25 mg steps to 50–150 mg/day depending on the extent of side effects. Difficulties in urination, constipation, dry mouth, and dizziness are typical side effects, which may prevent further dose escalation. Arrhythmias caused by amitriptyline contraindicate its further use. If amitriptyline is intolerable or ineffective, carbamazepine can be tried instead. It is started at 100 mg b.i.d., and the dose is escalated in 100-mg steps over several days until 400–800 mg/day is reached. If side effects (dizziness, headache, ataxia, or nystagmus) appear, the dose should be reduced.

Pregabalin has been shown effective for spinal cord injury pain, but it is not available in every country.

Gabapentin has the same mechanism of action and can be used instead. It is started with 300 mg in the evening, and the dose is escalated in steps of 300 mg daily or every other day. The daily dose is divided into three doses. The effective dose is 900–3600 mg/day, divided into three daily doses. Gabapentin has no pharmacokinetic interactions. It can be tried also for central poststroke pain if amitriptyline and carbamazepine fail.

Central neuropathic pain is unfortunately quite refractory to treatment, and pain relief is usually only partial. Based on information from open studies and clinical experience, transcutaneous electrical nerve stimulation (TENS) can be helpful for central pain in cases where there is well-preserved sensibility to vibration and touch.

What is the prognosis of central neuropathic pain?

The natural course of central pain is not known exactly. Resolution of pain has been reported in 20% of patients with central poststroke pain, occurring over a period of years. It is still not known whether treatment of the pain has any modifying effect on the duration of central neuropathic pain.

Pearls of wisdom

- Central neuropathic pain may be present from the start of the neurological symptoms or may appear after a delay of days, months, or even years.
- The most common qualities of central pain are burning, pricking, and pressing.
- Remember that nearly all patients with central neuropathic pain have abnormalities of pain and temperature sensation.
- Amitriptyline, carbamazepine, and gabapentin can be used for symptomatic treatment.

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Guide to Pain Management in Low-Resource Settings

Chapter 26
The Management of Pain in Adults and Children Living with HIV/AIDS

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What is the scope of the problem?

In 2007, UNAIDS estimated that 33.2 million people were infected with HIV. Most of the HIV-infected men, women, and children resided in sub-Saharan Africa. Globally, 2 million children under the age of 15 are living with HIV. Even though antiretroviral therapy is becoming increasingly available in resource-poor settings, many HIV-infected people, including children, do not know their status and may never have access to treatment and care. Although huge strides have been made to make HIV/AIDS a chronic manageable condition, little is done to address the issues of pain caused by HIV disease, by concomitant opportunistic infections, or by HIV-associated cancers or as a result of side effects of antiretroviral therapy. Pain in HIV/AIDS is highly prevalent, has varied syndromal presentation, can result from two to three sources at a time, is underestimated by doctors, and has the potential to be poorly managed. In South Africa, the prevalence of neuropathic pain in AIDS patients prior to antiretroviral treatment was 62.1%, with men significantly more likely to experience pain than women.

What are the principles for successful management of pain?

Five principles are fundamental to the successful management of pain symptoms:

1) Taking the symptom seriously.
2) Conducting an adequate assessment.
3) Making an appropriate diagnosis.
4) Implementing treatment.
5) Evaluating pain management.

The best approach to treating pain in HIV/AIDS is multimodal: pharmacological, psychotherapeutic, cognitive-behavioral, anesthetic, neurosurgical, and rehabilitative. Therapy should begin according to the World Health Organization (WHO) ladder, with a nonopioid such as paracetamol (acetaminophen). Opioids should be the first-line therapy for moderate to severe pain. Nonsteroidal anti-inflammatory drugs (NSAIDs), adjuvants (tricyclic antidepressants and anticonvulsants), and nonpharmacological modalities may be important supplements to effective analgesia. NSAIDs use in HIV infection could exacerbate bone marrow disease and worsen gastrointestinal effects seen with HIV or with antiretrovirals. Continuous use of long-acting opioids is the treatment of choice in chronic pain. The WHO analgesic ladder is a stepwise approach to pain management that was developed to manage pain (particularly cancer pain) in a consistent manner and can be applied to all cases of pain management.

Case report 1 ("pain in infants")

Flavia is a 4-month-old HIV-infected female who is referred by the local hospital with a CD4 of 15% (absolute value 489) for enrolment into an antiretroviral treatment

program. She has a history of a single episode of bronchopneumonia, for which she was hospitalized and received intravenous antibiotics at the age of 2 months. She has no known tuberculosis (TB) contacts, and a tuberculin skin test done in the ward was nonreactive. Her mother complains that she is "weak," is not drinking well, and has had persistent sores in her mouth for more than 2 months despite treatment with oral Mycostatin drops. On examination she is 79% of her expected weight for her age, with generalized lymphadenopathy, severe oral candidiasis extending into her pharynx, and a 3-cm hepatomegaly.

Should we be bothered about procedural pain in HIV-infected children?

Children infected with HIV experience frequent needle pricks for procedures such as venipuncture to obtain blood samples, intravenous insertion, injection of medication, or immunizations. Children who are hospitalized may experience nasogastric tube insertion, lumbar punctures, and bone marrow aspirates. Painless, but anxiety-provoking procedures such as CT scans, X-rays, or magnetic resonance imaging can also cause distress. A study by Stafford (1991) found that 22 children with HIV experienced a total of 139 painful procedures in 1 year. The management of procedural pain should be considered by doctors and nurses who look after HIV-infected children both for outpatient and in-hospital facilities. Children should be provided with a multicomponent package, based on cognitive-behavioral therapy, that teaches effective coping skills and could include: preparation, rehearsal, breathing exercises for relaxation and distraction, positive reinforcement, and pharmacological approaches.

Should parents be asked to leave the room when a HIV-infected child undergoes a procedure?

Though children tend to display more behavioral distress when a parent is present, children prefer to have their parents present and may experience less subjective distress. In addition, parents generally prefer to be to be present when their children undergo a medical procedure. The parent can encourage and coach the child and reinforce coping strategies.

How do we assess pain in HIV-infected children?

It is important to define the characteristics of the pain: How intense is it, what is the quality, where is it distributed, and what triggers it? It is necessary to look at the developmental level of the child, and to encourage parent and child communication on pain (see the chapter on pain management in children). The history and examination should attempt to delineate the area where pain is occurring. Children may complain about having pain "all over" and may not be able to tell health care workers the exact location of the pain. Training parents and caregivers to observe their children may provide helpful insights into the origin, severity, and nature of the pain. It is very important to treat the underlying cause of the pain in addition to prescribing analgesia. If the pain is treatment related, the drug causing the pain should be switched (e.g., antivirals ddI or D4T for peripheral neuropathies), and an alternate drug used. If the pain is due to an underlying infectious disease, part of the pain management should be to treat the underlying infection.

What treatment can we prescribe for HIV-infected children who are in pain?

The cause of the pain needs to be established. The health care worker can initiate pain relief with paracetamol (acetaminophen) (30 mg/kg every 4–6 hours). Therapy should be given regularly, *not* "as necessary." If this regimen does not relieve the pain, codeine phosphate can be added to the paracetamol and given every 4–6 hours. The next step is morphine 0.4 mg/kg orally or 0.2 mg/kg i.v. every 4 hours, which can be increased by 50% or more with each subsequent dose until pain is controlled. Once pain control has been achieved, the total daily amount of soluble morphine is divided into 12-hourly doses and given as long-acting morphine sulfate in a controlled-release form. Neither addiction nor respiratory depression is a significant problem when morphine is used to produce analgesia. A side effect of morphine is constipation. Drowsiness and itching can occur initially on initiation of morphine.

How can painful oral lesions be managed?

Symptomatic relief for stomatitis and other painful oral lesions can be achieved by avoiding irritating food like orange juice, by using a straw to bypass the oral lesions, and by giving cold food, ice cubes, and popsicles. Topical medications such as lidocaine 2% (20 mg/mL) can be used before meals, applied directly to the lesions in older children to a maximum of 3 mg/kg/day (not to be repeated within 2 hours).

Table 1
Causes of pain in HIV-infected children

Pain in the oral cavity If the pain is bad, the child may stop eating and drinking. In babies, there may be drooling.	Oropharyngeal candidiasis, dental caries, gingivitis, aphthous ulcers, herpetic stomatitis
Pain related to infections in the esophagus The cause and diagnosis of pain in the esophagus may be very hard to determine. Immunosuppressed children with oral candidiasis may have esophageal candidiasis as well. Older children may complain of heartburn or pain during swallowing.	Candida, cytomegalovirus, herpes simplex, and mycobacterial esophagitis
Pain in the abdomen Pain in the abdomen could be constant or intermittent, dull or sharp. The pain may occur after eating or when the stomach is empty. There may be associated diarrhea and vomiting along with the pain	Infectious gastroenteritis, pancreatitis, hepatitis, or infrequently, gastrointestinal lymphoma
Pain in the nerves and/or muscles HIV can cause muscle pain or joint pain. HIV encephalopathy can be accompanied by hypertonicity or spasticity. Certain antiretroviral medications such as D4T can cause peripheral neuropathy.	Hypertonicity/spasticity, peripheral neuropathies, headache, myelopathy, myopathy, herpes zoster, and postherpetic neuralgia
Pain due to procedures Much of the pain from procedures can be minimized.	Venipuncture, tuberculin skin testing, lumbar puncture, bone marrow aspirates, intravenous infusions, nasogastric tube insertions, immunizations
Pain due to side effects of treatment	Peripheral neuropathies, pancreatitis, renal stones, myopathy, headache

*Adapted from Children's Hope Foundation. Pain assessment and management of pediatric HIV infection. Pediatric HIV/AIDS Training Module; 1997.

How can we manage procedural pain in HIV-infected children?

Establishing a diagnosis is critical. The underlying cause should be treated in addition to the administration of analgesia. For procedural pain a multicomponent intervention is recommended (see Table 2).

Do children experience pain from antiretroviral medications?

Many of the antiretrovirals, especially the protease inhibitors, cause abdominal discomfort, nausea, and diarrhea. Headaches, pancreatitis, and peripheral neuropathies are other common side effects of treatment. It is

Table 2
Multicomponent intervention for procedural pain management

Intervention	Procedure
1) Preparation	Provide detailed information on the events that will follow. Rehearse what is going to happen. Tailor the level of information depending on the developmental level of the child.
2) Relaxation and distraction	Promote relaxation through the use of breathing exercises. Could use aids like blowing bubbles. Children who are taught a specific technique such as breathing exercises believe they have more control over a painful situation, which improves pain tolerance.
3) Reinforcement	Mostly in the form of verbal praise, stickers, badges, sweets, or small toys that reward and encourage children to attempt to comply, e.g., by sitting still. Such reinforcement provides an incentive for engaging in coping behaviors.
4) Pharmacological approach	Applying EMLA (eutectic mixture of local anesthetics) cream and increasing the role of parents during procedures can reduce distress and pain. Apply EMLA 1 hour before the procedure and cover with an airtight bandage. Parents play an important role in efforts to promote children's coping during painful procedures.

*Adapted from Schiff et al. 2001.

important to look at the package inserts of the antiretroviral drugs that are being prescribed to assess side effects and drug interactions.

What is the most likely cause of swallowing disorder, and how can you manage it?

Esophageal candidiasis is the most likely diagnosis and should be suspected on the basis of a history of difficulty in feeding and the presence of extensive thrush into the oropharynx.

While mild oral candidiasis may respond well to topical therapy, the efficacy of Mycostatin drops is largely dependent on the length of time that the medication remains in contact with the lesions. It is important to explain to mothers that they need to try and remove the thick plaques that form and then apply the drops directly to the lesions (giving the drops as one would give a syrup). Allowing the baby to swallow it quickly will prove ineffective. This procedure should be repeated at least 4 times per day. Alternatively, one could prescribe a gel formulation like Daktarin oral gel, which will adhere to the affected areas.

Severe oral candidiasis and esophageal candidiasis will not respond to topical therapy. This is often a severely painful condition, and it is often present in infants and toddlers, causing loss of appetite or difficulty in feeding. Systemic therapy is required, and the first-line drug of choice is fluconazole. The decision needs to be made whether the child will need to receive fluco needs to nazole intravenously, thus requiring hospital admission and possible separation from her mother, or whether the child can tolerate it orally. A child who is still taking in some oral feeds will often be able to tolerate treatment orally. Of course, esophageal candidiasis is a CDC (Centers for Disease Control and Prevention) category C ("severely symptomatic") diagnosis, and highly active antiretroviral therapy (HAART) is also an important part of the treatment.

As mentioned above, this condition can be extremely painful, and analgesia should also be prescribed for this patient. According to the WHO analgesic ladder, one could begin with oral paracetamol (acetaminophen) syrup if the patient is able to take oral medication or else paracetamol suppositories. This drug can be safely and easily administered 6-hourly in children. It is often useful to advise the mothers to try to give the dose 30 minutes before a scheduled feed so that the maximum efficacy is reached at the feed time, reducing pain on swallowing. If this therapy proves inadequate, the next step would be an NSAID, for example diclofenac suppositories, but children who are in this amount of pain will most likely need admission for intravenous (i.v.) fluids and parenteral analgesia in addition to i.v. fluconazole.

One week later, the mother reports that that her child shows weakness, but the oral sores have resolved and there are no new complaints. The child's baseline blood work reveals no contraindications to antiretroviral therapy, so she is started on stavudine, lamivudine, and lopinavir/ritonavir.

Case report 1 (cont.)

Four weeks after initiating HAART, the mother complains that her baby has developed a lump under her right arm but is otherwise well. Examination reveals a 4-cm mobile mass in her right axilla. The baby is clearly miserable and cries on examination of the lesion. A new workup to exclude TB is started, but a working diagnosis of BCG-related immune reconstitution inflammatory syndrome (IRIS) is made.

The TB workup proves negative, so a decision is made to await the results of specimen culture before considering TB treatment. The node continues to enlarge, causing further discomfort to the baby, and eventually it becomes red, hot, and fluctuant. The child is referred to the pediatric surgery department for incision and drainage of the node, and a course of oral prednisone is started. The surgeons then duly perform an incision and drainage (I&D) in the outpatient department. The baby is sedated with valerian syrup and is also given a dose of paracetamol (acetaminophen) prior to the procedure. Six-hourly paracetamol is prescribed for analgesia at home.

The node improves, somewhat, following I&D and prednisone, but two new areas of fluctuation develop later on. The lesions are aspirated in the consulting rooms under the same sedation and analgesia as before. The results of the sputum test and fine needle aspiration (FNA) finally show that the sputum is negative for TB, and the FNA reveals Mycobacterium bovis as the causative agent. No TB treatment is started, HAART is continued, and the baby receives a total of 6 weeks of prednisone. No further procedures are required, and the node improves slowly over time, with resolution after 1 year of HAART.

What other options were available for manag the initial axillary abscess?

1) Conservative. This is not an advisable option as the pus will need to be drained, and if a controlled

drainage procedure is not undertaken, a poorly healing sinus or fistula may develop. Also not addressed, is that the abscesses are extremely painful, particularly in an area such as the axilla, which will be manipulated during dressing, transportation, and so on. Relief of the pressure is in itself an effective pain management procedure.

2) Aspiration. Small abscesses can be aspirated with ease with minimal pain to the child. This process allows the pus to be drained to the surface and prevents sinus formation as well as relieving the pain of the abscess itself. Unfortunately, inadequately aspirated abscesses often recur with resultant recurrence of pain. It is difficult to adequately aspirate large abscesses, particularly those which have been present long enough to begin develop into separate locations.

3) Incision and drainage (I&D) under general anesthesia. In some cases this method is preferable to the outpatient procedures for children as the pain of the procedure is completely dealt with by the anesthetic. It allows the abscess to be completely drained and to ensure that all septae are broken for good drainage. On the other hand, general anesthesia requires that the child be separated from her mother, admitted to hospital, and exposed to an unfamiliar and scary operating room. And, of course, the postoperative pain still has to be managed, just as for the outpatient procedure.

Case report 2 ("psychological pain due to recurrent procedures")

Edith is a 2½-year-old girl who has been attending the antiretroviral clinic since she was 6 weeks of age. She was started on HAART at 12 weeks of age and was seen monthly for the first year of her life. Blood samples were taken every 3 months. Since she was 6 months old, the necessary blood samples have been taken from her external jugular vein, which involved her being held supine on an examination bed with her neck slightly extended over the edge of the bed while her hands were held by a nurse to prevent her from trying to pull the needle out. Her mother has a fear of needles and couldn't bear the sight of the doctors inserting a needle into her baby's neck, so she would always place the baby on the examination bed in the care of the nurse ready for the blood drawing and then leave the room until the procedure was complete, when she would be called back in. Two years later, it now takes two nurses to hold her down firmly enough to make phlebotomy safe for her, with the doctor performing the procedure. As soon as she is supine, she begins to gag until she induces vomiting and brings up her breakfast all over the clinic floor, making the procedure exceedingly challenging for the staff.

What are some possible things that could have been done to have prevented this state of affairs?

While it is often traumatic for parents to watch blood being drawn from their child, it is more often more traumatic for the child to face the procedure alone feeling abandoned by their mother, whom they trust to protect them from pain. It is therefore advisable to encourage parents to remain in the room and speak words of comfort to their child during the procedure (they do not necessarily need to watch the procedure). Also, parents or caregivers should be encouraged to explain why the blood has to be taken as far as the child can understand. They should also be encouraged not to mislead their children and promise that no blood will be taken. Parents should be discouraged from "villainizing" the staff performing the procedure. It is often the natural instinct of mothers in particular to vindicate their child's pain by promising them that they will hit the doctor or, as one patient's mother promised, report them to the police! This behavior serves to increase the child's fear of the staff and makes the child begin to doubt their mother's word or ability to offer the protection promised.

What can be done in future to alleviate the situation?

The multicomponent approach described in Table 2 should be introduced. EMLA should be used in an attempt to reduce pain. As soon as the child is old enough to make brachial vein blood sampling as easy as external jugular vein sampling, this option should be adopted. The child will be able to remain on her mother's lap with her mother's loving arms as her unforced restraints. Offering some form of comforting compensation like a chewy sweet or lollipop will often stop the tears or at least attenuate the trauma of the procedure with some positive association.

Case report 3 ("pain due to opportunistic infection with exacerbating psychosocial factors")

Abigail is a 12-year-old girl who is brought to the clinic having just been diagnosed with HIV. Her parents died 2 years ago from AIDS-related illnesses, and her maternal aunts have been caring for her since then. When they

saw that she was losing weight rapidly over a period of a few months, they decided she needed to be tested for HIV as well. At the local clinic Abigail and her aunt had pre-test counseling together as it was felt she was mature enough to understand the implications of the test and to give consent herself. When the results were available they were given to Abigail alone without her aunt present. No post-test counseling was done, and Abigail was simply told that she needed to go to the clinic as she was HIV positive and needed treatment.

At the first visit, Abigail, is clearly disturbed by the diagnosis. She is a bright child who obviously understands the meaning of the diagnosis and is hence somewhat reserved and noticeably scared—worried about her future, scared of rejection, her whole life upturned. She has had a chronic cough for more than 4 weeks and is wasted, listless, and in respiratory distress, with a temperature of 40°C. A chest X-ray reveals a bilateral patchy infiltrate. She clearly requires hospital admission but is reluctant as she is afraid of leaving the care of her aunts and of being abandoned in the hospital. Her aunts reassure her of their love, and the doctor assures her that it is necessary and in her best interest, and she finally agrees.

She is admitted with a diagnosis of community-acquired pneumonia and is started on intravenous antibiotics. Her CD4 count is 4. On admission it is also noted that she has severe abdominal pain. The ward doctors note that the pain is generalized, with some apparent rebound tenderness, and order an abdominal X-ray and serum lipase level. They start her on tilidine drops (an oral opioid analgesic) to be given 6-hourly. Investigations prove normal, but her tenderness does not seem to improve. In the meantime, her condition appears to be worsening. She appears weaker and more tired than ever.

Due to her deteriorating condition, Abigail is seen by a palliative care specialist. She recommends that the tilidine be changed to paracetamol (acetaminophen) and codeine (a weak opioid with much less sedative effect.) She also arranges for Abigail to be seen by her team's psychologist when she is more lucid. In the meantime her temperature and symptoms are still not controlled, despite various different intravenous antibiotics including tazobactam, amikacin, and even imipenem. Sputum results are delayed due to a backlog at the laboratory, and the cause for abdominal tenderness still has not been found. An abdominal ultrasound is ordered, which shows splenic microabscesses. She is diagnosed with disseminated TB and started on TB treatment. Three days later, her temperature has settled, her constitutional symptoms have improved, her abdominal pain is much better, and she is back to her usual self and able to be discharged home.

What are some possible contributing factors to her pain?

1) Intra-abdominal pathology: splenic tuberculosis. It is also likely that with splenic involvement, there was also further lymphatic involvement. Tuberculosis of the mesenteric lymph nodes could cause partial bowel obstruction, resulting in the signs of peritonitis found on examination.

2) "Referred" pain. After 4 weeks of coughing and in the face of disease-induced malnutrition, the patient's diaphragm and accessory respiratory muscles have been sorely overexerted. Her abdomen may be tender due to the prolonged muscular strain.

3) "Psychological" pain. Children, particularly younger children, often present with generalized or nonspecific abdominal pain without any apparent pathology. The pain may often simply be a sign of emotional distress (although, of course, physical pathology must first be excluded). Caution must be exercised to differentiate real pain and peritonism from psychological pain. Often by distracting the patient with conversation and questions or, for younger children, toys or mobiles, you will be able to elicit whether or not the pain is real. Real pain will cause a grimace and even an interruption in the conversation. Peritonism will result in obvious rebound tenderness in spite of the distraction. Purely psychological pain (or even feigned pain) will result in no obvious signs of tenderness during the examination while the child is distracted.

What are some possible reasons for the deterioration in the patient's condition?

1) Incorrect diagnosis with worsening of her opportunistic infection. This child had several symptoms that should have alerted the clinicians to the strong possibility of tuberculosis. She had a chronic productive cough, an unresponsive fever, and significant weight loss with suspicious chest radiograph changes. With a CD4 count of 4, the likelihood of TB and especially disseminated TB was very strong.

2) New nosocomial (i.e., hospital-acquired) infection. While this is often the cause of deterioration in severely immunocompromised in-hospital patients, it was unlikely in view of the lack of positive specimen

cultures and lack of response to potent intravenous antibiotic therapy.

3) Psychological pain. Loss of the will to continue fighting and resignation to the possibility of death. The loss of both parents, the tragic way she received her diagnosis, and the lateness of her presentation, together with her severe ill health and opportunistic infection, comprise a daunting load for a young psyche. The temptation to give up hope must certainly be strong. The need for a strong, loving family support system with external psychosocial intervention is crucial. Fortunately, Abigail has very loving aunts who visited her daily and caring school friends who sent cards and gifts during her hospital stay. The palliative care psychologist was also able to counsel and encourage her and her family and provide them with the extra care they needed at this difficult time.

4) Drug side effects. Tilidine is a strong opioid. Opioid analgesics are known to cause sedation and mood changes (euphoria or dysphoria.) Tilidine itself can also cause dizziness, drowsiness, and confusion. According to the WHO analgesic ladder, strong opioids should be reserved for pain that does not respond to less strong analgesia. They should not be used as a first-line analgesic, except postoperatively or where clear pathology requiring strong analgesia is required, such as pancreatitis.

How to manage pain in HIV-infected adults

The pain syndromes seen in HIV-infected adults may be directly related to HIV infection, immunosuppression, or HIV therapy. Pain can be divided into two categories: nociceptive or neuropathic. The most common syndromes reported in HIV-positive adults include painful peripheral neuropathies, as well as pain caused by extensive Kaposi's sarcoma, headache, oral and pharyngeal pain, abdominal pain, chest pain, arthralgias and myalgias, and painful dermatological conditions.

Are the principles of pain management different in HIV?

The principles of pain management in HIV are similar to those in other medically ill patients. At each visit, both in the outpatient and inpatient facility, it is useful to take "pain vital signs" to assess the degree of pain and the response to the current analgesic program (also see the Brief Pain Inventory).

- Ask patients if they have experienced pain in the last week.
- Ask them to describe the intensity of pain: mild, moderate, or severe.
- Ask them to tell you what it feels like: burning, shooting, dull, or sharp.
- Find out what makes it better or worse.
- Ask them to rate the pain (at its worst and at its best) on a 0–10 numerical scale.
- Ask them to rate their quality of life on a 0–10 scale.
- Ask about sadness, fatigue, and depression.

After obtaining the history, a careful medical examination will help elucidate the causative factors. The baseline assessment can be used as an indicator as to whether the analgesia is effective or not.

Do women with HIV infection have more pain?

Women experience pain differently from men due to biological, psychological, and social factors. Men and women respond differently to pharmacological and nonpharmacological treatments. Women with pain are often underdiagnosed and undertreated. They may not have the information or education to understand that their painful conditions may be part of HIV disease. Culture also influences pain experience.

Table 3
Common sources of pain in HIV/AIDS

Cutaneous/Oral	Visceral	Deep Somatic	Neurological/Headache
Kaposi's sarcoma Oral cavity pain Herpes zoster Oral/esophageal candidiasis	Tumors Gastritis Pancreatitis Infection Biliary tract disorders	Rheumatological disease Back pain Myopathies	Headaches: HIV-related (encephalitis, meningitis, etc.) Headaches: HIV-unrelated (tension, migraine) Iatrogenic (zidovudine-related) Peripheral neuropathy Herpes neuritis Neuropathies associated with ddI, D4T toxicities, alcohol, nutritional deficiencies.

*Modified from Carr DB. Pain in HIV/AIDS: a major health problem. IASP/EFIC (press release). Available at www.iasp-pain-org.

Case report 4 ("postherpetic neuralgia")

A 44-year-old HIV-positive man, compliant and stable on antiretroviral therapy for 3 years, complains of sudden-onset fatigue and severe pain in his left shoulder. He describes the pain as the worst pain he has ever felt, with a burning quality, waking him up from his sleep, worse with movement of the left shoulder, causing him to break out into a sweat and incapacitating him. He has no history of trauma. He recalls experiencing a mild flu-like illness 1 week ago. His daughter was ill recently with chicken pox. On examination of the skin, two vesicles are found at the tip of the left shoulder, and the pain extends unilaterally in a dermatomal distribution. Oral valacyclovir, a combination paracetamol (acetaminophen)-codeine tablet, and ibuprofen, were initiated.

What treatments may be used to alleviate the pain and itchiness of zoster rash?

This condition is extremely painful, and analgesic use should be liberal. Topical calamine lotion and water dressings may help relieve the itchiness. Paracetamol, ibuprofen, and dihydrocodeine will be necessary as well. Secondary infection of the blisters may occur and may exacerbate pain, and so should be treated with antibiotics and a topical agent such as chloramphenicol, tetracycline, or gentian violet. There is some evidence that corticosteroid use with acyclovir decreases acute pain, but steroids should be used with caution, especially in immune-compromised patients.

How can one manage the pain of postherpetic neuralgia?

Amitryptiline and carbamazepine should be considered for postherpetic neuralgia. Carbamazepine has drug interactions with antiretrovirals and should be used with caution. Consider the use of pregabalin, a new drug in the anticonvulsant class, for postherpetic neuralgia patients who are not responding to tricyclic antidepressants, gabapentin, and other analgesics. The initial dose of pregabalin is 75 mg b.i.d., but the dose may be increased to 150 mg b.i.d. after three days. Pregabalin would require dose adjustment if creatinine clearance is below 60 mL/min. Dizziness and somnolence has been reported frequently with pregabalin, and we suggest care when coadministering the drug with efavirenz, which has similar side effects in the initial weeks of treatment.

What complications of zoster are more common in immune-compromised individuals?

Extensive skin involvement, disseminated disease, pneumonitis, ocular involvement, meningoencephalitis, myelitis, and involvement of cranial nerves have been described.

Case report 5 ("cryptococcal meningitis")

An 18-year-old, pregnant, HIV-infected woman with baseline CD4 count of 38 × 10^6/L and viral load >500,000 copies/mL has been receiving stavudine/lamivudine/nevirapine for 3 weeks. She now presents with a 7-day history of headache, described as mild, initially, but worsening with time, persistent, stabbing, no longer responsive to paracetamol, exacerbated by movement and associated with photophobia and vomiting. On examination, she is mildly pyrexial, fully awake, alert and oriented but restless. Five papular skin lesions measuring 2 mm in diameter have been noted below the lower right eyelid since prior to antiretroviral induction, which were thought to be molluscum contagiosum. She displays neither focal neurological deficits nor papilledema. Serum cryptococcal antigen is positive, and cerebrospinal fluid results are as follows: opening pressure 20 cm H_2O, slightly turbid fluid, CSF-protein 0.5 g/L, CSF: serum glucose 40%, chloride 125 mmol/L, acellular, Gram stain negative, CSF-cryptococcal latex agglutination test positive, India ink positive. Skin biopsy results culture Cryptococcus neoformans. Intravenous amphotericin B and oral dihydrocodeine were given, and the patient reports complete pain relief by the third day of treatment.

Which signs will alert the clinician to raised intracranial pressure in a patient with cryptococcal meningitis?

Focal neurological deficits. Transient loss in visual acuity, diplopia, hearing loss, confusion, and papilledema.

How should one manage and treat patients with raised intracranial pressure >25 cm H_2O?

To avoid herniation, prior to lumbar puncture, a CT or MRI scan of the brain should exclude mass effect. Drainage of small amounts of cerebrospinal fluid daily for a maximum of 2 weeks, with monitoring of pressure, usually improves headache and other symptoms associated with cryptococcal meningitis. After 2 weeks,

consider surgical placement of a ventriculoperitoneal or lumbar-peritoneal shunt if increased pressure persists.

Which analgesics are contraindicated for use with raised intracranial pressure?

Morphine sulfate, pethidine (meperidine).

Case report 6 ("peripheral neuropathy")

A young woman, 23 years old, is referred to the antiretroviral (ARV) clinic with a recent positive HIV-ELISA test and absolute CD4 of 19 × 10^6/L. She is ARV-naive. She complains of a burning sensation on the soles of both feet. Positive findings on examination include marked muscle wasting, malnourishment, a weight of 50 kg, pallor, a right-sided 5-cm supraclavicular lymphadenopathy, and a grade 1 sensorimotor peripheral neuropathy. Of note in the blood results is HIV-1 viral load by branched DNA, 238,810 copies/mL, and normocytic normochromic anemia. Chest X-ray reveals hilar adenopathy. A fine needle aspirate is undertaken of the lymph node and is consistent with TB. She is commenced on cotrimoxazole prophylaxis, TB treatment, pyridoxine 25 mg daily, and vitamin B complex.

Ten days after starting TB treatment, she calls the doctor at 3 am to complain of worsening foot pain, and is advised to present herself to the clinic at 8 am that day. She does so, in a wheelchair and wearing slippers, and complains that she cannot bear to walk on her own because of the pain in her feet, so she sleeps all day. At the consultation, the causes and course of her peripheral neuropathy, now grade 2 sensory and grade 3 motor, are explained to her. Amitryptiline 25 mg at night, ibuprofen and paracetamol, are started, and pyridoxine dosage is increased to 50 mg daily. Vitamin B_{12} and folate levels are normal, and iron studies suggest anemia of chronic disorders.

Three days later she calls the doctor at 1 am and complains of the nonresolution of her foot pain. She is asked once more to come in, and is assessed again as having grade 2 peripheral neuropathy. Pyridoxine is increased to 75 mg daily, amitryptiline to 50 mg at night, and a highly active antiretroviral therapy (HAART) regimen of nucleoside analog reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) is started. After 3 months, the neuropathy regresses to grade 1, and after 6 months the neuropathy has resolved completely.

Name all the contributory factors of the peripheral neuropathy!

HIV itself, possible vitamin B deficiencies, and isoniazid prophylaxis or treatment.

Which NRTI agents should be avoided, if possible, in such a case?

Stavudine and didanosine, as both can cause peripheral neuropathy with long-term use owing to mitochondrial toxicity.

Which nutritional deficiencies can cause peripheral neuropathy?

Vitamin B_1 (Thiamine), vitamin B_3, vitamin B_6, vitamin B_{12}.

Why did the neuropathy progress to grade 2?

The initial presenting neuropathy was most likely secondary to HIV. The pain was exacerbated by the addition of isoniazid, a component of TB treatment and a cause of peripheral neuropathy via vitamin B_6 (pyridoxine) depletion. Peripheral neuropathy has also been reported as a side effect of cotrimoxazole (used in higher doses for treatment and lower doses in prophylaxis of *Pneumocystis jirovecii* pneumonia treatment).

What drug used to treat peripheral neuropathy may be unsuitable for this patient?

Carbamazepine may be unsuitable because it induces the metabolism of efavirenz and nevirapine via the cytochrome P450 3A4 system.

Remember the WHO analgesic ladder for pain management

Step 1: MILD PAIN

Paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs) (NSAIDS) (and adjuvants if needed)

Adjuvants include (if there is neuropathic pain): tricyclic antidepressants (TCAs), anticonvulsants, steroids

Step 2: MILD TO MODERATE PAIN

Mild-acting opioids + step 1 nonopioids (and adjuvants if needed)

Mild-acting opioids: codeine, dihydrocodeine, dextropropoxyphene

Step 3: MODERATE TO SEVERE PAIN

Stronger opioids + Step 1 nonopioids (and adjuvants if needed)

Stronger opioids: morphine, diamorphine, fentanyl, hydromorphone

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Management of Chronic Noncancer Pain

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Guide to Pain Management in Low-Resource Settings

Chapter 27
Chronic Nonspecific Back Pain

Mathew O.B. Olaogun and Andreas Kopf

Case report 1

A 27-year-old chemical engineer who has had back pain for about the past 10 years was referred for physiotherapy. He reported with a recent radiograph, which showed no serious pathology aside from straightening of the lumbar lordosis. Pain is constant but is relieved with rest; it radiates in a nonradicular pattern into the upper limb. The patient has taken a series of periodic medications, particularly analgesics, with no lasting modulation of pain. The back pain is often exacerbated in attempts to get up from a lying position to a sitting position, and often the patient has experienced pain around the waist. On questioning, the patient complains that carrying heavy loads has damaged his spine. He had the first episode of acute pain at the age of about 16, when he carried a 50-kg keg of water (about 100% or more of his body weight at that time). The pain subsided after taking medication, but he has not been completely free of the pain since then. The pain has been undulating in intensity, and he has continued to live with it, but he has seen a doctor occasionally for medication. Now he explains that he has come to the teaching hospital in Ile-Ife, Lagos, Nigeria, to have his pain treated "once and for all," and, he says, "even it requires surgery."

On examination, the pain is axial around L3–L5, not referred and nonradicular. The X-ray shows no degenerative disk disease. When he lies supine on a table there is no pain, and Lasègue's sign (straight leg raising in supine position) is negative. He can perform an abdominal curl (sitting up from the supine position) without pain. With the patient prone, Ely's test (hip extension with a straight knee) is negative, and back extension does not elicit pain. Thus, there is no evidence of disk herniation, facet-joint osteoarthritis, or lumbar spinal stenosis.

The patient is rather disappointed that the doctor does not prescribe a strong pain killer or propose a surgical intervention. He is not really taken with the extensive explanations on the structure and pathomechanics of the spine. The education of the patient involves using a plastic model to demonstrate correct lifting techniques (not exceeding 70% of body weight) and correct sitting posture, while at the same time explaining the extraordinary functional reserves of the spinal column. The patient is advised to use a portable back support for his car and for chairs with poor ergonomic design, but to avoid extended rest and not look after himself too much. When leaving the consultation room, the patient—as could be seen—was not fully convinced, and nobody expected to see him again. Interestingly, he came back a few days later for his scheduled "education consultation" and was now less demanding about invasive procedures but was asking for more advice on the etiology and the prevention of back pain. He seemed to have a high motivation for changing his attitudes and behavior, with an overall positive approach to the future. He was satisfied after

the attention he received, and he left with the hope of becoming pain free afterwards. In a phone contact later his condition was reviewed. He was radiant on the phone. He expressed gratitude and stated that he has been feeling a lot better. He has been rigorously carrying out the exercises prescribed and has been obeying the prophylactic instructions without any exacerbation of the waist pain. Given that this is not the case in many patients with the same pain syndrome, this news was very encouraging for the therapists as well.

Case report 2

A 71-year-old pharmacist (Papa) had been on conservative management for back pain for about 3 years. The regime of treatment, aside from the earlier, occasional, analgesics, had been back extension exercises, spinal manual treatments, thermotherapy, and education on the care of the back. Though a pharmacist, Papa had not resorted to symptomatic use of medication for his chronic back pain. Sometimes pain would radiate to the posterior thigh, which may be "referred pain" from the facet joints or the iliosacral joint.

A significant achievement in the course of treatment was that his pain usually subsided lying down in either a supine or prone position. Papa was therefore advised to have a table in his office in an adjacent portion of his office. He was advised to lie on the table at his midday break from work for continuous decompression of intradiskal pressure. He complied very well.

However, back pain was preventing Papa from walking very far. He was advised to use a lumbar corset (appropriate for patients with instability who do not have access to stabilizing surgery) and elbow crutches for partial weightbearing on the lumbar and lumbosacral joints. The orthesis and the walking aid eliminated his back and posterior thigh pain. However, he started going out less as he became anxious about using the walking aid and orthosis, purely for cosmetic reasons. He confessed that he had often felt embarrassed by people staring at him or asking him about the walking aids. He complained and felt that more could still be achieved to stop his pain without the use of the corset and elbow crutches.

In late 2006, his children invited him to go abroad for medical treatment. Besides initial medication, after diagnosis of lumbar instability with considerable spondylolisthesis, he underwent surgery for spinal fusion at the level of L4/L5. When he came back to Nigeria, after about 10 weeks, he was free of pain but still had movement restrictions. His condition has been stable since then. His local doctor (his son) saw him with a radiant smile—pain free during walking and without any symptoms in his back and thigh. Papa returned to his work immediately and still observes the midday practice of lying supine for 30 minutes at his office.

This case report illustrates not a typical "nonspecific back pain patient" but a "specific pain" due to functional spinal stenosis caused by spondylolisthesis. While conservative techniques are desirable, nonpharmacological techniques are recommended, such as exercise therapy, behavioral therapy, and education on the care of the back and on compliance with the use of rehabilitation aids. Otherwise, specific interventions, including surgery like the one described above, can bring long-lasting relief from back pain. Differentiating between nonspecific back pain (which is very frequent) and specific back pain (which is rare) is crucial to avoid making nonspecific back pain worse with interventional techniques and analgesics, and to avoid unnecessary suffering in patients with specific back pain needing local—and sometimes invasive—therapy as well as analgesics to improve.

Why is chronic back pain so important?

Chronic nonspecific back pain is very common. Few of us never have back pain; most people have periodic back pain and some have chronic back pain. Chronic back pain is mostly located in the lumbosacral and posterior neck region.

In industrialized countries, low back pain (LBP) is the most common cause of activity limitation in persons younger than 45 years. It is defined as pain in the low back that persists longer than 12 weeks. Although acute LBP has a favorable prognosis, the effect of chronic LBP and its related disability on society is tremendous. For example, approximately 80% of Americans experience LBP during their lifetime. An estimated 15–20% develop protracted pain, and approximately 2–8% have chronic pain. Every year, 3–4% of the population is temporarily disabled, and 1% of the working-age population is disabled totally and permanently, because of LBP. It is estimated that the costs of LBP approach $30 billion annually in the United States.

Why is the "6-week rule" is so important?

Most normal connective tissues heal within 6–12 weeks unless instability or malignant or inflammatory tissue destruction is present. Therefore, in any prolonged back pain, these pain etiologies should be ruled out. Pain that radiates to the legs in a radicular pattern should be thoroughly investigated, especially if sensory or motor deficits are noted in the patient.

If the pain etiologies mentioned above are ruled out and the back pain persists, how should the pain should be interpreted?

Overinterpretation of CT or MRI findings should be avoided. Although disk protrusions have been popularized as causes of LBP, asymptomatic disk herniations on CT and MRI are common even in young adults. Furthermore, there is no clear relationship between the extent of disk protrusions and the degree of clinical symptoms. Therefore, other causes for persistent LBP have to be taken into consideration. If diagnostic studies reveal no structural cause, physicians and patients alike should question whether the pain has a psychosomatic, rather than purely somatic, cause. Physical and nonphysical factors, interwoven in a complex fashion, influence the transition from acute to chronic LBP. The identification of all contributing physical and nonphysical factors enables the physician to design a comprehensive approach with the best likelihood for success.

Is low back pain a worldwide problem?

Disability because of LBP has reached endemic proportions, with enormous socioeconomic consequences, in industrialized societies. Studies indicate that the prevalence of LBP is not as dependent on genetic factors that could predispose persons of specific ethnicity or race to this disorder. Men and women are affected equally. But lifestyle may be one of the most important predisposing factors for LBP. Therefore, LBP is starting to become a major health care problem in all countries in which economic and cultural changes are transforming their societies to modern industrialized societies for the benefit of their citizens.

When is periodic back pain "normal" and chronic back pain "not normal"?

The lumbar spine can support heavy loads in relationship to its cross-sectional area. It resists anterior gravitational movement by maintaining lordosis in a neutral posture. Unlike the thoracic spine, the lumbar spine is unsupported laterally. The intervertebral disks are composed of the outer annulus fibrosis and the inner nucleus pulposus. The outer portion of the annulus inserts into the vertebral body and accommodates nociceptors and proprioceptive nerve endings. The inner portion of the annulus encapsulates the nucleus, providing the disk with extra strength during compression.

The nucleus pulposus of a healthy intervertebral disk constitutes two-thirds of the surface area of the disk and supports more than 70% of the compressive load. Until the third decade of life, the gel of the inner nucleus pulposus is composed of approximately 90% water; however, the water content gradually diminishes over the next four decades to approximately 65%. Until the third decade of life, approximately 85% of the weight is transmitted across the disk. However, as disk height decreases and the biomechanical axis of loading shifts posteriorly, the posterior articulations (facet joints) bear a greater percentage of the weight distribution. Bone growth compensates for this increased biomechanical stress to stabilize the trijoint complex.

Therefore, to some extent, hypertrophy of the facets and bony overgrowth of the vertebral endplates constitute a normal physiological reaction to the age-dependent degeneration of the disks to stabilize the spine. Only in patients with inadequate "self-stabilization" do these changes contribute to progressive foraminal and central canal narrowing. Spinal stenosis reaches a peak later in life and may produce radicular, myelopathic, or vascular syndromes such as pseudoclaudication and spinal cord ischemia. LBP is most common in the early stages of disk degeneration and "self-stabilization."

What types of pain may be identified?

Specific pain

Back pain that lasts longer than 3 weeks with major functional impairment should be thoroughly evaluated to identify serious causes, especially malignant diseases

(e.g., bone metastasis), inflammation (e.g., spondylodiskitis), instability (e.g., spondylolisthesis), or local compression (e.g., spinal or foraminal compression). It has to be repeated that generally the proportion of back pain patients with specific pain is rather low (around 5%). On the one hand, the pain causes mentioned above should never be overlooked, but on the other hand, overinterpretation of radiographic results should be avoided.

As a rule of thumb, unrelenting pain at rest should suggest a serious cause, such as cancer or infection. Imaging studies and blood workup are usually mandatory in these cases and in cases of progressive neurologic deficit, too. Other historical, behavioral, and clinical signs that should alert the physician to a nonmechanical etiology will require diagnostic evaluation.

Evidence for specific back pain might be the following diagnostic "red flags":

- Colicky pain or pain associated with visceral function (or dysfunction).
- History of cancer or fatigue, or both, and weight loss.
- Fever or immunosuppressed status.
- History of older age and osteoporosis (with increased risk of fractures).
- Progressive neurological impairment, or bowel and/or bladder dysfunction.
- Severe morning stiffness as primary complaint.

Nonspecific pain

Evidence for nonspecific back pain might be the following diagnostic "red flags" (nonorganic signs and symptoms):

- Dissociation between verbal and nonverbal pain behaviors.
- Use of affective pain descriptions.
- Little pain modulation, with continuous high pain intensity.
- Compensable cause of injury, out of work, seeking disability (conflict of interest between compensation and wanting to be cured).
- Signs of depression (having difficulty falling asleep, waking up early in the morning, loss of interest, and loss of energy and drive, especially in the first half of the day) and anxiety (continuous worrying and restlessness).
- Psychoactive drug requests.
- History of repeated failed surgical or medical treatments.

Diskogenic pain

Many studies have demonstrated that the intervertebral disk and other structures of the spinal motion segment can cause pain. However, it is unclear why mechanical back pain syndromes commonly become chronic, with pain persisting beyond the normal healing period for most soft-tissue or joint injuries. Inflammatory factors may be responsible for pain in some cases, in which epidural steroid injections provide relief. Corticosteroids inhibit the production of arachidonic acid and its metabolites (prostaglandins and leukotrienes), inhibiting phospholipase A_2 (PLA_2) activity. Levels of PLA_2, which plays a role in inflammation, are elevated in surgically extracted samples of human herniated disks. Furthermore, PLA_2 may play a dual role, inciting disk degeneration and sensitizing annular nerve fibers.

Radicular pain

Surprisingly, the pathophysiology of radicular pain is unclear. Likely etiologies include nerve compression because of foraminal stenosis, ischemia, and inflammation. Often, the cause of radiculopathy is multifactorial and more complex than neural dysfunction due to structural impingement. In clinical practice, structural impairment is usually considered to be responsible, if inflammation is found. Therefore local epidural, often para-radicular, steroid injections are used for therapy, although their long-term effect is rather questionable.

Facet-joint pain

The superior and inferior articular processes of adjacent vertebral laminae form the facet or zygapophyseal joints. They share compressive forces with the intervertebral disk. After trauma or with inflammation they may react with pain signaling, joint stiffness, and degeneration. Interestingly, there is no strong relation between radiographic imaging results and pain; therefore, the diagnosis is strictly clinical (pain radiating to the buttocks and dorsal aspects of the upper limb, provoked by retroflexion of the back and/or rotation). Unfortunately, long-term effects of local steroid injections into the joint or into the vicinity as well as electrical ablation of the nerves innervating the joints ("medium bundle block") have failed to demonstrate long-term effects.

Sacroiliac pain

The sacroiliac joint receives its primary innervation from the dorsal rami of the first four sacral nerves. Arthrography or injection of irritant solutions into the sacroiliac

joint provokes pain with variable local and referred pain patterns into regions of the buttock, lower lumbar area, lower extremity, and groin. Certain maneuvers (e.g., Patrick's test) may provoke typical pain, too. Local blocks sometimes accelerate recovery and facilitate physical therapy. In young male adults in particular, Bechterew disease (ankylosing spondylitis) has to be ruled out.

Muscular pain

Muscular pain is most often the cause of chronic back pain. Pain receptors in the muscles are sensitive to a variety of mechanical stimuli and to biomechanical overload. Anxiety and depressive disorders often play an important role in sustaining muscular pain due to the "arousal reaction," with a continuous increase of muscular tension. Muscular pain may be described as "myofascial pain," if muscles are in a contracted state, with increased tone and stiffness, and contain trigger points (small, tender nodules that are identified on palpation of the muscles, with radiation into localized reference zones). In most patients myofascial pain is the result of a combination of factors: the "arousal reaction," direct or indirect trauma, exposure to cumulative and repetitive strain, postural dysfunction, and physical deconditioning.

On the cellular level, it is presumed that abnormal and persistently increased acetylcholine release at the neuromuscular junction generates sustained muscle contraction and a continuous reverberating cycle. If muscular back pain does not resolve within a few weeks (usually 6 weeks is seen to be crucial), it should be seen as a complex disease with physiological ("biological"), psychological, and psychosocial influences (according to the biopsychosocial model of chronic pain evolution). Therefore, when local therapies alone fail to give long-term pain relief, a major diagnostic and therapeutic workup including physical, psychosocial, and neuropsychological aspects ("multimodal therapy") may be needed.

If adequate therapy is delayed over several months with a trial of unimodal therapies, such as analgesics or injections only, long-term positive effects of multimodal therapeutic approaches become unlikely or very limited.

What are the diagnostic strategies in back pain lasting more than 3 weeks?

Unrelenting pain at rest and the other "specific pain red flags" should generate suspicion for cancer or infection. Appropriate imaging is mandatory in these cases. In cases of progressive neurological deficit, imaging should be done without losing any time, when imaging is available, or the patient can be transferred to a location where imaging is available. Plain anteroposterior and lateral lumbar spine radiographs are indicated first for identifying cancer, fracture, metabolic bone disease, infection, and inflammatory arthropathy. In these diseases, more sophisticated (and expensive and rare) further diagnostic imaging will not add substantial information for most patients. CT scanning is an effective diagnostic instrument when the spinal and neurological levels are well identifiable and bony pathology is suspected. MRI is most useful when the exact spinal and neurological levels are unclear, when a pathological condition of the spinal cord or soft tissues is suspected, when disk herniation is possible, or when an underlying infectious or neoplastic cause is suspected. If interpretation of MRI or CT scans is difficult and nerve root or myelon compression is suspected clinically, myelography may be useful to get a clearer picture, especially in patients with previous lumbar spinal surgery or with a metal fixation device in place. Non-radiographic tests include electromyography (EMG) and somatosensory evoked potential testing (SEP) and help to localize nerve lesions and to differentiate between older and newer lesions.

Therapeutic approaches

Is bed rest an appropriate therapeutic approach in back pain?

Bed rest is only appropriate for acute radiating pain (sciatica), but it should not exceed 1–3 days to avoid progressive inactivity and avoidance, which reinforces abnormal illness behaviors. For all nonspecific myofascial pain, inactivity would have deleterious physiological effects, leading to shortened muscles and other soft tissues, joint hypomobility, reduced muscle strength, and bone demineralization. Therefore, bed rest should not be advised. The patient should be instructed to continue "normal daily activities" as much as possible. Any bed rest recommendations would only reinforce malcognitive and malconditioned behavior ("fear avoidance beliefs"), resulting in a viscous circle of bed rest—increased fear of movement—increased pain on movement because of muscular deconditioning—more bed rest. For these reasons, bed rest is definitely not recommended as a treatment for nonspecific back pain.

What medications are recommended in nonspecific back pain?

Unfortunately, many patients with nonspecific back pain are treated as in acute specific diseases causing pain, with long-term prescriptions of nonsteroidal analgesics, opioids, and centrally acting muscle relaxants, although there is no evidence in the literature for use of these drugs for this indication, and a number of guidelines do not recommend them. Only a few medications are indicated. Tricyclic antidepressants in low to moderate doses are useful to alleviate insomnia, enhance endogenous pain suppression, reduce painful dysesthesia, and help the patient's ability to cope. If a depressive disorder is diagnosed, higher doses would be needed. In some patients, the anxiolytic and sleep-quality-improving calcium channel blockers gabapentin or pregabalin might be helpful. Other coanalgesics and narcotics may only be used if the pain is of malignant, chronic inflammatory, or severe degenerative origin.

Are invasive therapeutic techniques indicated in nonspecific back pain?

In carefully selected patients, such as those with concomitant sacroiliacal or facet joint affection, local injections might facilitate recovery with physical therapy. Local injections into paravertebral soft tissues, specifically into myofascial trigger points, are widely advocated. However, study results are rather disappointing.

If conventional analgesics and invasive techniques are not recommended, what therapy is best for chronic nonspecific back pain?

Behavioral and cognitive behavioral multidisciplinary pain programs have proven effective for many patients, but they need dedicated, well-trained personnel and rather high financial resources to be effective. Therefore, prevention of chronic nonspecific back pain is the key to therapeutic success. Morbid obesity, smoking, general fitness, and job satisfaction should be addressed in all patients to avoid development of chronic nonspecific back pain. Adequate and knowledgeable patient guidance seems to be the most important prophylactic and therapeutic instrument in nonspecific back pain. The goals of chronic pain management are to relieve discomfort (partially) and (more importantly) to improve or restore physical, psychological, and social function. Management involves knowing the cause and course of the pain, educating patients in simple terms, and selecting appropriate "resource-oriented" physical and psychological modalities and techniques. For success, it is vital to achieve a "change motivation" in patients and to educate them on what can be done as self-care.

Pearls of wisdom

- Chronic nonspecific back pain is one of the most frequent patient complaints.
- It is crucial to differentiate nonspecific back pain from specific back pain because the therapeutic techniques differ considerably. This differentiation should be made at the earliest possible moment, because nonspecific back pain tends to take on a life on its own within a couple of weeks or months, resulting in a difficult-to-treat disease.
- "Red flags" help to identify indications for specific and nonspecific pain.
- In general, opioids, NSAIDs, and central muscle relaxants as well as invasive procedures are ineffective in nonspecific back pain and even have the risk to further promote chronic pain development. Instead, intensive counseling, patient education, physical activation, and behavioral interventions have been proven to be effective.
- Psychiatric comorbidity is frequent and should not be overlooked.
- An important goal in advanced chronic back pain patients is concentration of therapeutic efforts on functional improvement rather than pain reduction.

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http://www.rcep7.org/projects/handbook/back.pdf

International Association for the Study of Pain
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Guide to Pain Management in Low-Resource Settings

Chapter 28
Headache

Arnaud Fumal and Jean Schoenen

How is headache classified?

Headache is a leading reason for medical consultation and particularly for neurological consultation. A tremendous range of disorders can present with headache. A systematic approach to classification and diagnosis is therefore essential both for clinical management and research. Headache disorders were poorly classified and defined until 1988. At that time, the International Headache Society (IHS) published its International Classification of Headache Disorders (ICHD-1), in which headaches were classified into 13 major groups. This headache classification with operational diagnostic criteria was an important milestone for clinical diagnosis and is accepted worldwide. Its second edition (ICHD-2) has fine-tuned the classification of different specific headaches and expanded the number of groups to 14 (Table 1). For each disorder, explicit diagnostic criteria are provided. These diagnostic criteria are very useful for the clinician because they contain exactly what needs to be obtained from the patient while taking the history. Nevertheless, it is surprising and disappointing that headache patients remain poorly diagnosed and treated in most countries.

There are four groups of primary headache disorder: (1) migraine, (2) tension-type headache, (3) trigeminal autonomic cephalalgias, and (4) other primary headache. The criteria for the primary headaches are clinical and descriptive and, with a few exceptions (i.e., familial hemiplegic migraine) are based on headache features and the exclusion of other disorders, not etiology. In contrast, secondary headache are classified based on etiology and are attributed to another disorder. Because primary headaches are the most common, this discussion focuses on the diagnosis and management of those syndromes. The epidemiology and experiences of patients with headache disorders in the developing world are uncertain, because the majority of research on headache disorders comes from a limited number of high-income countries. Where sought, regional variation in the incidence, prevalence, and economic burden of headache disorders has been found. Social, financial, and cultural factors can all influence the experience of the individual headache sufferer, and patients in resource-poor settings could presumably experience an even greater impact of these influences.

What are important issues for non-headache specialists?

Caring for a patient complaining of headaches requires above all a thorough history taking and physical examination that includes a neurological examination. First, one needs to distinguish primary from secondary headaches. To evaluate the likelihood of a secondary, symptomatic headache, the most crucial feature, besides clinical examination, is the duration of the headache history. Patients with a short history require prompt at-

Table 1 Tension-type headache (episodic form): general diagnostic criteria (ICHD-2)
General Diagnostic Criteria
A. Headache lasting from 30 minutes to 7 days
B. At least 2 of the following pain characteristics: Bilateral location Pressing/tightening (non-pulsating) quality Mild or moderate intensity Not aggravated by routine physical activity such as walking or climbing stairs
C. Both of the following: 1. No nausea or vomiting (anorexia may occur) 2. No more than one of photophobia or phonophobia
D. Not attributed to another disorder

tention and may need quick complimentary investigations, while those with a longer headache history generally require time and patience rather than speed and imaging. Patients with a headache history of more than 2 years definitely have a primary headache disorder. Red flags (see Table 2) that should alert to the possibility of a secondary headache include pain of sudden onset, fever, marked change in pain character or timing, neck stiffness, pain associated with neurological disturbances, such as cognitive dysfunction or weakness, and pain associated with local tenderness, for example of the superficial temporal artery.

Table 2 Migraine with aura diagnostic criteria (ICHD-2)
Diagnostic Criteria for Migraine without Aura
A. At least 5 attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
C. At least 2 of the following pain characteristics: Unilateral location Pulsating quality Moderate or severe intensity Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least one of the following: 1. Nausea and/or vomiting 2. Photophobia and phonophobia
E. Not attributed to another disorder

Patients with recent onset headache or with neurological signs require at the least brain imaging with computed tomography (CT) or magnetic resonance imaging (MRI). To classify primary headaches, the following questions are crucial:

- Frequency and duration of attacks.
- Headache severity.
- Is the pain on one or both sides?
- Is it aggravated by physical activity?
- The presence of trigger zones and lancinating quality suggest a neuralgia.
- Is a migraine aura present?
- Very importantly, are there accompanying symptoms such as nausea, hypersensitivity to light and sound, or autonomic symptoms such as tearing, stuffy nose, sweating, ptosis, or miosis?

The next question is whether the patient has one or more different kinds of headache. This must be elucidated skillfully. The reason for the consultation must be made clear. Is it because the usual headache is getting worse, or is it because of a new kind of headache? We have to keep in mind that if headache is the fifth most common complaint seen in United States emergency department, the minority of these patients have a secondary cause for headache, and an even smaller number have a grave and potentially catastrophic cause for headache, such as meningitidis or subarachnoid hemorrhage.

In clinical practice, it is known that patients may not easily identify and recall certain features of their headaches, such as the presence and type of aura symptoms, specific associated symptoms, and the coexistence of several types of headache. Therefore, the use of monitoring instruments becomes crucial in the diagnosis of these disorders. Using headache diaries and calendars, the characteristics of every attack can be recorded prospectively, increasing the accuracy of the description and making it possible to distinguish between coexisting headache types.

Moreover, headache diaries provide the physician with information concerning other important features, such as the frequency and temporal pattern of attacks, drug intake, and the presence of trigger factors. Use of acute drugs can be checked for optimal dosing. Frequent use (10 days or more per month) of acute medication is an alert for medication overuse headache. The diary could even be sent to headache patients before their first consultation at the headache center as it can improve the clinical diagnosis from the first interview.

What is essential to know about migraine?

Migraine is the commonest cause of severe episodic recurrent headache. Migraine affects approximately 12% of Western populations, and prevalence is higher in females (18%) than males (6%). Migraine is a recurrent

headache manifesting in attacks lasting between 4 and 72 hours. Typical features of this headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia (see Table 3 for diagnostic criteria of migraine without aura from the ICHD-2).

The headache may be preceded in 15–20% of patients by an aura, so-called migraine with aura. The aura may last between 5 and 60 minutes. The most common type is visual aura, causing scotomas, teichopsia, fortification spectra, and photopsias. It can also comprise other neurological symptoms such as focal paresthesias, speech disturbances and, in hemiplegic migraine, a unilateral motor deficit. The heterogeneity of the clinical phenotype of migraine is underestimated. Despite a common diagnostic denominator, some clinical features such as type of aura symptoms, pain intensity, presence of prodromes, coexistence of migraine with and without aura, or associated symptoms such as vertigo, may characterize subgroups of patients bearing different underlying pathophysiological and genetic mechanisms.

In migraine, premonitory symptoms and trigger factors are manyfold, and they may vary between patients and during the disease course. The most frequently reported premonitory symptoms are fatigue, phonophobia, and yawning. Concerning trigger factors, the most common ones are stress, the perimenstrual period, and alcohol. Overuse of acute antimigraine drugs, in particular of combination analgesics and ergotamine, is another underestimated factor leading to chronification.

If the migraine is a benign condition, the severity and frequency of attacks can result in significant disability and reduced quality of life, even between attacks. Although migraine is one of the most common reasons for patients to consult their doctor, and despite its enormous impact, it is still under-recognized and undertreated. This lack of recognition has various reasons. On the one hand, there are no biological markers to confirm the diagnosis, and many doctors lack knowledge, time, interest, or all three, to manage migraineurs. On the other hand, there is no cure for migraine, and, although effective therapies do exist, they have only partial efficiency or are not accessible to all. Finally, perception of migraine may vary between cultures, some of which tend to negate or trivialize its existence. As a result, a proportion of affected individuals do not seek (or have given up on) medical help.

Migraine is a neurovascular disorder (i.e., both neuronal and vascular factors are involved) in which genetic susceptibility renders the brain hyperresponsive to stimuli and probably metabolically vulnerable, setting a "migraine threshold" on which trigger factors may act to precipitate an attack. The consensus is now that the migraine aura is caused by the neuron-glial phenomenon of so-called "cortical spreading depression," where a brief front of neuronal depolarization ("scintillations") is followed by a wave of arrest of neuronal activity due to hyperpolarization; both spread over the cortex with a velocity of 3–5 mm/minute.

The migraine headache probably results from activation of the trigeminovascular system, the major pain-signaling system of the visceral brain composed of nociceptive afferents belonging to the visceral portion of the ophthalmic nerve (V1) and surrounding meningeal blood vessels. The precise pathogenic relationship between aura and migraine headache is not fully clarified.

Table 3
Typical symptoms of migraine and tension-type headache

	Migraine	Tension-Type Headache
Sex ratio (F:M)	2 to 3:1	5:4
Pain		
Type	Pulsating	Pressing/tightening (non-pulsating) quality
Severity	Moderate to severe	Mild or moderate intensity
Site	Unilateral	Bilateral
Aggravated by routine physical activity	Yes	No
Duration of attack	4 to 72 h	30 minutes to 7 days
Autonomic features	No	No
Nausea and/or vomiting	Yes	No
Photophobia and/or phonophobia	Yes, both	No more than one of photophobia or phonophobia

What are the options for acute migraine treatment?

During the last decade, the advent of highly effective 5-$HT_{1B/1D}$ agonists, the triptans, has been a major breakthrough in treatment. Triptans are able to act as vasoconstrictors via vascular 5-HT_{1B} receptors and to inhibit neurotransmitter release at the peripheral as well as at central terminal of trigeminal nociceptors via 5-$HT_{1D/B}$ receptors. The site of action relevant for their efficacy in migraine is still a matter of controversy; possibly their high efficacy rate is due to their capacity of acting at all three sites, contrary to other antimigraine drugs. Sumatriptan, the first triptan, was followed by several-second generation triptans (zolmi-, nara-, riza-, ele-, almo-, and frovatriptan), which were thought to correct some of the shortcomings of sumatriptan. A large meta-analysis of a number of randomized controlled trials performed with triptans confirms that the subcutaneous auto-injectable form of sumatriptan (6 mg) has the best efficacy, whatever outcome measure is considered. Differences between oral triptans do exist for some outcome measures, but in practice each patient has to find the triptan that gives the best satisfaction.

At present, the major reason for not considering triptans as first-choice treatments for migraine attacks is their high cost, and in some patients their cardiovascular side effects. However, stratifying care by prescribing a triptan to the most disabled patients has been proven cost-effective. In severely disabled migraineurs, the efficacy rate of injectable sumatriptan for a pain-free outcome at 2 hours is twice that of ergot derivatives or NSAIDs taken at high oral doses and of i.v. acetylsalicylic acid lysinate. The therapeutic gain tends to be clearly lower for simple analgesics or NSAIDs, such as acetaminophen (1000 mg p.o.), effervescent aspirin (1000 mg), or ibuprofen (600 mg), than for oral triptans, when severe attacks are considered.

For mild and moderate attacks, however, it has proven difficult to show superiority of oral triptans in randomized controlled trials. Combining analgesics or NSAIDs with an antiemetic and/or with caffeine or administering them as suppositories clearly increases their efficacy, often up to that of oral triptans. Recently, combining a triptan plus an NSAID as a single tablet for acute treatment of migraine resulted in more favorable clinical benefits compared with either therapy used alone, with an acceptable and well-tolerated adverse-effect profile.

As expected, the triptans have not solved patients' problems. There is room for more efficient and safer oral acute migraine treatments. As triptans are contraindicated in patients with cardiovascular disorders, non-vasoconstricting agents are the holy grail in acute therapy research. Serotonin 5-HT_{1F}-receptor agonists and a novel calcitonin gene-related peptide (CGRP) antagonist are currently being investigated, with promising results. Treatment algorithms should be inspired by

Table 4
Red flags in the diagnosis of headache

Red Flags	To Consider	Possible Investigation(s)
Sudden-onset headache	Subarachnoid hemorrhage, brain bleeding, mass lesion (especially posterior fossa)	Neuroimaging, lumbar puncture (after neuroimaging)
Worsening-pattern headache	Mass lesion, subdural hematoma, medication overuse	Neuroimaging
Headache with systemic illness (fever, neck stiffness, cutaneous rash)	Meningitidis, encephalitis, Lyme disease, systemic infection, collagen vascular disease, arteritis	Neuroimaging, lumbar puncture, biopsy, blood tests
Focal neurologic signs, or symptoms other than typical visual or sensory aura	Mass lesion, arteriovenous malformation, collagen vascular disease	Neuroimaging, collagen vascular evaluation
Papilledema	Mass lesion, pseudotumor, encephalitis, meningitidis	Neuroimaging, lumbar puncture (after neuroimaging)
Headache triggered by cough, exertion or Valsalva	Subarachnoid hemorrhage, mass lesion	Neuroimaging, consider lumbar puncture
Headache during pregnancy or postpartum	Cortical vein/cranial sinus thrombosis, carotid dissection, pituitary apoplexy	Neuroimaging
New headache type in a patient with cancer, Lyme disease or HIV	Metastasis, meningoencephalitis, opportunistic infection	For all neuroimaging and lumbar puncture

Source: Bigal ME, Lipton RB. Headache Pain 2007;8:263–72.

personal experience, by the local pharmacoeconomic situation, as well as by the available literature.

What prophylactic therapy is available in migraine?

Prophylactic antimigraine treatment must be individually tailored to each patient, taking into account the migraine subtype, the ensuing disability, the patient's history and demands, and the associated disorders. A prophylactic treatment is also useful to prevent the transformation of episodic migraine into chronic daily headache with analgesic overuse (medication overuse headache).

A major drawback of most classical prophylactics (beta-blockers devoid of intrinsic sympathomimetic activity, valproic acid, Ca^{2+} antagonists, antiserotoninergics, and tricyclics), which have all on average a 50% efficacy score, is the occurrence of side effects. If the initial trial is successful in reducing frequency of attacks without causing significant chronic side effects, then the preventive therapy may be continued for 6 months. After 6 months, the dose is gradually decreased before stopping the treatment. If the treatment is not successful, dosing of the medication should be increased up to the maximum allowed, or a new preventive treatment should be initiated.

In recent years, some new prophylactics with less side effects have been studied. Well-tolerated, but poorly effective in comparison to the classical prophylactics, are high-dose magnesium or cyclandelate. A novel preventive treatment for migraine is high-dose (400 mg/d) riboflavin, which has an excellent efficacy/side-effect ratio and probably acts by improving the mitochondrial phosphorylation potential. Coenzyme Q_{10} (100 t.i.d.), another actor in the mitochondrial respiratory chain, is also effective in migraine prophylaxis. Lisinopril (10 mg b.i.d.), an inhibitor of angiotensin-converting enzyme, and even more so, candesartan (16 mg b.i.d.), an angiotensin II inhibitor, well-known for the treatment of hypertension, were found useful in migraine.

Recent preliminary but encouraging results with novel antiepileptic compounds such as gabapentin need to be confirmed in large randomized controlled trials, whereas topiramate was found effective in several placebo-controlled trials. Lamotrigine is up to now the only preventive drug that has been shown effective for migraine auras, but not for migraine without aura. Nonpharmacological and herbal treatments are increasingly subject to controlled studies, and some, like butterbur (*Petasites*), were found clearly more effective than placebo. Several nondrug therapies (such as biofeedback and psychologically based interventions) have proven efficacy in migraine prophylaxis.

How is the pharmacological prophylaxis therapy in migraine selected?

Interestingly, the recommendations for prophylactic treatment of migraine differ around the world. Beta-blockers and valproate are usually among the first choices. The choice of drug should nevertheless be individualized according to the drug's side-effect profile. For example, older patients might benefit from the antihypertensive properties of beta-blockers, while younger ones may suffer considerably from beta-blocker-induced sedation.

Apart from the drugs in the list, there are other pharmacological options with weaker evidence, including magnesium (24 mmol daily, especially for migraine associated with the menstrual period), *Petasites* (butterbur), *Tanacetum parthenium* (feverfew), candesartan (16 mg daily), coenzyme Q_{10} (100 mg t.i.d.) and riboflavin (400 mg daily).

Table 5
Selection criteria for prophylactic pharmacological treatment in migraine

Drug and Dose	Selected Adverse Effects
Valproic acid, 500–1000 mg nightly (sustained release)	Liver toxicity, sedation, nausea, weight gain, tremor, teratogenicity, possible drug toxicity, hair loss, drowsiness
Beta-blockers Propranolol, 40–240 mg Bisoprolol, 2.5–10 mg Metoprolol, 50–200 mg	Reduced energy, tiredness, postural symptoms, contraindicated in asthma
Flunarizine, 5–10 mg daily	Drowsiness, weight gain, depression, parkinsonism
Topiramate, 25–100 mg twice daily	Paresthesias, fatigue, nausea, cognitive dysfunction
Amitriptyline, 25–75 mg nightly	Weight gain, dry mouth, sedation, drowsiness
Methysergide, 1–4 mg daily	Drowsiness, leg cramps, hair loss, retroperitoneal fibrosis (1-month drug "holiday" required every 6 months)
Gabapentin, 900–3600 mg daily	Dizziness, sedation
Lisinopril, 10–20 mg daily	Cough

What is essential to know about tension-type headache?

Tension-type headache (TTH) is an ill-defined and heterogeneous syndrome, of which diagnosis is mainly based on the absence of features found in other headache types such as migraine (see Tables 4 and 5 for diagnostic criteria). It is thus above all a "featureless" headache, characterized by nothing but pain in the head. The diagnostic problem most often encountered is to discriminate between TTH and mild migraines. TTH is the most common form of headache, but it receives much less attention from health authorities, clinical researchers, or industrial pharmacologists than migraine. That is because most persons with infrequent or frequent TTH never consult a doctor; treat themselves, if necessary, with over-the-counter analgesics. However, chronic TTH, which causes headache ≥15 days per month represents a major health problem with an enormous socioeconomic impact. In a population-based study, the lifetime prevalence of tension-type headache was 79%, with 3% suffering from chronic TTH, i.e., headache ≥15 days per month.

It still is a matter of debate whether the pain in TTH originates from myofascial tissues or from central mechanisms in the brain. Research progress is hampered by the difficulty in obtaining homogeneous populations of patients because of the lack of specificity of clinical features and diagnostic criteria. The present consensus, nonetheless, is that peripheral pain mechanisms are most likely to play a role in infrequent episodic TTH and frequent episodic TTH, whereas central dysnociception becomes predominant in chronic TTH.

Simple analgesics (i.e., ibuprofen 600 to 1200 mg/d) are the mainstay of treatment of episodic TTH. Combination analgesics, triptans, muscle relaxants, and opioids should not be used, and it is crucial to even avoid frequent and excessive use of simple analgesics to prevent the development of medication overuse headache. Prophylactic pharmacotherapy should be considered in patients with headaches for more than 15 days per month (chronic TTH). A prophylactic treatment is useful to prevent the transformation of episodic TTH into medication overuse headache. The tricyclic antidepressant amitriptyline is the drug of first choice for the prophylactic treatment of chronic TTH, but nonpharmacological management strategies (relaxation, biofeedback, physical therapy) are equally effective. The initial dosage of tricyclics should be low: 10–25 mg of amitriptyline at bedtime. Many patients will be satisfied by such a low dose. The average dose of amitriptyline in chronic TTH, however, is 75–100 mg per day. If a patient is insufficiently improved on this dose, a trial of higher doses of amitriptyline is warranted. If the headache has improved by at least 80% after 4 months, it is reasonable to attempt discontinuation of the medication. Decreasing the daily dose by 20–25% over 2–3 days may avoid rebound headache. The best results are obtained by combining tricyclics with relaxation therapy.

What is essential to know about cluster headache and other trigeminal autonomic cephalalgias?

Trigeminal autonomic cephalalgias (TACs) are a group of rare primary headache syndromes that include cluster headache, paroxysmal hemicrania, SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), and SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms). Although rare, they are important to recognize because of their excellent but highly selective response to treatment. They share the same features in their phenotype of headache attacks, which is a severe unilateral orbital, periorbital, or temporal pain, with associated ipsilateral cranial autonomic symptoms, such as conjunctival injection, lacrimation, nasal blockage, rhinorrhea, eyelid edema, and ptosis. The distinction between the syndromes is made on duration and frequency of attacks.

As cluster headache (CH) is the commonest of the TACs, we will describe only this kind of headache in the present chapter. CH has a prevalence of about 0.3%, and male-female ratio of 3.5–7:1. The attacks of CH are stereotypical, being severe or excruciating, lasting 15–180 minutes, occurring once every other day up to eight times per day, and associated with ipsilateral autonomic symptoms. In most patients, CH has a striking circannual and circadian periodicity. Diagnosis is based on IHS criteria for the phenotype of attacks, but an MRI of the brain with contrast should be performed in order to rule out a secondary/symptomatic CH.

Cluster headache patients should be advised to abstain from taking alcohol during the cluster period. Because the pain of CH builds up so rapidly, abortive agents have to act quickly to be useful. By far the most efficient one is a subcutaneous injection of sumatriptan 6 mg. Inhalation of 100% oxygen, at 10 to 12 L/minute

via a nonrebreathing facial mask for 15 to 20 minutes, can be effective in up to 60–70% of attacks, but pain frequently recurs. The aim of the preventive therapy is to produce a rapid remission of the disorder and to maintain that remission with minimal side effects until the cluster bout is over according to its natural history, or for a longer period in patients with chronic CH. Steroids are very effective in interrupting a bout. Suboccipital injections of long-acting steroids should be preferred to oral treatment, to lessen the risk of "corticosteroid-dependence." Verapamil is the next preventive drug of choice, but lithium, topiramate, methysergide, or corticosteroids can also be used. Functional imaging data suggest the hypothalamus to be the origin for CH.

Can headache medication cause headache?

Overuse of acute medication is the most frequent factor associated with the transformation of episodic migraine into chronic daily headache. The latter is called "medication overuse headache" (MOH) in the 2nd edition of the International Classification of Headache Disorders (ICHD-II, 2004). It is classified as a secondary headache disorder, which may evolve from any type of primary headache, but mainly from episodic migraine, and in a lower proportion in tension-type headache. MOH is a disabling health problem, which may affect 1–2% of the general population.

The most efficient treatment for MOH is abrupt drug withdrawal and immediate prescription of a preventive drug (an antimigraine agent if the primary headache is a migraine, or tricyclics in case of TTH), but there are no studies comparing different strategies. There are thus no clear, worldwide accepted guidelines regarding modality of withdrawal or treatment of withdrawal symptoms. Oral prednisone, acamprosate, tizanidine, clomipramine, and intravenous dihydroergotamine were found useful for withdrawal headaches, but results are conflicting, for example, prednisone shows both positive and negative results. It seems clear that after the first 2-week physical withdrawal period, comprehensive long-term management of the biopsychosocial problem of these patients is necessary to minimize relapse.

Pearls of wisdom

- Recurrent headache disorders impose a substantial burden on individual headache sufferers, on their families, and on society.
- Although headache is one of the most common reasons for patients to consult their doctor, and despite its enormous impact, it is still under-recognized and undertreated.
- Inaccurate diagnosis is probably the most common reason for treatment failure. A systematic approach to classification and diagnosis is therefore essential both for clinical management and research.
- Improvements in treatment have been less dramatic than remarkable revelations from basic and clinical research on headaches.
- Finally, while the effective newer treatments are quite expensive, e.g., newer antiepileptics and triptans, older drugs are still available everywhere with a good benefit-cost ratio: NSAIDs (for acute treatment) and beta-blockers and/or riboflavin (for prophylactic treatment) in migraine, and oxygen (for acute treatment) and verapamil (for prophylactic treatment) in cluster headache.

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International Headache Society (IHS): http://www.i-h-s.org/

Following the listing by the World Health Organization of the world's 100 poorest countries (British Medical Journal 2002;324:380), IHS offers Associate Membership free to individuals living in those countries who qualify for Ordinary Membership. Associate Membership carries the responsibilities to the Society of Ordinary Membership (other than payment of the membership fee), but offers limited benefits. These include on-line access to the Society's journal Cephalalgia.

American Headache Society (AHS): www.americanheadachesociety.org/

World Headache Alliance (WHA): http://www.w-h-a.org/

International Association for the Study of Pain
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Guide to Pain Management in Low-Resource Settings

Chapter 29
Rheumatic Pain

Fereydoun Davatchi

What is rheumatology?

Rheumatology is a subspecialty of internal medicine dealing with bone and joint diseases (connective tissue and related tissue disorders of bone, cartilage, tendons, ligaments, tendon sheets, bursae, muscles, etc.). Although modern rheumatology is based on advanced molecular biology, immunology, and immunogenetics, the daily practice and routine diagnosis is mainly clinical and based on symptoms and signs. In the majority of cases, laboratory tests and imaging have a confirmatory role, instead of being mandatory. Simple tests, such as complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), uric acid, and urinalysis, are sufficient in many cases. Sophisticated investigations are rarely mandatory in routine practice. The same is true regarding elaborate imaging technics.

How are rheumatological diseases classified?

They are divided in three groups: articular, extra-articular, and bone diseases. Articular manifestations can be divided into six categories: inflammatory, mechanical, metabolic, neurological, infectious, and tumoral disorders. Extra-articular manifestations are also called soft tissue rheumatism (tendonitis, tenosynovitis, bursitis, etc.). Bone diseases are divided into metabolic (osteoporosis, osteomalacia), infectious, tumoral (benign, malignant, metastatic), and genotypic malformations.

What is the connection between rheumatology and pain?

The most important symptom in rheumatology is pain. The pain can be inflammatory, mechanical, or continuous. Inflammatory pain occurs during rest and disappears or improves gradually with activity. It is accompanied by some degree of stiffness, especially in the morning when the patient wakes up. Mechanical pain appears with activity, increases gradually, and disappears with rest. It can be accompanied by gelling pain, which resembles inflammatory pain, but is of very short duration (a few minutes or less). Pure continuous pain is rare; usually one can find an inflammatory or mechanical feature. Joint swelling is the second most important symptom in rheumatology. It can be due to either effusion or synovial hypertrophy. Bony enlargement of the joint (bone hypertrophy) is the differential diagnosis. Limitation of joint movement is an indicator of joint involvement. Abnormal movement is an indicator of joint dislocation (cartilage destruction, ligament tear, and epiphyseal collapse).

How do you diagnose a rheumatological disease?

The characteristics of each joint, the chronology of the symptoms, the number and location of involved joints, and the pattern of involvement are usually enough to suspect a diagnosis, or better, to make a diagnosis. In many cases (soft-tissue rheumatisms, low back pain, or mechanical cervical pain), no laboratory investigation is necessary. In others, simple laboratory tests as mentioned above will be sufficient. When necessary, plain X-rays will often give sufficient information.

What are the principles of treatment?

Although treatment has made great advances in the last decade (biological agents, sophisticated immune modulators, etc.), in many cases good advice and minimal medications will control the patient's pain efficiently. The majority of low back pain will respond well to a few days of rest and anti-inflammatory drugs. After resting, patients have to be taught how to strengthen their musculature with adequate exercises and must be advised about maintaining daily activities. The same is true for cervical pain, osteoarthritis, and many of the soft-tissue rheumatisms. It is a false idea that mechanical pain, like osteoarthritis, needs analgesics or anti-inflammatory drugs for a long time or forever. *Continuous use of analgesics will lead to more cartilage damage in the joint, while correct use of the joint will help to arrest or slow down the cartilage degradation.* If nonsteroidal anti-inflammatory drugs (NSAIDs) are necessary, there is no need to go for the new generation of COX-2 drugs, which are very expensive. Indomethacin and diclofenac are cheap, effective, and widely available. New therapies, mainly biological agents, have changed the outcome of crippling rheumatic disease. Unfortunately, they are very expensive and not affordable in many places. However, tried and true medications, available since the mid-20th century, can still make a vast difference, if correctly combined and used. Some of them are relatively affordable (e.g., chloroquine, prednisolone).

What do you need to know about osteoarthritis?

Osteoarthritis (OA) is the mechanical disorder *par excellence*. It is due to degeneration of the cartilage and may be primary (related to age or menopause) or secondary (related to mechanical effort, metabolic disorders, or genetic malformation, inflammatory arthritis, infectious arthritis). It is seen in 9.6% of the population aged 15 or older in Asian-Pacific countries [1]. The starting age depends mainly on the joint, with individual variation, which is probably due to variation in genetics. At the beginning, OA may not be painful, or the pain may be episodic. Laboratory tests are unnecessary. CBC, ESR, CRP, RF, uric acid, and infectious diseases tests, mainly Wright for brucellosis and PPD (purified protein derivative) for tuberculosis, are normal.

Plain X-ray is not necessary for the diagnosis, helping essentially to demonstrate the severity of cartilage destruction. The radiographic signs appear late (months or years after the onset) and are mainly joint space narrowing and osteophytes.

There is no specific treatment to cure or even stop the progress of OA. Pain, on the contrary to what the patient thinks, is acting in his/her favor. Pain shows what activity is harmful to the joint and how much activity it can afford without interfering with the normal physiology of the cartilage. Pain-killing techniques are usually harmful for the joint, unless they are given concomitantly with rest. In many instances, there is no need for complete rest or medication. Explaining the physiology of pain is the best treatment for the prevention of fast degradation of the joint. Joint activity is permitted to the degree that pain is not too severe. In severe cases, anti-inflammatory drugs, either NSAIDs or steroids, are preferable as analgesics. They are given for 2 to 3 weeks (150 mg indomethacin or diclofenac, 15 mg prednisolone), along with moderate joint rest. After this period, medication is stopped, and the patient is advised about adequate joint activity. Exercise to improve muscle strength is very important, which by improving joint physiology helps to slow down the disease process.

What are specific recommendations for osteoarthritis of the knee?

Osteoarthritis of the knee is the most frequent type of OA, seen in 15.3% of cases. The pain starts with walking, in the beginning or later, depending of the severity of cartilage damage. With rest, pain disappears gradually. Gelling pain is seen at the start of walking, disappearing quickly. Pain may be located in the knee joint itself, or projected to the calf or thigh, or even to the

hip. Physical examination reveals cold skin with normal coloration. Scraping the patella against the femoral knee epiphysis will produce a sensation of shaving an irregular surface. The maneuver is usually painful. The range of motion is normal at the beginning, deteriorating gradually. Full extension and full flexion become impossible, and gradually the limitation increases. Abnormal movement (lateral motion in full extension) is a sign of advanced cartilage destruction. X-rays, especially if taken in a standing position, will demonstrate joint space narrowing, which is more pronounced in the internal compartment.

Episodically, an inflammatory attack of OA will occur, and the knee will become swollen. The pain worsens and becomes continuous, while maintaining its mechanical character. Physical examination reveals synovial effusion with limitation of joint movement. It will disappear with rest, in a few days to a few weeks, and symptoms will settle to what they were previously. Laboratory tests are not necessary when the history is evocative. They remain normal, as during the normal course of the disease. X-rays do not change during the inflammatory attack.

Treatment is indicated mainly for inflammatory attacks, when walking must be limited to allow the joint to rest. Exercise to strengthen quadriceps is essential, especially when walking is limited. When possible, bicycling is a very good choice, by preventing long displacements that are harmful to the knee joint, while exercising the quadriceps.

What about osteoarthritis in other locations?

Osteoarthritis of the hip is much like knee OA, except that the pain is localized to the groin and buttock. It can project to the thigh or even the knee joint. Distal interphalangeal joint (DIP) OA is named as Heberden's node. It is characterized by two nodes on the dorsal aspect of the joint. After a long progression, slight to moderate deformity may appear. The pain is sporadic and is mainly seen when the nodes appear, and thereafter during progressive attacks. No treatment is effective. NSAIDs are effective only for the duration of attacks. Proximal interphalangeal joint (PIP) OA is named Bouchard's node. It is characterized by a single node on the dorsal aspect of the joint. It has the same characteristic as Heberden's node. EULAR guidelines for diagnosis are of interest [7].

Pain in OA of the toes is mechanical. Deformity is seen after long progression. Moderate activity and a short of course NSAIDs with joint rest are the best strategy. Surgery, when possible, can be a good alternate choice. Primary OA of the elbow is very rare. Among the secondary forms, using a jackhammer produces a special type of OA. Patients have night pain, very similar to inflammatory pain, improving or disappearing as work resumes. In the ankle, shoulder, wrist, and metacarpophalangeal joints, OA is usually secondary.

What is the significance of "soft-tissue rheumatism"?

Soft-tissue rheumatism is the third most frequent cause of rheumatic pain. It is seen in 4.7% of the young and adult population [1]. Pain is due to periarticular components (tendons, tendon sheaths, bursae, and ligaments). In the majority of cases, pain is mechanical and related to the patient's activity. The pain has a high tendency to recur. Treatment outcome is unpredictable, from excellent with minimal intervention to resistant with the best known strategy. The best approach seems to be good patient education with minimal intervention: NSAIDs (high dose) or steroids (15 to 20 mg prednisolone) for few weeks, and if necessary local steroid injection (repeated once weekly as needed, usually not exceeding three consecutive injections).

Soft-tissue rheumatisms are numerous in types and location. The most frequent and important are located at the shoulder (tendonitis, acute and subacute periarthritis, frozen shoulder, rotator cuff rupture), the elbow (golfer's and tennis elbow), and the forearm (De Quervain's tenosynovitis), among others.

What should one know about osteoporosis?

Osteoporosis is a natural course of bone physiology if one lives long enough. From birth to young adulthood (around 30 years of age), bone mass increases. After that, the body gradually starts losing its bone reserves. In women the rate of loss is very low until menopause, and then it accelerates for 10 to 15 years before slowing down again. In men, the descending curve is uniform. The decrease of bone mass density (BMD) makes the bone fragile. The quality of bone also degrades with age, even if bone mass remains stable, increasing the fragility of bones. Both phenomena increase the risk

of fracture. With increasing lifespan, osteoporosis will become more frequent, in any region of the world. The World Health Organization (WHO) has classified it, since 1991, as "public enemy number one," along with cardiac infarction, stroke, and cancer.

Unfortunately, osteoporosis has no clinical manifestation until fracture occurs. The only way to make a diagnosis before a fracture occurs is by bone densitometry. It is a very expensive procedure, not available for general use in developing countries. X-ray diagnosis is difficult and late. More than 30% of the bone mass has to disappear for it to be diagnosed by a plain x-ray of the spine. The gold standard of treatment is bisphosphonates, mainly alendronate. Unfortunately it is an expensive drug. Natrium fluoride is cheap and can be made up by most pharmacies. It may increase bone mass, although results are controversial; 20 to 40 mg daily, used for 1 year and then stopped for 6 months before it is used again, may increase bone mass without decreasing bone strength. Calcium supplements or dairy products along with enough vitamin D (800 units daily of vitamin D_3) have to be added to the diet as well.

Is rheumatic arthritis a very frequent disease?

Rheumatic arthritis is not very frequent (affecting around 1% of the population). Other autoimmune diseases causing arthritis include spondyloarthropathies, connective tissue diseases (such as systemic lupus erythematosus, dermatopolymyositis, or progressive systemic sclerosis), and vasculitides (such as periarteritis nodosa or Wegener's granulomatosis).

The incidence of rheumatic arthritis is even lower in certain regions of the world; in Asia it affects only 0.33% of the population [1]. It mainly involves peripheral joints, but it can involve other organs too (lungs, heart, kidneys), although not frequently. Joint involvement will lead to progressive destruction, causing disability in a few years if the patient is not treated. Wrist and finger joints (metacarpophalangeal and proximal interphalangeal), are most commonly affected, but other joints are also involved (elbow, knee, ankle and foot, hip, and shoulder). The pain is an inflammatory pain. Morning stiffness may last until noon or even well into the afternoon in severe cases.

Examination reveals swelling of the joint, due to synovial effusion and synovial hypertrophy. ESR is raised, CRP is positive, and in more than 75% of cases, rheumatoid factor (RF) is positive in the serum. Recently, anti-CCP (cyclic citrullinated peptide) has gained much attention as being specific for RA, although not in all patients. X-rays will, after 6 months to 1 year's duration of arthritis, show joint demineralization, followed by joint surface erosion, and later joint destruction. The disease is chronic, lasting decades, but it can go in remission (temporary or definitive). Treatment is based on a combination of two or more disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, chloroquine, sulfasalazine, and low-dose prednisolone [2]. In refractory cases, biological agents will be of help. In countries where biological agents are not available or patients cannot afford them, a combination of several immunosuppressants can be considered.

Pearls of wisdom

Remember:

- The decision tree (Fig. 1) is self-explanatory. As an example: If the pain is mechanical and the spine is involved, it is important to find out if the pain started insidiously or if it had an acute onset. In case of insidious onset, ordinary low back pain or cervical pain is by far the most likely cause.
- The decision tree cannot give you a diagnosis, but it may be of help as to where to search for the diagnosis.
- The first step is to distinguish between mechanical and inflammatory pain, which should not be too difficult. The difficulty is when the patient complains of continuous pain. If you question the patient carefully, you can usually find a mechanical or inflammatory character in the continuous pain.
- Clinical examination will help to elucidate the diagnosis. If necessary, laboratory tests and X-rays will be of help.
- The remainder of the decision tree is used in a similar manner.

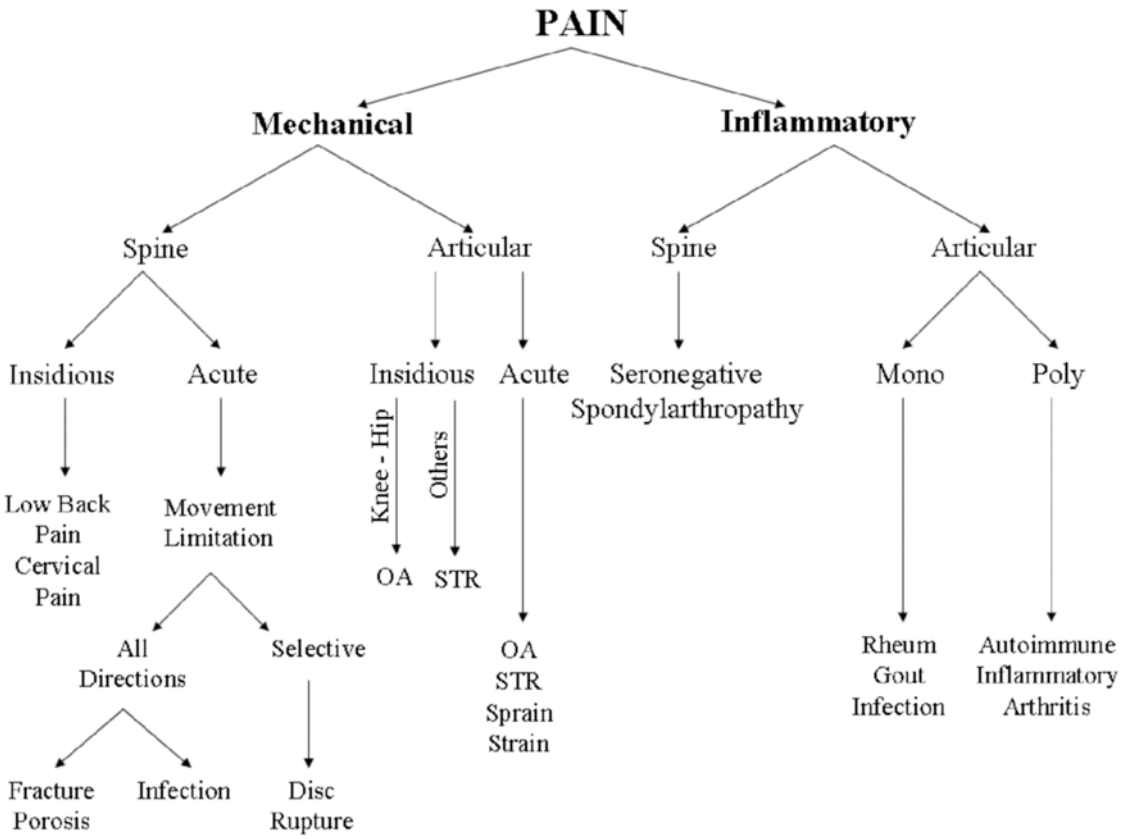

Fig. 1. Decision tree for rheumatic pain. OA, osteoarthritis; STR, soft-tissue rheumatism.

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Difficult Therapeutic Situations and Techniques

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Chapter 30
Dysmenorrhea, Pelvic Pain, and Endometriosis

Susan Evans

Case report

A 25-year-old married woman presents with pelvic pain on most days each month, especially during the time of her period. She suffers crampy period pain before and during her period, sharp stabbing pains that come at any time and wake her at night, bladder symptoms (urinary frequency, urgency, and nocturia), headaches, and dyspareunia (painful sexual intercourse).

What are the treatment options?

This woman has chronic pelvic pain, with a combination of different types of pain, and she probably has endometriosis. For pain control she will need treatment for each type of pain:

- The oral contraceptive pill and a nonsteroidal anti-inflammatory drug (NSAID) are good first-line options for her period pain. If the pain persists, and high-level laparoscopic surgery to remove endometriosis is not available, then continuous progestogen or a levonorgestrel intrauterine device are options.
- Amitriptyline starting at 10 mg at early evening, daily, and increasing slowly as tolerated up to 25 mg daily could be prescribed for her sharp stabbing pains and the bladder symptoms.
- A careful history should identify dietary triggers for her bladder symptoms and the cause of her dyspareunia (see below).
- Regular daily gentle exercise should be encouraged to help reduce pain levels.
- Her headaches should be managed.
- The decision to refer her to a surgeon will depend on whether her period pain becomes unmanageable or she has difficulty becoming pregnant. It will also depend on the surgical skills available.

How frequent is pelvic pain?

Pelvic pain is underreported, undertreated, and underestimated throughout the world. It affects approximately 15% of all women aged 18–50 years. Although it is complex to treat, the improvement in quality of life that can be achieved is very rewarding. Most women have more than one type of pain. Their symptoms include any, *or all* of:

- Dysmenorrhea
- Dyspareunia
- Neuropathic pain
- Bowel dysfunction
- Bladder dysfunction
- Vulval pain
- Bloating
- Chronic pelvic pain

Frequently, their pain symptoms have been present for years without diagnosis or management. The pain affects their education, employment, relationships, self-esteem, general wellbeing, sleep and sometimes fertility, so it is important to realize that patients needs emotional

as well as physical support. This chapter will provide an overview of pharmacological and non-pharmacological interventions for effective pelvic pain control.

How can I assess the cause of pain in a woman with pelvic pain?

Pelvic pain is assessed with a history, an examination, and special investigations.

History

Ask about the date of the last period in case of pregnancy, and make a list of each pain or symptom the patient has. For each pain, ask her to describe what it feels like, where it is, when it occurs, how many days she has it per cycle, and what aggravates or relieves it. Ask about bladder symptoms (nocturia, frequency, urine infections, urgency), ask about bowel function (constipation, diarrhea or bloating, pain opening her bowels during her period), ask about pain with movement and pain in other areas of the body (e.g., migraine or muscle tender points), ask whether intercourse is painful, and ask how many days a month she feels completely well.

Examination

Assess the patient's general well-being (depression, posture, and nutrition), the abdomen (for sites of pain, tenderness, peritonism, or masses), the vulva (for tenderness, skin lesions, or vulval infection), the pelvic floor muscles (for tenderness and spasm), the vagina (for nodules of endometriosis posterior to the cervix or in the rectovaginal septum, or congenital anomalies), and the pelvis (for uterine or adnexal masses, pregnancy). Vaginal examination is rarely necessary in virgins.

Investigation

Exclude pregnancy, including ectopic pregnancy, screen for sexually transmitted diseases if appropriate, and take a cervical smear if available (unnecessary for virgins). Ultrasound may show an endometrioma, but it is often normal, even with severe endometriosis.

How can I plan treatment for pelvic pain?

The treatment recommended depends on the symptoms present. Most women will have more than one pain symptom. Plan a treatment for each separate pain symptom. Remember to treat any coexisting health problems to allow patients more energy to cope with their pain:

- Premenstrual syndrome (PMS), depression, anxiety
- Menorrhagia
- Acne
- Constipation
- Poor nutrition, poor posture, lack of exercise
- Other pain conditions, including migraine

How can I treat dysmenorrhea on day 1–2 of the menstrual cycle?

Pain at this stage of the cycle is usually uterine pain. Management options at the primary care level include monophasic oral contraceptive pills, such as 20–35 μg ethinyl estradiol with 500–1,000 μg norethisterone or 150 mg levonorgestrel, as well as pain medication. The pain medication of first choice should be an NSAID taken early on in the episode of pain, such as ibuprofen at a dose of 400 mg initially and then 200 mg three times daily with food. For moderate or severe pain, opioids should be offered. Nonpharmacological options include hot or cold packs over the lower abdomen, *Vitex agnus castus* (chasteberry) 1 g daily (avoid if pregnant; ineffective if on oral contraceptive pills), vitamin E (400–500 IU natural vitamin E from 2 days before period until day 3) and zinc 20 mg (as chelate) twice a day. Traditional Chinese Medicine (acupuncture and herbal therapies) are also popular, but they should only be recommended if affordable and if the patient has a positive attitude.

Many women with severe dysmenorrhea become fearful as their period approaches. They fear pain that they cannot control. By providing them with strong analgesics to control severe pain if it occurs, this anticipation of pain can be reduced and they can regain control of the pain. Therefore, "on-demand" doses of analgesics should be provided.

How can I treat prolonged dysmenorrhea? Could the patient have endometriosis?

Dysmenorrhea (painful cramps) for more than 1–2 days is often due to endometriosis, even in teenagers. A woman with endometriosis also has a more painful uterus than other women. She thus has two causes for her pain. Management options include on the primary care level all the treatments used for dysmenorrhea above, a levonorgestrel intrauterine device, continuous progestogen (norethisterone 5–10 mg daily, dydrogesterone (a synthetic hormone similar to progesterone)

10 mg daily, or depot medroxyprogesterone acetate to achieve amenorrhea). If referral to a well-equipped hospital is an option, surgery, preferably laparoscopy, to diagnose and remove endometriosis, if medical treatments have failed, would be indicated. Hysterectomy is only indicated if the patient is older and her family is complete. Conserve the ovaries where possible in premenopausal women. Ovarian endometriomas can usually be treated with cystectomy rather than oophorectomy.

How can I treat ovulation pain?

Normal ovulation pain should only last for 1 day, occurs 14 days before a period, and changes sides each month. Management options include an NSAID when pain occurs, an oral contraceptive pill to prevent ovulation, or continuous norethisterone 5–10 mg daily to induce amenorrhea. If more than the primary care level is available, and pain is severe or always unilateral, a laparoscopy with division of adhesions and removal of endometriosis is indicated. An ovary should only be removed if severely diseased, and the patient's fertility needs have been discussed and carefully considered.

How can I treat a woman with pelvic pain and bladder symptoms?

Many women with pelvic pain describe frequent urination, nocturia, pain when voiding is delayed, suprapubic pain, vaginal pain, dyspareunia, or the feeling of having a urinary tract infection. This feeling is often due to interstitial cystitis of the bladder. There may be a history of frequent "urinary tract infections" but with negative urine culture. First, exclude urine infection, chlamydia, and gonococcal or tuberculous urethritis. Then ensure sufficient fluid intake to avoid concentrated urine. Identify and avoid dietary triggers if present. Common triggers include coffee, cola drinks, tea (including green tea), vitamins B and C, citrus fruit, cranberries, fizzy drinks, chocolate, alcohol, artificial sweeteners, spicy foods, or tomatoes. Peppermint and camomile teas are usually acceptable. If food triggers are present, pain usually follows within 3 hours of food intake. Provide instructions about how to manage symptom flares (drink 500 mL water mixed with 1 teaspoon of bicarbonate of soda. Take a paracetamol (acetaminophen) and an NSAID if available. Then drink 250 mL water every 20 minutes for the next few hours). For symptom control, try amitriptyline 5–25 mg at night, oxybutynin (start with 2.5 mg at night, increase slowly to 5 mg three times a day), or hydroxyzine, especially for those with allergies (start with 10 mg at night, increase slowly to 10–50 mg at night).

Many women with bladder symptoms develop secondary pelvic floor dysfunction with dyspareunia and severe muscular pelvic pain. If pain persists, consider cystoscopy with hydrodistension. All medications should be avoided in pregnancy, if possible. Also note that hydroxyzine is contraindicated in epileptics.

How can I treat sharp, stabbing pains?

Sharp, stabbing pains are usually a form of neuropathic pain. Treatment includes neuropathic pain medications (e.g., amitriptyline 5–25 mg in the early evening, gabapentin 100–1200 mg daily), regular sleep, regular exercise (start with regular low-level exercise to avoid initial worsening of pain), and stress reduction. Start all medications at a very low dose and increase slowly. Where high-level surgical skills are available, excision of endometriosis lesions, if present, can sometimes improve the pain, although frequently this type of pain continues after surgery.

How can I diagnose the cause of dyspareunia?

Dyspareunia (painful intercourse) may be the most distressing symptom for many women, as it interferes with the relationship they have with their husband. She may feel that she is letting her husband down when she is unable to have intercourse due to pain, and he may feel that she is avoiding intercourse because she no longer loves him. It is important to identify the cause of the problem:

- Examine the vulva visually for abnormalities (infection, dermatitis, lichen sclerosis).
- Use a cotton-tipped swab to test for tenderness of the posterior fourchette, even if it looks normal (to check for vulvar vestibulitis).
- Use one finger in the lower vagina to push backwards (to check for pelvic floor muscle pain or vaginismus). Use one finger to push anteriorly (to check for bladder or urethral pain).
- Use one or two fingers to check the upper vagina for nodules of endometriosis, pelvic masses, or uterine fixation. Push the cervix to one side to check for contralateral adnexal pain (to check for endometriosis, ovarian cysts, pelvic infection, or adhesions).
- Use a speculum to look for cervicitis, vaginal infection, vaginal anomaly, or endometriotic nodules in the posterior vaginal fornix.

If any part of the examination causes pain, ask the patient if this is the same pain she has with intercourse. It is important to examine the lower vagina gently with one finger before using the speculum, or pelvic floor/bladder pain may be missed. Generalized dyspareunia, especially where sharp pains are present, may be neuropathic. Include in the consultation a discussion about the relationship she has with her husband and whether he is supportive of her.

How can I help my patient with a painful vulva (vulvodynia)?

General vulval care is often helpful. The patient should not use soap and should avoid vulval products such as talc or oils. Recommend aqueous cream as a soap, soother, and daily vulval moisturizer. Recommend cotton underwear and loose clothing. Treat any vaginal infection. Prescribe amitriptyline 5–25 mg at night or an anticonvulsant for vulval pain if present. For vulvar vestibulitis, prescribe a course of oral ketoconazole (antifungal) 200 mg and betamethasone cream (0.5 mg/g) applied thinly daily for 3 weeks. For lichen sclerosis, prescribe steroid cream applied thinly daily for intermittent courses only when symptoms are present.

How can I help my patient with painful pelvic muscles?

The muscles are in spasm and do not relax normally. This type of pain can be secondary to painful bladder symptoms, any type of pelvic pain, previous sexual assault, or anxiety regarding sexual intercourse. Pain is severe, just as pain from back spasms can be severe. Typical symptoms include dyspareunia (with pain for 1–2 days afterwards), pain on moving, pain with insertion of a finger or a speculum, and pain with tampons. There may be pain on prolonged sitting. Pelvic floor muscle spasm is involuntary, and the patient cannot "just relax." The best treatment involves pelvic floor physiotherapy, instruction in relaxation techniques, and the regular use of vaginal dilators in a relaxed, secure, nonpainful situation. Intercourse should be avoided until the problem has resolved because the problem will worsen with repeated painful intercourse. If intercourse continues, a vaginal lubricant and a slow approach to intercourse may help. Other treatments include:

- Resolution of initiating factors, e.g., bladder symptoms/pelvic pain.
- Avoid straining with voiding or trying to stop passing urine in mid-void.
- Regular gentle exercise (e.g., walking, stretching, gentle yoga), improved posture, sitting square in a comfortable chair with good support, keeping both feet flat on the floor when sitting, and taking regular breaks.
- Heat packs to the pelvis and a warm bath 1–2 times daily for 3–6 weeks
- Management of anxiety and depression, if present.

When should I refer my patient with pelvic pain to a surgeon?

Surgery should be considered where nonsurgical treatments have failed. Laparoscopy is preferred to laparotomy where it is safe and available. However, laparoscopy requires advanced surgical equipment and skills, and major surgical complications do occur. It is therefore important to try nonsurgical options first. Endometriosis surgery is frequently difficult and requires the best surgical skills available. Situations that suggest severe disease, possibly requiring a bowel surgeon as well as a gynecologist, include:

- The presence of ovarian endometriomas.
- Nodules of endometriosis palpable in the rectovaginal septum.
- An immobile uterus.
- Pain opening the bowels during the menstrual period.

In premenopausal women, if postoperative estrogen replacement is unavailable, *bilateral* oophorectomy should be avoided, if possible. Endometriomas in young women should be managed with cystectomy rather than oophorectomy in most cases. Drainage alone of an endometrioma is usually followed by rapid recurrence.

What are common barriers to effective pain management?

A long delay between the beginning of symptoms and the diagnosis and management of pelvic pain is common for many reasons. The patient's family may not believe that her pain is real and severe, she may believe that severe pain with periods is normal, or her local doctor may believe that she is too young for endometriosis or underestimate how severe her pain is.

Other barriers to effective pain management include fear of gynecological examination, especially where a female doctor is unavailable; fear of surgery, infertility, and cancer; and fear of the unknown.

It is therefore important to explain to the patient *and her family*:

- The pain is real, and the pain is not her fault.
- She does not have cancer, and her pain is not life-threatening.
- Although it may not be possible to *completely* cure all her pain, she can optimistically look forward to less pain and living better with what pain remains. It is important to be positive.
- Resources she can contact if she needs help.
- What extra pain relief she can use if the pain becomes more severe; her anxiety will decrease when she knows that she can manage pain if it occurs.
- To ensure that she is not overworked, because tiredness will worsen her pain.
- To ensure that she has activities in her life that she enjoys.

What should I ask at follow-up visits?

Follow-up assessments are important because the pain will vary over time, and the patient will need continued support to be well. At each follow-up:

- Ask about each of the pains she reported at her first visit to assess progress. Pain that has been resolved is often forgotten. She may feel that no progress has been made if any pains remain.
- Ask about any new pains. Ask about sexual function. Offer treatment for any new pains.
- Discuss lifestyle issues again, such as regular exercise, healthy diet, stress management, relationship issues, and activities that she enjoys.
- Make sure she understands that her pain may change over time but that help is available if she needs it.

Pearls of wisdom

- Most women with chronic pelvic pain have several different pain symptoms. Each pain needs to be assessed, and a treatment plan made. Pelvic pain cannot be considered as a single entity.
- Many common causes of pelvic pain cannot be seen during an operation, including bladder pain, neuropathic pain, uterine pain, pelvic floor muscle pain, and bowel pain. Some women have endometriosis *and* all these other pains. Migraine headaches are also common.
- Women with chronic pain who appear "worn down" emotionally or depressed often have a neuropathic component to their pain. This will be worse if the patient is stressed or overworked.
- Recognize that many women have had pain for long periods of time, resulting in loss of confidence, employment and education opportunities, relationships, and sometimes fertility.
- It is important that the patient's family value her health and happiness, and that she has activities in her life that bring her joy, relaxation, and satisfaction. "Fit, happy people have less pain."
- Recognize that while surgery can be very helpful, it does not cure all pain. The decision whether to proceed to surgery or use nonsurgical treatment will depend on the surgical facilities available.
- Be careful to explain the pain to the patient and make sure she knows that you believe in her pain. Most women with this type of pain have been told that "it is all in their head," which lowers their self-esteem.
- Make sure that the family knows that the pain is real. The patient will need the support of her family to access care.

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[2] Howard FM. Pelvic pain: diagnosis and management. Lippincott Williams and Wilkins; 2000. (A textbook for doctors describing all aspects of pelvic pain in detail.)
[3] Stein A. Heal pelvic pain. Available from: www.healpelvicpain.com. (A book for patients with all types of musculoskeletal pelvic pain.)

Websites

www.endometriosis.org (world forum for patients and doctors)

www.endometriosisnz.org.nz (for teenagers with endometriosis)

www.ic-network.com (for bladder symptom information)

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Guide to Pain Management in Low-Resource Settings

Chapter 31
Pain Management Considerations in Pregnancy and Breastfeeding

Michael Paech

Case report 1 (analgesics in pregnancy)

You are visited by a woman, Shillah, and her partner, Alusine, from a large rural town. They have recently married, and they plan to move to the regional city and stay with relatives because they are hoping to start a family. Alusine says: "Doctor, my wife has bad back and leg pain, and every day she takes medication prescribed by the local doctor. We are trying to have a baby, so I am worried about how those drugs might affect the baby. Is it okay for her to keep taking them?"

You ask Shillah about her pain, and learn that she has had it for over a year since a motor vehicle accident in which she broke some lumbar vertebrae. The pain has persisted and is a burning sensation that radiates from the low back down through the buttock past the back of her knee, often occurring at night when she is lying quietly. She also has an area near her spine in the lower back that tingles and feels sore, even when it is only touched lightly. He doctor has tried her on several different analgesic drugs, and the only one that helps a little is a tablet she takes at night before bed, although she is also taking an anti-inflammatory drug, and she takes some codeine when the pain is bad—but it makes her constipated, so she doesn't like to use it much. On examination she has no obvious spinal abnormality. You later learn she is taking a low dose of amitriptyline (10 mg) at night, regular diclofenac (100 mg twice a day), and codeine (30–60 mg every 6 hours as required, but only once or two days each fortnight).

Should you be concerned about prescribing pain killers in a pregnant or lactating woman?

We should be cautious about prescribing any drug to a pregnant woman! Nevertheless, almost 90% of women take prescribed drugs during pregnancy. Although the incidence of analgesic use during pregnancy varies across different countries, it is probably 5–10% during the first trimester and is likely to be much higher in later pregnancy. The incidence of perinatal use of illicit drugs (including opioids) also varies widely, but it ranges from 10% to 50%. Thus, it is extremely common for pregnant women and their fetuses to be exposed to drugs relevant to pain management during pregnancy and lactation. The incidence of fetal abnormalities among live births is approximately 2%, so this background rate should be considered when comparing rates in the whole pregnant population with those among women taking specific drugs.

Despite the prevalence of their use, there is very little information about the effects of analgesic drugs being taken prior to conception on fertility. There are limited human epidemiological or observational data on the effects of pain-relieving drugs during early pregnancy. With the exception of aspirin and the nonsteroidal anti-inflammatory drugs (NSAIDs), the embryo appears protected in the first 2 weeks. The fetus is most

at risk during the period of organogenesis, between 17 and 70 days postconception; however, the use of some drugs during the second and third trimesters of pregnancy can also cause organ abnormalities, especially in the central nervous and cardiovascular systems. It is thus important to know, in detail, the potential risks associated with analgesic drug administration at any stage of pregnancy.

Fortunately, we know it is likely that millions of women have taken some of the commonly used pain killers, both at the time of conception and during early pregnancy. For a number of analgesic drugs, extensive clinical experience indicates a very low risk of problems, which is reassuring. When clinical information is combined with analysis of animal data about potential teratogenic or carcinogenic effects, or data about how much drug is transferred into the breast milk, the level of concern about a drug can be estimated. Consequently, regulatory bodies and educational organizations in many countries have classified drugs into risk categories that are used to guide a risk versus benefit assessment in the pregnant and lactating woman. For example, there is no evidence that opioids are risky in early pregnancy, but they may cause depression of the neonate at birth, so most opioids are classified as drugs that have harmful but reversible pharmacological effects on the human fetus or neonate, without causing malformations.

It is imperative to relieve maternal suffering, but at the same time, harm to the fetus should be avoided. Breastfeeding is also a critical imperative for optimizing the infant's health, possibly with life-long benefits. It is important that we know where to look and are able to access information about these topics when specific information is required.

What would be the ideal approach to pain management in pregnancy and lactation?

During and immediately prior to pregnancy, nonpharmacological pain management options should be considered and explored before analgesic drugs are used. Ideally, if available in the regional city, and prior to Shillah becoming pregnant, she should be reviewed by a group of health care providers, particularly those with an interest in pain medicine and clinical experience dealing with patients with difficult pain management problems. In Shillah and Alusine's case, for example, this group might include an orthopedic surgeon, a rehabilitation physician, an obstetrician, a family doctor, an anesthetist or pain specialist, a physiotherapist, a chiropractor, a psychologist, a pharmacist, and/or a community nurse. This multidisciplinary team approach will optimize her care, and regular review of her pain management can be organized. Shillah may well have physical and psychological factors contributing to her pain that can be treated in various ways, including physical therapies and even invasive pain therapy procedures or surgery, such that her reliance on drugs might be reduced or even eliminated. The latter would, of course, solve all the issues related to the potential pharmacological toxicities of drugs administered during pregnancy. Even if drug treatment remains the only way of controlling her pain, her response to the types of drugs, their doses, and the regimens prescribed will need to be reviewed once she becomes pregnant and as pregnancy advances.

What would your advice be for Shillah and Alusine?

Shillah has chronic nonmalignant pain with neuropathic features, and you should refer to the chapters on back pain and neuropathic pain for information. You also need to be in a position to advise her about the specific risks of the drugs she is currently taking and about any risks associated with alternative drugs. First, what about a tricyclic antidepressant such as amitriptyline, an NSAID such as diclofenac, and an opioid such as codeine?

It is important to be honest and transparent in all communication. Although there can be no guarantees of complete safety with any drug, and because controlling neuropathic pain can be challenging, it is not necessary for her to abandon all pain killers. Indeed, there is no evidence that continuing amitriptyline in early pregnancy significantly increases the risk of malformations. This is a drug many pregnant women have used, so the couple can be reassured of its relative safety, and it could be continued. The NSAIDs such as diclofenac and indomethacin (and a similar drug, aspirin) are not effective against neuropathic pain but may be very helpful for a few days for musculoskeletal or postoperative wound pain. However, unless there is active inflammation, which is unlikely in Shillah's case, they should not be continued long-term. Although these drugs do not cause fetal malformations, they adversely influence fertility, increase the risk of miscarriage by interfering with blastocyst implantation, and can cause serious problems in late

pregnancy (see below). You should advise Shillah to stop the diclofenac, and if available to try paracetamol (acetaminophen) instead, this being a much safer option. Although it is not ideal, there is no reason why Shillah should not continue to take codeine when she needs it (at a maximum dose of 240 mg per day), especially if you check her diet and advise her as to how to reduce her risk of constipation. Codeine has been used by many pregnant women and is considered safe for the fetus in early pregnancy. The main problem with codeine is that some people lack the liver enzyme required to demethylate it to its active metabolite, morphine, rendering it completely ineffective. Other people are ultrarapid codeine metabolizers and will experience higher plasma concentrations and more side effects (sedation, dysphoria, constipation, and neonatal depression), even after small to modest doses.

Are there any other analgesics that might be available when Shillah attends the large city hospital?

There are some other pain killers that might prove more effective or cause fewer side effects. Instead of codeine, oxycodone (5–15 mg repeated as required) is an example of an oral opioid, effective against moderate to severe pain, which causes less constipation. Long-term opioid administration continued until delivery of the baby has some significant disadvantages, however (see case 3 below), so it would be essential to confirm that Shillah's pain is opioid-sensitive. She could be admitted to hospital, her pain evaluated (pain scores, functional disability, and opioid-related side effects) and documented, and then the opioid introduced at a low dose, escalating the dose over a few days until the drug is effective with acceptable side effects, or until failure (lack of effect, or benefit limited by excessive side effects).

Another possibility is tramadol, which has oral and intravenous formulations. Doses of 400–600 mg per day are effective against both acute pain and neuropathic pain. Tramadol has several antinociceptive actions (serotoninergic, noradrenergic, and weak mu-opioid activity from its principal metabolite), is useful for moderate to severe pain, and does not cause respiratory depression. Tramadol should be avoided in women who are at increased risk for seizures, such as those with preeclampsia or eclampsia, or those taking other drugs that increase central nervous system levels of serotonin. Common side effects are nausea and dizziness. Animal studies indicate that tramadol is a low-risk drug for fetal abnormalities, but experience in early pregnancy is very limited, so it would be preferable to use an opioid instead for Shillah. After the period of organogenesis, limited data suggest that tramadol is probably of low risk to the fetus, although high dosing near delivery should be avoided (see case 3 below).

In some countries, transdermal clonidine patches (100 μg/day) are available, but clonidine is of questionable effectiveness, and despite extensive clinical use during pregnancy without evidence of causing congenital abnormalities, data on its safety in the first trimester are very limited. Therefore, the use of clonidine is not recommended.

What if Shillah continues to have neuropathic pain later in pregnancy?

Good levels of evidence support both the efficacy and safety of typical doses of amitriptyline (initially 10–25 mg orally at night). Ketamine, another potent analgesic, can be effective for both acute and neuropathic pain, although oral tablet or lozenge forms are still being developed. Ketamine has been used in large numbers of pregnant women without links to malformations, so it is considered safe, making it a valuable option when patients are admitted to hospital when either acute or neuropathic pain is difficult to manage(bolus up to 0.25 mg/kg and initial infusion rate 5–10 mg/h). Because local anesthetics are safe during pregnancy, lidocaine (lignocaine) infusion (1 mg/kg over 20 minutes then 10–30 mg/h, see the chapter on neuropathic pain) is another option that is effective in a minority of patients with neuropathic pain.

If gabapentin is available, it can be considered. It does not cause major malformations in animal studies and has not demonstrated evidence of harm in limited human experience to date. Mexiletine also appears to be of low risk to the fetus, but it is less effective and has more side effects. In contrast, carbamazepine, although still used during pregnancy in some epileptic patients because its benefit is considered to outweigh the risk of harm, should be avoided, even after the first trimester, because it causes major and minor abnormalities, including spina bifida, craniofacial defects, and coagulation disorders in humans. The selective serotonin reuptake inhibitors and similar drugs (citalopram, paroxetine, venlafaxine), lamotrigine (an anticonvulsant) and pregabalin (a voltage-gated calcium channel blocker) have limited information available and are best avoided.

Case report 2 (analgesia when breastfeeding)

Agnes is a 28-year-old multigravid woman who has two children and is now 34 weeks pregnant. She comes from a good and sensible family that is well known to you. She has come to you for advice because the obstetrician has just booked her for an elective repeat cesarean delivery in 1 month. She has been told that the baby appears to be much bigger than last time, when she experienced failed progress of labor and had to have an urgent cesarean section. Although she has been doing well and understands why it would be best to have another cesarean, she is very anxious and is not sure whether to have her operation at the district mission hospital or whether to ask if she can go to the referral hospital in the nearby city with better facilities.

Agnes is worried for two reasons. First, after her last cesarean she had a lot of pain, especially during the first two days, and she is scared about suffering the same experience. Second, local women elders had told her that if she had any strong painkillers after the operation, the baby would not be able to breastfeed—but she cannot afford to use milk formula. You listen sympathetically because you are aware that many women are not getting very good pain management after their cesarean at the district hospital. You are planning to talk to the doctors there to suggest some simple changes that you think will improve the situation significantly. You discuss with Agnes the options that are likely to be available for her postoperative analgesia at the two hospitals and their implications when she starts to breastfeed—and then you make some recommendations and promise to contact the hospital to try and make sure she gets satisfactory treatment.

Does pain after cesarean delivery really need to be treated well?

Most women experience moderate to severe pain in the first 48 hours after abdominal surgery, including cesarean section, and both mother and baby will benefit from good pain relief. If the mother is able to move in relative comfort, she can mobilize soon after recovering from the anesthetic (within a few hours of surgery after a spinal anesthetic), which reduces the risk of pulmonary infections and venous thromboembolism, an important cause of sudden death from pulmonary embolism. She will be able to eat within hours of the operation and continue to care for and interact with her baby, while establishing lactation and breastfeeding. Effective, regular, and early pain relief reduces the risk of moderate or severe pain after the first one to three days such that most women need only paracetamol (acetaminophen) and/or an NSAID by the third to fifth postoperative day (and may reduce the risk of chronic wound pain later!). Most methods of postcesarean pain relief are based on opioids, the majority of which are considered safe for the breastfed baby if used only short-term during lactation.

What should the "district" hospital be able to offer Agnes?

The best approach to acute pain management for Agnes is a "multimodal" approach, which means combining different painkillers or analgesic methods to reduce the dose and thus side effects of each component. An opioid such as morphine should be prescribed, preferably using regular doses with extra supplementary doses if requested, for the first 24–48 hours. If an intravenous method (patient-controlled analgesia or continuous infusion, see below for these referral hospital methods) is unavailable, then the oral or subcutaneous route can be used. Intramuscular injections are more painful than subcutaneous (especially if the latter are given through a small cannula or 'butterfly" needle); they have a higher risk of deep infection and are no more reliable in their efficacy. Giving the opioid "as required" leads to undertreatment and poor pain relief because of inconsistent absorption pharmacokinetics and individual response. If a range of doses is prescribed, then the smallest can be used first and substituted with a larger dose subsequently if required. The drug of choice is morphine, which may be available as a tablet or oral syrup (30–45 mg every 8 hours) or a parenteral formulation (subcutaneous 10–15 mg every 6 hours). Oral codeine (60 mg every 6 hours) should only be used if another oral opioid is not available. During lactation, pethidine (meperidine) should be avoided unless there is no other alternative. It has an active metabolite, norpethidine (normeperidine), that has a very long elimination half-life in the newborn (approximately 72 hours), and as both accumulate in the neonate, the baby becomes sleepier and less active, and its ability to suck on the breast is impaired. These effects are prominent when intravenous doses are given after cesarean delivery, but they also occur from lower intramuscular dosing during labor. If the baby is very premature and has worrisome apneic spells, all

opioid doses should be minimized and if possible substituted with tramadol, which is safe for the baby in the first few days after delivery when breastfeeding is being established.

Every attempt should be made to make sure that Agnes also gets either an NSAID such as diclofenac (a second choice is indomethacin, which has more side effects), paracetamol (acetaminophen), or even both. These painkillers reduce the dose of morphine needed by 30–40% and 10–20% respectively, and an NSAID can reduce "cramping" pain from the uterus. Oral paracetamol (1 g every 6 hours) has almost no side effects and is contraindicated only in patients with severe liver dysfunction. An NSAID, preferably given at its maximum recommended dose (e.g., diclofenac 50 mg t.i.d. [three times daily] or indomethacin 100 mg b.i.d. [twice daily]) and with food to avoid gastrointestinal upset, is contraindicated in women with hypertensive disease including preeclampsia, renal impairment, peptic ulcer, or symptomatic reflux disease, and in women with a bleeding disorder or current bleeding risk.

An additional measure for the surgeon, that is not too expensive, is infiltration of local anesthetic (for example, 0.25% bupivacaine up to a maximum dose of 2 mg/kg) into the wound. Skin infiltration alone is not effective, but injection beneath the rectus sheath fascia and subcutaneously may reduce the amount of opioid needed, with a low risk of complications.

What are the effects of these drugs on the breastfed baby?

With a couple of exceptions, especially those applying to pethidine (meperidine), Agnes can be assured that all these drugs have been evaluated well and that they are considered safe and acceptable to use in the first few days after delivery. At this time, production of breast milk is increasingly rapidly, but the content is still changing from protein-rich colostrum, which is a poor transfer medium for most drugs, to fat-rich milk. The transfer of morphine and codeine, paracetamol, and NSAIDs into breast milk is only 2–4% of the weight-adjusted maternal dose, and none has adverse effects in the infant.

Aspirin is not as good a choice as paracetamol/acetaminophen, which has no detectable effects despite immature glucuronide conjugation. Aspirin is contraindicated in those at risk of bleeding due to its effect on platelet function, and although considered acceptable for use during lactation, it has been associated with the rare and serious condition of Reye's syndrome in newborns, so prolonged administration should be avoided.

You should explain to Agnes that she should try to time her feeds to avoid the peak milk concentrations of the opioid she is taking, which will usually coincide with 1–2 hours after the last dose.

What other methods might the city referral hospital be able to offer Agnes?

There may be a number of potentially superior methods of postoperative pain relief at the referral hospital that Agnes can consider and request. Intravenous morphine (and in some countries the metabolite-free but more expensive opioid fentanyl) provides better quality pain relief than subcutaneous or intramuscular morphine and is preferably administered using a patient-controlled analgesia (PCA) device (standard setting, e.g., 1 mg bolus on demand, no continuous infusion, 5-minute lockout interval) to safeguard patients from unintentional overdosing.

Neuraxial (spinal or epidural) opioid methods of analgesia provide better relief than intravenous, subcutaneous, intramuscular, or oral opioid administration. If spinal anesthesia is used, then intrathecal morphine 100–150 μg is a very safe and effective means of achieving excellent pain relief.

Morphine's long elimination half-life in cerebrospinal fluid results in clinically good or excellent pain relief for 4–24 hours (on average 12 hours), especially if an oral NSAID is also given. Sedation, nausea, and vomiting are common side effects after opioids. In general, sedation will be greater after systemic administration (oral, intramuscular, and intravenous) and itch more severe after neuraxial (spinal or epidural) administration. All patients receiving opioids, especially neuraxial, should be monitored for oversedation and low respiratory rate, although serious morbidity is rare in the obstetric population. Many hospitals and doctors appear especially concerned about spinal or epidural opioids, but when they are used correctly, case series suggest a significantly higher risk of clinically important respiratory depression associated with intravenous opioid. Postoperative epidural analgesia is less likely to be available but is highly effective. It can be achieved with single or repeated (8–12 hourly) doses of morphine 3 mg or in technology-rich hospitals, with epidural infusion or patient-

controlled epidural analgesia (PCEA) using fentanyl (2 μg bolus, 15 minute lockout time) or pethidine/meperidine (20 mg bolus, 15 minute lockout time). These epidural methods are associated with lower rates of opioid consumption (by 20–50%) than intravenous opioid and although short-term epidural opioid administration after cesarean delivery has not been well investigated, clinical experience suggests the breastfed neonate is not affected.

Immediate-release oxycodone (e.g., 5–10 mg regularly 4 hourly for 48 hours, with additional doses on request) is a more effective oral opioid than codeine and also tastes less unpleasant than oral morphine. Tramadol (50–100 mg intravenous or oral, repeated 2 hourly to a maximum of 600 mg per day) is also an excellent choice for postoperative pain relief. Agnes can also be reassured that short-term use for a couple of days immediately postpartum is associated with low transfer of drug into breast milk (less than 3%) and that there are no apparent effects on the baby. In some countries the new generation of NSAIDs, the cyclooxygenase-2-specific inhibitors (COX-2 inhibitors) such as intravenous parecoxib (40 mg daily) and oral celecoxib (400 mg then 200 mg 12 hourly) may be available, and because they have no effect on platelet function they are the best choice for women who are bleeding or at high risk of bleeding. However, they have not yet been adequately evaluated during human lactation, and although the risk of affecting the breastfeeding baby appears low, safety cannot be guaranteed. Some countries may also have intravenous paracetamol/acetaminophen, which provides higher and more rapid peak plasma concentrations than an equivalent oral dose.

Might any other local anesthetic blocks be useful in reducing Agnes's risk of having poorly controlled pain?

Wound infusion of local anesthetic (or perhaps even diclofenac) is effective in reducing the dose of opioid needed, but it requires expensive pumps and wound catheters, so it is not likely to be available. If there is a doctor with suitable training, bilateral ilioinguinal and iliohypogastric blocks into the abdominal wall near the anterior iliac crest, or a rectus sheath block, can achieve similar opioid dose-sparing in the first 12–24 hours. The best peripheral nerve block, if someone has the knowledge and expertise, would be for Agnes to receive bilateral transverse abdominis plane (TAP) blocks. This regional analgesic block is performed using, for example, 20 mL of 0.25% bupivacaine or 0.5% ropivacaine on each side. The injection is made just above the pelvic brim in the posterior section of the triangle of Petit, in the gap between latissimus dorsi and the external oblique muscle. A "two-pop" (or in some countries ultrasound-guided) technique (as the blunt-tip needle passes through the external oblique fascial extension, then internal oblique fascia) allows local anesthetic to be deposited between the internal oblique and transverse abdominis muscles. Combined with oral analgesics, an effective TAP block covers the incision for cesarean delivery well (T10 to L1 dermatomes) and lasts up to 36 hours.

Case report 3 (analgesics in later pregnancy)

The nurse comes to tell you that Martine, a healthy woman in her fourth pregnancy at 33 weeks gestation who is attending the antenatal clinic, has been complaining of severe stabbing pain both at the back of her pelvis and low down at the front. The pain has been getting progressively worse for several weeks, and Martine can no longer care properly for her children. She finds it very painful to rise from a sitting position and is more comfortable crawling around the house on all four limbs than walking. When you see Martine, she explains that it took her 2 hours to walk from her house to the clinic, a journey that usually takes her 20 minutes. She is very tender to palpation over both the suprapubic region and upper buttocks. The pain is increased by "springing" the pelvis. "Please, is there anything that you can do to help me?"asks Martine. You explain that she appears to have symphysial diastasis with significant separation and secondary disruption and inflammation at the sacroiliac joints. You explain the problem and discuss an initial plan of management with her. You tell her that she can start on some strong medications if she has not improved within a week.

What sort of painful conditions occur during pregnancy?

Diastasis of the pubic symphysis is an example of a very painful and disabling condition that frequently occurs during and after pregnancy. However, the principles of drug treatment for pain present after the first trimester of pregnancy can be applied to most painful conditions or diseases, including musculoskeletal pain (other examples are lumbar vertebral facet pain, disk protrusion or rupture); visceral pain (cholecystitis, renal

colic, degenerating uterine fibroids, or bowel pain); neuropathic pain (intercostal neuralgia, meralgia paresthetica of the lateral cutaneous nerve of the thigh, iliohypogastric and genitofemoral neuralgia, various cancer-induced neuralgias, post-traumatic complex regional pain syndrome, or post-amputation pain); migraine; and invasive cancer pain.

What initial treatment would you suggest for Martine?

Irrespective of the cause of the pain, nonpharmacological pain management options should be considered and tried, where possible, before analgesic drugs are used for acute pain that appears likely to require prolonged treatment or a stepwise approach to continued management. Your plan for Martine should start with physical therapies (for example referral to a therapist for a sacroiliac pelvic support belt; gentle manipulation and postural exercises; and local application of heat or ice, transcutaneous electrical nerve stimulation, acupuncture or similar treatments), but it would also be reasonable to introduce nonopioid analgesic drugs, bearing in mind their safety for the fetus and neonate. Paracetamol (acetaminophen) has been used in millions of pregnant women and is safe. Aspirin is acceptable, but its prolonged use is best avoided (see case 2 above). Tramadol has not been evaluated in large trials during pregnancy but is widely used after the first trimester, so it would be acceptable for short-term use for Martine to reduce the severe pain until other measures have had a chance to become effective. It would not be ideal to continue tramadol for several weeks until the time of delivery, because a neonatal withdrawal syndrome at 24–36 hours has been reported.

NSAIDs have a limited role during pregnancy, and it is very important to understand the implications of prescribing them. These drugs prevent prostaglandin-induced myometrial gap junction formation and transmembrane influx and sarcolemmal release of calcium, making indomethacin an effective tocolytic drug that has been used to prevent preterm labor after the period of organogenesis. However, they are contraindicated in later pregnancy, certainly after 32 weeks gestation (as applies to Martine), and some would argue from the start of fetal viability (23–24 weeks in resource-rich countries and hospitals). This leaves only a short period during the second trimester of pregnancy when these drugs may be useful. Fetal exposure in late pregnancy may result in oligohydramnios due to renal impairment, premature closure of the ductus arteriosus with subsequent neonatal pulmonary hypertension, and neonatal intracranial hemorrhage. There is insufficient information about the effects of the COX-2 inhibitors (e.g., celecoxib), so these agents should also be avoided.

Would local anesthetics or opioid drugs be suitable in this case?

It is the case with many painful conditions (including Martine's) that the treatment you start with ultimately proves insufficient. The possibility of a neuropathic component should be considered in Martine's case, and the appropriate drug treatment is discussed in case 1 above. However, the two main options to consider next for Martine are local anesthetic infiltration and oral opioid analgesia. Infiltration with local anesthetic provides temporary (and sometimes prolonged) relief of joint pain (another example is into the coccyx for coccydynia, or into the facet joint for back pain) and myofascial pain (for example into trigger points in the abdominal wall, neck, or shoulders or the costochondral and intercostal area). A steroid such as triamcinolone could be included if inflammation is suspected, but steroids are best omitted in the first trimester and in repeated injections. Provided the operator has knowledge of the relevant anatomy and adequate expertise, infiltration is generally a low-risk procedure that can be useful both diagnostically and therapeutically. The local anesthetic drugs are of no or minimal risk to the fetus, although maximum dose limits for the individual drug and the type of block should be applied. Extra care must be taken when injecting near major organs or the fetus (for example, when injecting near the bladder and lower uterine segment or cervix at the pubic symphysis). As a final option, if epidural techniques are available in a referral hospital, a period of epidural analgesia with a combined local anesthetic and opioid can be very beneficial.

If opioid analgesia is commenced during pregnancy, it would be best to arrange inpatient care for a few days. This strategy allows oral opioid titration and stabilization (see case 1 above) and supplementation with intravenous opioid or intravenous ketamine to establish pain control. Oral or sublingual opioids (morphine, methadone, codeine, and in some countries oxycodone, buprenorphine, and fentanyl) can be used safely for short periods during pregnancy (and in some cases will already be prescribed or are

being used by patients illicitly). If prolonged administration is expected, drugs without active metabolites are preferable, for example methadone rather than morphine for maintenance therapy in opioid addicts. Although there is a slightly higher rate of low birth weight and stillbirth among women on chronic opioid therapy, the majority have good neonatal outcomes. It has been suggested that chronic opioid use in pregnancy is associated with addictive behavior in later adult life, but observational evidence does not prove causality, and such findings should be viewed with some scepticism. Women who become opioid tolerant and need escalating doses will provide a number of challenges in managing pain during labor, as well as during and after cesarean section. Options such as opioid rotation and multiple opioids may need to be considered (see chapter on chronic opioid therapy). These women need more interventions and increase the staff workload.

The neonatal effects of opioid analgesics being used at the time of childbirth are important, so a number of staff need to be aware of opioid consumption, including the obstetrician, midwife, pediatrician, and local doctor. Neonatal respiratory depression may be present at birth, so staff skilled in neonatal resuscitation may be required; if possible, naloxone should be available. Also, the baby should be observed in a high-dependency care area if possible, and staff trained to watch for neonatal withdrawal/neonatal abstinence syndrome. This syndrome usually commences in the hours or days following birth (depending on the half-life of the specific opioid, i.e., 6–36 hours for morphine and 24–72 hours for methadone and buprenorphine), but it is occasionally delayed for several days. The risk is greatest if the mother has become opioid-tolerant and has needed an escalation dose or high maintenance doses (30–90% incidence with long-term methadone use and 50% incidence, but less severe, with buprenorphine maintenance therapy). Unfortunately, breastfeeding does not prevent the syndrome. The signs and symptoms in the baby are due to autonomic overactivity (which can manifest as yawning, sneezing, or fever) and cerebral irritability (for example tachypnea, tremor, increased tone, poor feeding behavior, and in severe cases, seizures). The severity of the syndrome also correlates partly with the maternal dose, so is most severe in opioid-tolerant or addicted women. The baby should be swaddled and nursed in a quiet environment, and some will need treatment with sedative drugs such as phenobarbitone (10 mg/day), diazepam, clonidine, or morphine (starting at 0.4–1.0 mg/day in divided doses and increasing 10–20% every 2–3 days as needed). Treatment may need to be continued for 4–20 days and sometimes much longer.

Pearls of wisdom

- Know which common analgesics are considered safe in early pregnancy, and know where to find an information resource describing drug safety in pregnancy and lactation. Be guided by published recommendations and liaise with other medical and nursing staff involved in pain management.
- Choose a postoperative analgesic regimen after cesarean section that is not only effective but also minimizes neonatal drug exposure through breast milk. There should be a multimodal opioid-based approach, preferably using the spinal (subarachnoid) route of opioid administration. If a systemic opioid is used it should be combined with nonopioid analgesics and/or a regional analgesic method (e.g., the transversus abdominis plane block).
- Use of opioids during pregnancy does not cause fetal malformations but may result in neonatal respiratory depression at birth and a neonatal abstinence syndrome starting the first or second day after birth.
- During and immediately after pregnancy, paracetamol (acetaminophen) is the safest nonopioid analgesic, and opioids other than codeine and pethidine are preferred.
- Nonsteroidal anti-inflammatory drugs are valuable analgesics but should be reserved for use during the second trimester of pregnancy and must be avoided after 32 weeks' gestation.
- Use the following table to make an individual risk-benefit-ratio for your patient before starting analgesia:

Drug	Recommendation during Pregnancy	Recommendation during Breastfeeding
Paracetamol (acetaminophen)	Compatible throughout	Compatible
Aspirin	Avoid at conception and avoid chronic high doses during pregnancy	Potential toxicity
Indomethacin	Avoid at conception, during first 10 weeks of gestation, and after 32 weeks of gestation	Probably compatible
Diclofenac	Avoid at conception, during first 10 weeks of gestation, and after 32 weeks of gestation	Compatible
Ibuprofen	As indomethacin	Compatible
Naproxen	As indomethacin	Compatible
Ketoprofen	As indomethacin	Compatible
Ketorolac	As indomethacin	Compatible
Celecoxib	As indomethacin	Limited data, potential toxicity
Tramadol	Probably avoid in the first trimester, but thereafter low risk (neonatal abstinence syndrome is possible)	
Morphine	Compatible, but possible neonatal depression at birth and abstinence syndrome with third-trimester use	Probably compatible
Codeine	As morphine, but less effective	Probably compatible
Pethidine (meperidine)	As morphine, but use alternative opioids if possible	Compatible, but use alternative opioids
Methadone	As morphine	Probably compatible
Oxycodone	As morphine	Probably compatible
Fentanyl		As morphine
Amitriptyline	Low risk throughout	Limited data, potential toxicity
Carbamazepine	Compatible if used for epilepsy, but preferably avoid (risk of malformations)	Compatible
Gabapentin	Limited evidence suggests low risk	No data—probably compatible
Pregabalin	Insufficient data	No data—probably compatible
Ketamine	Low risk throughout	
Clonidine	Probably avoid in the first trimester	Probably compatible
Bupivacaine	Low risk throughout	Probably compatible
Ropivacaine	Compatible throughout	Probably compatible
Lidocaine (lignocaine)	Compatible	Probably compatible

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Chapter 32
Pain in Sickle Cell Disease

Paula Tanabe and Knox H. Todds

Case report

Ruben is a 25-year-old male with sickle cell disease who presents for evaluation of moderate, constant right hip pain (rated as 6/10) and intermittent episodes of severe pain, reported as "crisis pain." Ruben describes these crises as severe, occurring monthly, and feeling "as if all my bones are breaking." The pain is most often experienced in his legs.

How often do individuals with sickle cell disease have pain?

This case depicts a typical scenario faced by therapists around the globe. Often, the pain associated with sickle cell disease (SCD) is poorly understood. Persons with SCD often experience both acute and chronic pain. It is now clear that more than half of patients with SCD report some type of pain on a daily basis. "Crisis pain," the most severe pain experienced by persons with SCD, has been reported on up to 13% of all days. Crisis pain (acute pain) has been described as "if all my bones are breaking" or "being hit with a board."

These lifelong episodes have an abrupt onset, are episodic and unpredictable, and are associated with very severe pain. Individuals are usually not able to conduct normal activities during a painful crisis, which may last for several hours and up to a week or more.

The severity and frequency of pain crises varies with the specific genotype. Patients with SS and SB0 typically have more severe pain episodes when compared with patients with SC and SB+. This is not to say that patients with SC and SB+ cannot experience painful episodes—the episodes are just more uncommon and infrequent.

Both physiological and psychological factors can trigger a painful crisis. Common triggers of painful crises include infection, temperature changes, and any type of physical or emotional stress. Common causes of acute pain include:

- Hand-foot syndrome in children (dactylitis)
- Painful crises: vasoocclusion
- Splenic sequestration
- Acute chest syndrome
- Cholelithiasis
- Priapism

In addition to experiencing acute painful crisis, persons with SCD also often experience chronic pain. Specific causes of chronic pain include:

- Arthritis
- Arthropathy
- Avascular necrosis (often in the hips and shoulders and more common in persons with SC genotype)
- Leg ulcers
- Vertebral body collapse

How can pain be managed pharmacologically?

Therapists must consider the need for chronic pain management as well as rescue medication for acute painful crises. Persons with more than three painful crises per year are candidates for hydroxyurea therapy, which has been shown to significantly decrease the number of painful crises, as well as the incidence of acute chest syndrome.

General recommendations include:

- Treat pain as an emergency
- Assess pain levels frequently
- Assess hydration status and maintain adequate hydration
- Investigate other possible causes of pain/complications of the disease (acute chest syndrome, priapism, splenic sequestration, cholelithiasis)
- Do not withhold opioids when pain is severe

Analgesics for mild to moderate pain include acetaminophen (avoid if liver disease is present) and nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or ketorolac (contraindicated in patients with gastritis/ulcers and renal failure: monitor renal function if used chronically).

Moderate to severe pain should be treated with opioids such as morphine sulfate or hydromorphone. Many patients with SCD-associated chronic pain may require daily doses of opioids to maintain optimal function. High doses of opioids are often necessary to treat painful crises. Meperidine is NOT recommended, since it may be associated with seizures and renal toxicity. Acetaminophen or NSAIDs in combination with opioids may be helpful in treating severe pain crises.

Should I be concerned about the risk of addiction if prescribing opioids?

Opiophobia, the fear of prescribing opioids, is a worldwide phenomenon. And certain pain syndromes remain poor indications for opioids (e.g., chronic back pain, headache). But SCD seems to have a good indication for opioids, and there are no data to suggest persons with SCD are at an increased risk of becoming addicted to opioids. The unjustified fear of causing addiction results in undertreatment of the severe and debilitating effect of SCD pain. Pain in SCD should, therefore, always be aggressively treated. Behaviors often thought of as being suspicious for addiction are frequently an indication of undertreatment of pain or disease progression (called "pseudo-addiction").

Are there any nonpharmacological therapies for chronic and acute pain episodes?

Many therapies have been reported by persons with SCD as helping either avoid painful crises or treat chronic pain. These are listed below:

- Maintaining adequate hydration
- "Journaling" or keeping a diary of diet, activities, and stressors, which helps to identify triggers of painful crises
- Heat and massage
- Use of a variety of herbs and vitamins (in particular, folic acid)
- Careful attention to a healthy diet (high quantities of fruits and vegetables, low amounts of protein).

What complications may be important to recognize other than a pain crisis?

Sickle cell disease is associated with early mortality in many countries, although accurate life expectancy estimation is not available. Historically, children with SCD would not survive into adulthood. However, due to the use of prophylactic penicillin until age five to prevent sepsis, children are surviving, and many adults in the United States are living well into their 60s. The following is a list of serious complications that should always be considered when treating a person with SCD. These complications are more common in childhood; however, they can also occur in adults:

- Chronic anemia
- Acute splenic sequestration
- Sepsis
- Aplastic crisis
- Acute chest syndrome
- Stroke

Chronic complications common in adults include:

- Pulmonary hypertension
- Progressive renal disease
- Chronic anemia
- Retinopathy

- Gallbladder, liver, and lung infarction
- Iron overload (if the patient has received numerous blood transfusions)
- Depression

What is the pathophysiological mechanism of sickle cell disease?

Pain crises are triggered by deoxygenation and by the resulting polymerization of the hemoglobin. A triad of ischemia, infarction, and inflammation contribute to the pathophysiology of pain. Mechanisms include damage to the vascular endothelium and chemical mediators of inflammation, microinfarctions caused by local capillary sickling, ischemia, somatic symptoms (muscles, tendons, ligaments, bone, and joints), and visceral symptoms (spleen, liver, and lungs), often described by the patient as being vague, diffuse and/or dull pain.

Tips from a complementary medicine specialist

Many complementary alternative medicine strategies have been found to both limit the frequency of pain crises and improve patients' quality of life. Careful attention to nutrition, obtaining adequate sleep, the use of heat, and massage have all been reported by persons with SCD who function at a very high level. Use of complementary strategies should therefore be encouraged.

Pearls of wisdom

- Many persons with SCD experience pain on a daily basis.
- Individuals with SCD often experience both acute and chronic pain.
- Pain episodes begin in childhood and continue throughout the lifespan.
- Acetaminophen and NSAIDs are helpful in managing mild and moderate pain.
- Opioids are often required to manage acute painful crises.
- Some patients will require chronic use of opioids on a daily basis to manage pain and improve daily function.
- Complementary strategies such as the use of heat, sufficient sleep, hydration, massage, and excellent nutrition are reported as being helpful.
- Again, opioids are very effective and should not be withhold from a patient suffering from sickle cell disease.

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Guide to Pain Management in Low-Resource Settings

Chapter 33
Complex Regional Pain Syndrome

Andreas Schwarzer and Christoph Maier

In 1865, the neurologist Silas Weir Mitchell reported about soldiers complaining of strong burning pain, pronounced hyperesthesia, edema, and reduction of motor function of the limb following injuries of the upper or lower extremity. Mitchell named these disturbances "causalgia." In the following years, these symptoms were described again and again after extremity injuries but were labeled differently (algodystrophy, reflex sympathetic dystrophy, Morbus Sudeck). Currently, this disease pattern is referred to as complex regional pain syndrome (CRPS). Two types are recognized: CRPS type I without nerve injury and CRPS type II associated with major nerve injury.

What are the main characteristics of patients with CRPS?

As a general rule, the symptoms of CRPS manifest themselves in the distal extremity (usually in the upper limb, and less often in the lower limb). Almost all patients (90–95%) suffer from pain, which is described as burning and drilling and is felt deep in the tissue. Furthermore, an edema of the affected extremity, with an emphasis on the dorsal areas (dorsum of the hand or foot) can be observed in almost all patients. Pain and edema increase when the limb is hanging down. Further essential disease features are the following: (1) patients suffer from sensory, motor, and autonomic impairment; (2) the symptoms spread beyond the area of the primary damage and cannot be assigned to the supply area of one single nerve, e.g., the whole hand is affected following fracture of the radius; (3) usually both joints and nerves are affected; (4) patients often present with psychological disturbances. There are no clinical differences between CRPS type I and type II; except for the nerve damage.

What is the incidence of CRPS, and are there specific triggers?

CRPS is a rare disease. Approximately 1% of patients develop CRPS following a fracture or nerve injury. However, exact data on prevalence do not exist. In a current study from the Netherlands, the incidence was estimated 26/100,000 persons per year, with females being affected at least three times more often than males. In another population-based study from the United States, the incidence was estimated at 5.5/100,000 persons per year. The upper extremity is more often affected, and a fracture is the most common trigger (60%).

What is the explanation for development of CRPS?

In almost all of the patients (90–95%) there is an initiating noxious event (trauma) in the clinical history. The reason why only some patients develop CRPS is still unclear. There is also no comprehensive theory that can explain the diversity and the heterogeneity of the symptoms (edema, central nervous symptoms,

joint involvement, etc.). Current attempts explain single symptoms, but not the overall picture. An essential hypothesis about the main pathomechanism for developing CRPS includes inflammatory processes. This point of view is supported by the fact that the classic inflammatory signs (edema, redness, hyperthermia, and impaired function) are prominent, especially in the early stages of the disease, and that these symptoms are positively influenced by the use of corticosteroids.

What is the prognosis of patients who have developed CRPS?

The number of favorable cases that heal up spontaneously or following adequate treatment (and avoidance of mistreatment), are unknown. Prognosis regarding the full recovery of function of the affected limb is unfavorable, and only 25–30% of all patients fully recover, according to the degree of severity and their comorbidity. The extent of the effects of osteoporotic changes on the prognosis is still unclear. The following symptoms point to an unfavorable course of the disease: a tendency to stiff joints, contracture in the early stages, pronounced motor symptoms (dystonia, tremor, and spasticity), edema, and psychological comorbidity.

Which treatment strategies play an important role in the management of CRPS?

Treatment should take place in three steps: in the beginning, treatment of pain at rest and treatment of edema have utmost priority. Next to pharmacological treatment, rest and immobilization are most important. In the second stage, the therapy should include treatment of the pain during movement as well as during physical and occupational therapy. Pain treatment takes a back seat in the third stage, when the emphasis is on the treatment of functional orthopedic disorders as well as on psychosocial reintegration. The intensification of physical therapy can be limited due to reoccurrence of pain or edema. The main rule is that the treatment must not cause any pain.

Case report

Etta, a 58-year-old office worker, had bad luck when she left her house on a rainy day and fell on the slippery steps of her front porch. A fracture of the left distal radius was diagnosed in the hospital. Everything seemed fine after the fracture was treated by osteosynthesis and cast, but within a few days after discharge she felt an increasing constant burning pain in her forearm, and her fingers got swollen. When visiting her surgeon, she complained about the pain, and the cast was removed.

Are the symptoms a "normal" consequence of her fracture?

After the application of a looser cast and the prescription of pain medication, the pain was tolerable, even though her fingers remained swollen. Six weeks later, the cast was removed, and physiotherapy commenced. A few days later, Etta reported an increase in swelling after the removal of the cast and said she felt a stinging, partly burning pain circularly around the wrist, radiating to the fingers. Furthermore, the movement of her fingers was reduced; the hand was shiny, swollen, and blueish-reddish.

Once again, is this a "normal" consequence of her fracture?

Dr. Jones, the attending physician, recommended intensifying the physical treatment and increasing the doses of the pain medication. During intensification of physical therapy, Etta's fingers were trained forcefully, which was very painful. With exercise, the pain and swelling increased, and the hand was still bluish-reddish colored and shiny. Moreover, Etta noticed an increased growth of her finger nails and the hair on the dorsum of her left hand. Although physical therapy was intensified, the lack of mobility of the fingers worsened, the hand was constantly swollen, and the pain was burning and almost unbearable, at rest as well as during movement. Etta became desperate, and Dr. Jones was at the limit of his wisdom on how to help her.

What should be done? Why has Dr. Jones' therapy failed?

Six weeks passed, and Dr. Jones referred Etta to a pain management center. She was still complaining about the pain, which at that point was radiating to the forearm and elbow as well. Additionally, she reported strong functional deficits in the hand (it was not possible to make a fist, and the finger-palm distance was 10 cm). In the past few days, she had also noticed a restriction in the shoulder movements (especially abduction). Dr. Ndungu, the attending doctor from the pain center, recognized the problem and recommended an appropriate treatment; Etta was lucky.

What are Dr. Ndungu's options for further diagnostic procedures?

Based on the diagnostic criteria defined by IASP (see below) and the course of the disease, Dr. Ndungu diagnosed a complex regional pain syndrome. Upon start of the treatment at the pain center, he explained to Etta the disease pattern and the principles of therapy, which require her active cooperation, understanding, and patience because progress may be slow, with relapses and periods of stagnation. He prescribed Etta a splint and recommended that she position the hand and the forearm higher than the heart, until the edema is reduced. Coxibs (celecoxib) and anticonvulsants (gabapentin) were prescribed as pain medications. Physical and occupational therapy was started one week after the decrease of the edema and the pain at rest.

Are there any other therapeutic options? What are the main rules for therapy?

At the beginning of physical therapy, focus was put on the shoulder, and 2 weeks later, normal mobility was regained. The progress of improvement in hand function was much slower. As soon as Etta exercised too strongly with her hand or used it for household tasks, the edema developed again and the pain became stronger. After approximately 3 months, with physical and occupational therapy, Etta was able to achieve an improvement in hand function and a reduction in pain. It took 6 more months before she was able to return to her office and operate her computer with her left hand.

Was this a typical course of CRPS?

This case exemplifies a typical course of CRPS with respect to sex, age, injury, and symptoms. However, especially in the early stages of the disease, it is often difficult to differentiate between the symptoms of CRPS and the normal or slightly delayed fracture healing. The diagnosis of CRPS is possible only after the development of typical symptoms, such as an impairment of sensory, vasomotor, motor, and sudomotor function. In Etta's case, attention should be focused on two typical clinical phenomena: first, the negative influence of forced physical exercises on the further course of the disease, and second, the commonly observed involvement of the shoulder during the course of the disease. The mobility of the elbow joint is mostly unaffected, whereas abduction and rotation of the shoulder joint are often disabled. Patience and individually adjusted physical activity are essential requirements for patients.

What are the clinical symptoms of CRPS?

The clinical pattern of CRPS is characterized by sensory, motor, and autonomic impairment. Additionally, patients with CRPS often feel as if the hand or the foot does not belong to them anymore or as if it is not perceptible or controllable; movements can only be performed under direct visual control ("neglect-like syndrome"). Furthermore, the following features occur in almost all cases:

- The impairment due to CRPS is disproportionate to the inciting event.
- There is a tendency for a distal generalization for all symptoms, i.e., not a single finger, but the whole hand is affected, and the hand is more strongly affected than the forearm.
- The joint and soft tissue structures are also affected, with according mobility impairment.
- An edema, depending on position and physical activity, usually occurs, especially in the early stages of the disease.

Sensory impairment: Spontaneous pain and hyperalgesia in the hand or foot, which is not restricted to the supply area of a single peripheral nerve, are main characteristics of the clinical pattern of CRPS. The pain is described as burning and is felt in the deep tissues; additionally, sudden pain attacks, described like electrical shocks, are often present. A periarticular pressure pain of the finger joints is almost always present. As a rule, strong hypersensitivity to mild painful stimuli (hyperalgesia) or pain following usually nonpainful stimuli (allodynia) can be observed.

Motor impairment: In 90% of all cases, the voluntary motor function of all distal muscles is impaired. Complex movements, such as fist closure or finger-thumb opposition, are restricted. These movements are only possible under visual control. Approximately 50% of patients with involvement of the upper limb develop a tremor; dystonia or spasticity is seldom found.

Autonomic impairment: Skin temperature differences of more than 2°C between the affected and the unaffected extremity are often present (the affected side is warmer in about 75% of cases), and they correspond to an altered skin blood flow. About 60% of patients have hyperhidrosis, and 20% have hypohidrosis. In the early stages, hair and nail growth on the affected extremity is often increased, in the further course of the disease it is often decreased. Dystrophic symptoms (i.e.,

skin and muscle atrophy, connective tissue fibrosis) are typical for the later stages of the disease; however, they are not always found.

What are the diagnostic criteria for CRPS?

CRPS is a clinical diagnosis. There are no laboratory parameters that confirm the presence or absence of the disease. Patchy demineralization especially in the periarticular regions appears in the radiography some weeks or months after the disease begins, but it can be seen in less than 50% of patients with CRPS. CT and MRI examinations are not specific for the diagnosis of CRPS. However, triple-phase bone scintigraphy plays an important role for the diagnosis of CRPS during the first year after trauma. Band-shaped increased radionuclide accumulation in the metacarpophalangeal and interphalangeal joints of the affected extremity during the mineralization phase is a very specific diagnostic criterion.

The current diagnostic criteria are listed below according to Harden and Bruehl [3]. Aside from differentiation between sensory, vasomotor, sudomotor, and motor impairment, the physician should discriminate between anamnestic hints (symptoms) and current clinical signs during the physical examination.

What is the differential diagnosis for CRPS?

In the clinical routine, it is most essential to differentiate between CRPS and a delayed healing of a trauma or complaints after long-term immobilization. In the case of CRPS, not only an increase in pain intensity, but also a change in the characteristics of pain usually occurs. Differential diagnosis is nerve or plexus injury, especially after an operation to treat nerve entrapment syndromes (carpal tunnel syndrome). However, in these cases, the symptoms are limited to the area supplied by the injured nerve. Autonomic impairment does not prove the diagnosis of CRPS. Furthermore, self-injurious behavior is another differential diagnosis to CRPS.

What are the treatment options for CRPS?

The treatment of CRPS should be based on a multidisciplinary approach. Next to pain treatment, the recovery of limb function should play an important role.

Pharmacological options: Traditional NSAIDs (ibuprofen 3 × 600 mg) or COX-2 inhibitors (celecoxib 2 × 200 mg) can be taken temporarily for treatment of CRPS pain. Additionally, metamizol (4 × 1000 mg)

Table 1
Diagnostic criteria for CRPS (according to Harden and Bruehl [3])

1	Persistent pain, which is disproportionate to any known inciting event	
2	The patient must report at least one symptom in three of the following categories (anamnestic hints):	
2.1	Sensory	Reports of hyperesthesia and/or allodynia
2.2	Vasomotor	Reports of temperature asymmetry and/or skin color changes and/or skin color asymmetry
2.3	Sudomotor/edema	Reports of edema and/or sweating changes and/or sweating asymmetry
2.4	Motor/trophic	Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
3	The patient must display at least one sign in two or more of the following categories during the current physical examination:	
3.1	Sensory	Evidence of hyperesthesia and/or allodynia
3.2	Vasomotor	Evidence of temperature asymmetry and/or skin color changes and/or skin color asymmetry
3.3	Sudomotor/edema	Evidence of edema and/or sweating changes and/or sweating asymmetry
3.4	Motor/trophic	Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nails, skin)
4	There is no other diagnosis that would otherwise account for the signs and symptoms and the degree of pain and dysfunction.	

and opioids (controlled-release) can be prescribed. The most important adjuvants for the treatment of neuropathic pain are tricyclic antidepressants (amitriptyline) and anticonvulsive drugs (gabapentin). After taking into consideration their possible contraindications and their anticholinergic effects, the physician should increase the dose slowly. Furthermore, the dose should be high enough before its efficacy is evaluated. The dose of amitriptyline should be initially 25 mg in the evening (alternatively 10 mg). The dose can be increased every seven days in 25-mg steps up to a maximal dose of 75 mg. The starting dose of gabapentin is 3 × 100 mg, and the dose should be increased in 300-mg steps every three days. A dose of at least 1800 mg/d should be achieved. Especially in cases of arthrogenic pain (particularly during physical examination), oral glucocorticoids are indicated (prednisolone in decreasing doses of 90/60/30/10/5 mg for 14 days).

Invasive therapies: The sympathetic nervous system can be blocked either by unilateral anesthetic blockades of the lower cervical sympathetic ganglion (stellate ganglion) (10–15 mL bupivacaine 0,5%) or by blocks of the lumbar or thoracic sympathetic chain (5 mL bupivacaine 0.5%). Intravenous regional anesthesia blocks are seldom performed because of poor effect and painful procedures. The indication for a sympathetic block is pain at rest despite immobilization and/or pronounced allodynia. Sympathetic blocks not only reduce the pain, but can often also improve the motor and autonomic impairment. However, it is important to prove that the sympatholysis was technically successful by noting a significant skin temperature increase in the supplying area.

Nonpharmacological options: As long as pain at rest prevails, therapy should be restricted to consistent immobilization of the affected extremity in a position higher than the heart, supported by a splint and by lymphatic drainage. After a distinct decrease of the pain, physical and occupational therapy come to the fore. Initially, the proximal joints of the affected and the contralateral extremity should be treated. Especially in cases of sensory impairment and allodynia, desensitization exercises are indicated. The main treatment principle should start with stimulus adaptation, followed by exercises aiming at pain-free mobility and improvement of fine motor skills, and ultimately movements against strong resistance.

Therapy for CRPS, with regard to the use of medical and nonmedical treatment, does not require any particular setting and meets the standards of a community or primary care level. The application of nerve block techniques should be reserved for specialized pain management centers ("referral hospital level"). The advantage of treatment in specialized pain management centers is, besides the reliability of making the diagnosis of CRPS and the use of sympathetic blocks, the greater experience in dosing the physical and the occupational treatment—finally, it is perhaps the most essential issue for the function recovery of the affected extremity.

What are today's insights about the pathophysiology of CRPS?

Currently, there is no global pathophysiological concept that explains all the symptoms in CRPS. There are several possible explanations. Next to hints for a genetic predisposition, inflammation seems to play an important role. In the context of a neurogenic inflammation, C fibers and some receptors may release neuropeptides, inducing clinical signs such as vasodilatation and edema. Additionally, experts are discussing the concept of a disease of the central nervous system, in which changes of the afferent neurons, such as pathological connections with the sympathetic nervous system, may cause spontaneous and evoked pain. The pattern of symptom spread resembles that of diseases of the central nervous system. The central nervous dysregulation is assumed to result in maladaptation, for example a change in the ambient temperature induces an inadequate reaction of skin blood flow and sudomotor function. Furthermore, cortical reorganization processes seem to play an important role, wherein the degree of the reorganization correlates positively with the spread of the mechanical hyperalgesia and the pain, which in turn is reversible using the appropriate treatment.

Pearls of wisdom

- Three important aspects account for the diagnosis of CRPS: pain or functional impairment, which is disproportionate to the inciting event; hints of sensory, vasomotor, sudomotor, or motor impairment in the past; and current findings of sensory, vasomotor, sudomotor, or motor impairment in the clinical examination
- The treatment must not induce pain. If a treatment procedure leads to escalation of pain, this procedure must be given up. The following three

therapeutic steps should be followed: first, treatment of the pain and edema; second, treatment of the pain, allowing movement; and third, treatment of the functional orthopedic impairment.

- The intensity of physiotherapy must be reduced if pain increases again or after a new physical trauma.

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Chapter 34
Pain Management in Children

Dilip Pawar and Lars Garten

This chapter will cover the difficulties in treating pain in children and provide you with an overview of pharmacological and nonpharmacological interventions for effective pain control in acute pain (injury/trauma-related and postoperative pain) and chronic pain (cancer and HIV-related pain) in children.

Do children feel pain?

Until recently, many believed that children do not feel pain, a belief based on lack of understanding, and on fear of using narcotics with potential respiratory depression and addiction in children, rather than on any scientific rationale. Today it is well known that the sensory nervous system and pain pathways develop around midgestation, with connections and function maturing over the first 3 months after birth.

There is no evidence to support the view that pain is less intense in neonates and young children due to their developing nervous system. However, pain is subjective, and the pain response is individual and is modified through social learning and experience. Early pain experience plays an important role in shaping an individual's later pain response by alternation in the stress-axis and antinociceptive circuitry.

Aren't children just "little adults"?

The pediatric age group is heterogeneous, ranging from the newborn to the adolescent. Children's pain perception and responses are different both qualitatively and quantitatively compared to adults. The pain response is more intense at the beginning, but wears off much earlier than in adults. Hence, no single formula is going to work for everyone, and customized pain relief measures are required.

Parental understanding and support is helpful because of their emotional attachment. As children may not ask for analgesia as adults can or do, an effort has to be made to anticipate pain, especially in infants and children who cannot express themselves verbally.

Most of the general principles of analgesia can be applied to children, but there are some significant physiological differences between adults and children that can cause problems, especially in neonates and small infants. Just look at the case reports and imagine you have to deal with these clinical situations.

Case reports

You are in a small rural hospital with limited drugs. Consider the following real-life cases. How might you manage them?

Case report 1 ("acute trauma")

Ahmed, a 3-year-old boy, with acute burns over a large part (more than 20%) of his body, has been admitted. He is in severe pain. How will you manage analgesia in this child?

The boy suffers from severe post-traumatic pain, so he needs fast analgesia. Use morphine as an intravenous (i.v.) bolus (if not possible, substitute enteral

morphine) followed by enteral morphine (if the child needs to be ventilated, use morphine i.v. infusion) on a regular basis for ongoing background pain. For any additional procedures, e.g., change of dressing, use an additional morphine bolus as necessary. Think also about anxiety management, which plays an important role in children with burns. Often the use of benzodiazepines such as oral lorazepam or i.v. midazolam is beneficial. Combine medication with nonpharmacological methods (see below). Use a behavioral pain assessment scale (e.g., the FLACC scale) for monitoring pain severity and assessing the effect of your therapy. When pain decreases, wean the patient off the medication.

Case report 2 ("postoperative pain in the neonate")

Joyce, a 7-day-old newborn baby, was operated on for esophageal atresia. Now the nurse reports that the child seems to be in great pain. How can you assess and treat the pain in this child?

The baby suffers from acute postoperative pain. Evaluate the pain with help of a pain rating scale for neonates and infants (e.g., NIPS). After major surgery you should expect moderate to severe pain. The baby needs very close monitoring in a neonatal intensive care unit. Use i.v. morphine for pain management, combined with nonpharmacological methods.

Case report 3 ("cancer pain")

Dhanya, a 10-year-old girl with an incurable metastatic tumor of the bone who is on oral paracetamol (acetaminophen) and codeine, is experiencing increased pain. How could you help her? Assess pain with, e.g., the Faces pain rating scale. If paracetamol and codeine are at maximum dose, a change of opioid is necessary. Stop codeine and start oral morphine medication. Continue oral morphine on a regular basis at home, after instructing the parents properly. Think of opioid side effects—if not already started, begin prophylactic therapy by giving preventive remedies. Combine medication with nonpharmacological methods.

Case report 4 ("neuropathic pain")

Nasir is a 6-year-old boy suffering from AIDS. He is brought to you by his parents. He is on antiretroviral therapy but has severe neuropathic pain in his legs related to the HIV infection. What would be your first line of therapy? Assess pain with, e.g., the Faces pain rating scale. Even if neuropathic pain is often declared to be "opioid-resistant," start oral morphine medication on a regular basis as first-line therapy, and increase the dosage if an additional reduction in pain without dangerous medication side effects is possible. Try nonsteroidal anti-inflammatory drugs in addition. Combine medication with nonpharmacological methods. If there is no satisfactory pain relief with this regime sometimes the use of adjuvants (e.g., gabapentin, tricyclic antidepressants, or anticonvulsants) has to be considered—application of adjuvants should be done by experienced pain specialists.

What is the present status of pain management in children?

Despite the fact that we understand pediatric pain better now, children tend to receive less analgesia than adults, and the drugs are often discontinued sooner. The safety and efficacy of analgesic drugs are not well studied in this age group, and the dosages are often extrapolated from adult studies or pharmacokinetic data. Also, the fear of respiratory depression and addiction to opioids are two important issues for reduced usage of these potent analgesics in children.

The major problem in treating pain in children, especially younger ones, is the difficulty of pain assessment. When we cannot assess pain levels or pain relief effectively, we are not sure which pain relief measures are needed and when. The other important factor in most of the developing countries (where 80% of the world's population lives) is the lack of infrastructure in terms of availability of trained nursing staff or lack of drugs and equipment for even simple procedures.

What is the physiology of pain in children?

Right or wrong? Procedures such as circumcision, suturing, or other minor operations on young infants can be performed without anesthetic or pain medication, because children's nervous systems are immature and unable to perceive and experience pain as adults do.

Wrong. Even neonates respond to noxious stimulation with signs of stress and distress. Today, we know that a 24-week-old fetus possesses the anatomical and neurochemical capabilities of experiencing nociception, and related research suggests that a conscious sensory perception of painful stimuli is present at these

early stages. Pain means relevant stress in all pediatric patients, and is associated with an inferior medical outcome. Lower morbidity and mortality have been reported among neonates and infants who received proper analgesia during and after cardiac surgery. Surgery in young infants who are receiving inadequate treatment for pain evokes an outpouring of stress hormones, which results in increased catabolism, immunosuppression, and hemodynamic instability, among other effects. It is thought that younger children may even experience higher levels of distress during painful procedures than older children, because they tend to cope with pain more behaviorally.

Do children become accustomed to chronic pain or repeated painful procedures?

No. Children exposed who are given repeated painful procedures often experience increasing anxiety and perception of pain. Therefore, especially children experiencing chronic or repeated pain, such as in tumor diseases or HIV, have a high demand for accurate pain management.

Is pain in children with HIV or cancer always related directly to the disease?

No, not always. In HIV, between 20% and 60% of HIV-infected pediatric patients have pain daily. Pain in HIV not only reduces quality of life, but is also associated with more severe immunosuppression and increased mortality, and therefore, it should be treated with care. Pain not directly related to the HIV infection can be caused by (1) adverse drug effects, e.g., peripheral neuropathy, drug induced pancreatitis or abdominal pain from vomiting (a common side effect of zidovudine), (2) invasive medical procedures (it has been estimated that 20–25% of HIV-positive patients will require surgery during their illness), (3) opportunistic infections such as esophageal candidiasis, herpes zoster, pneumonia (e.g., *Pneumocystis carinii, Cytomegalovirus,* or *Cryptococcus*), or tuberculosis infections, and (4) additional malignancy. For cancer in children additional pain mainly occurs from (1) surgery, (2) chemotherapy, and (3) radiation therapy. Children undergoing surgery for excision of a primary tumor experience postoperative pain. Chemotherapeutic agents used can also be a cause of pain during treatment. Vincristine, a plant alkaloid, is most commonly associated with peripheral neuropathies, characterized by dysesthetic pain that presents as a burning sensation, causing pain upon light contact with the skin. Mucositis is a common side effect of chemotherapy, often seen in children receiving anthracyclines (e.g., daunorubicin), alkylating agents (e.g., cyclophosphamide), antimetabolites (e.g., methotrexate), and epipodophyllotoxins (e.g., VP-16). Radiation therapy to the head and neck area is associated with severe mucositis in children. Postradiation pain may occur in certain body regions, caused by skin reactions, fibrosis or scarring of connective tissues, and secondary injury to nerve structures. Other treatment-related side effects that cause pain include abdominal pain from vomiting, diarrhea, constipation, and infections such as typhlitis, cellulitis, or sinusitis.

Barriers to effective pain management

Do children become addicted to opioids more easily than adults?

Opioids are no more dangerous for children than they are for adults, when appropriately administered. The prevalence of physical dependence (defined as an involuntary physiological effect of withdrawal symptoms noted following abrupt discontinuation of opioids, or administration of a narcotic antagonist such as naloxone) on opioids in children is comparable to that in adults. If opioids are given regularly in high doses for more than a week, do not stop medication abruptly. Slow tapering of the opioid is recommended to prevent withdrawal symptoms. As a rule of thumb, reduce the opioid to 3/4 of the previous dose over each 24-hour periods (e.g., day 1: 100 mg/d, day 2: 75 mg/d, day 3: 55 mg/day, day 4: 40 mg/d). Sometimes tapering may last 1–2 weeks. If seizures occur during tapering, treatment with diazepam (i.v. 0.1–0.3 mg/kg every 6 hrs) is recommended.

Is respiratory depression a common problem in opioid-treated children?

Respiratory depression is a serious and well-known side effect of opioids; however, it rarely occurs in children when opioids are administered appropriately. As children develop a tolerance to the analgesic effect of opioids, they often develop a tolerance to an initial respiratory

depressant effect as well. The most common opioid side effect is constipation, not respiratory depression. It is important to note that pain acts as a natural antagonist to the analgesic and to the opioid side effects of respiratory depression. However, opioid analgesics should be given cautiously if the age is less than 1 year. Opioids are not recommended for babies aged less than 3 months, unless very close monitoring in a neonatal intensive care unit is available, as there is higher risk of respiratory depression and low blood pressure.

When can children be treated at home with oral opioids?

With proper instruction, the administration of oral opioids by parents at home is safe. Parents have to be taught that oral opioids are strong pain killers and have to be given to their child as prescribed. Frequency and regularity are important to prevent the return of the pain, and this has to be made clear. Parents have to be prepared for opioid side effects (nausea and drowsiness, which usually go away after a few days and do not come back; constipation always occurs). Preventive remedies such as dried papaya seeds or a laxative such as senna at night should always be given. Parents should be told to contact a health worker if (1) the pain is getting worse (the dose may be increased), (2) an extra dose of oral opioid was given to the child, (3) drowsiness comes back, or (4) the dose was reduced. Opioid medication MUST NOT be stopped suddenly, because severe withdrawal symptoms may occur. All instructions should be written out clearly (Fig. 1).

Pain assessment

How is pain assessed?

The visual analogue scale (VAS) is the gold standard for assessment of pain in adults. The traditional scale is a 10-cm (100-mm) scale with markings at 1-cm intervals from 0 to 10. Zero denotes "no pain" and 10 denotes "excruciating pain." The patient is asked to identify the mark on the scale that corresponds to his/her degree of pain. This VAS has been found to be effective in children from 5–6 years on. Younger children present a real challenge, and the VAS has been modified for ease of comprehension of children by incorporating facial expressions at either end or at intervals in the scale. In a 10-step ladder scale with a toy, a child is asked how many steps the toy would be able to climb if it had the same degree of pain. All these scales have been used for children 3–5 years of age (Fig. 2).

Besides perception of pain, a noxious stimulus produces other physiological and behavioral changes, which are more marked in children and maybe utilized to assess pain. The most common changes are:

1) Facial expression with certain degree of pain (CHEOPS, Oucher, Facial)

2) Heart rate

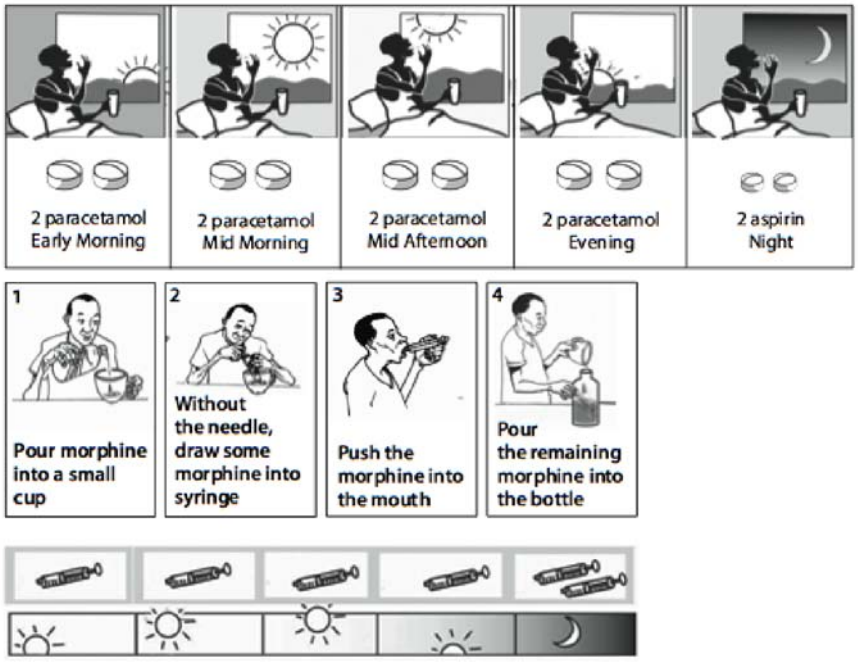

Fig. 1. Medication instructions (from: World Health Organization. Palliative care: symptom management and end-of-life care. Interim guidelines for first-level health workers. World Health Organization; 2004. Reprinted with permission.)

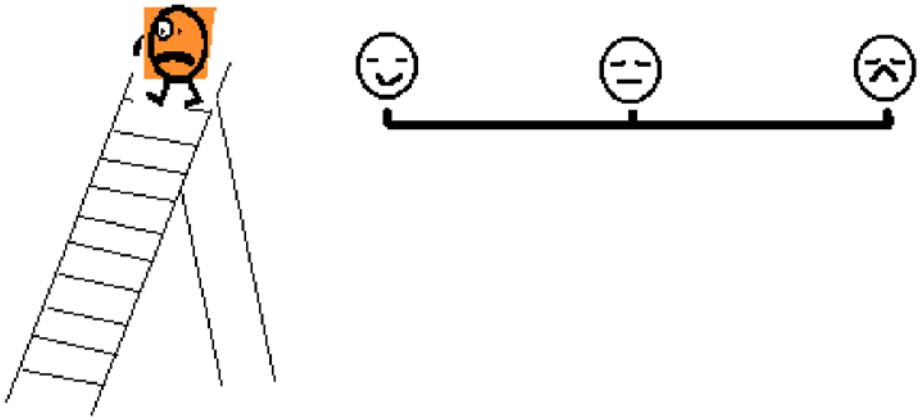

Fig. 2. Adapted pain intensity scales (left: pain ladder, right: modified VAS-scale).

3) Respiratory rate

4) Body movements and crying (AIIMS, FLACC, OPS)

5) Crying is also the ultimate expression of the non-pain-related needs of a child such as hunger, thirst, anxiety, or parental attention. These factors should be carefully excluded before considering crying as a sign of pain.

Do children express their pain in the same manner as adults?

No, they do not. Due to developmental differences, pain expression varies among different pediatric age groups.

1) Infants may exhibit body rigidity or thrashing, may include arching, exhibit facial expression of pain (brows lowered and drawn together, eyes tightly closed, mouth open and squarish), cry intensely/loudly, be inconsolable, draw knees to chest, exhibit hypersensitivity or irritability, have poor oral intake, or be unable to sleep.

2) Toddlers may be verbally aggressive, cry intensely, exhibit regressive behavior or withdraw, exhibit physical resistance by pushing painful stimulus away after it is applied, guard painful area of body or be unable to sleep.

3) Preschoolers/young children may verbalize intensity of pain, see pain as punishment, exhibit thrashing of arms and legs, attempt to push a stimulus away before it is applied, be uncooperative, need physical restraint, cling to a parent, nurse, or significant other, request emotional support (e.g., hugs, kisses), understand that there can be secondary gains associated with pain, or be unable to sleep.

4) School-age children may verbalize pain, use an objective measurement of pain, be influenced by cultural beliefs, experience nightmares related to pain, exhibit stalling behaviors (e.g., "Wait a minute" or "I'm not ready"), have muscular rigidity such as clenched fists, white knuckles, gritted teeth, contracted limbs, body stiffness, closed eyes, or wrinkled forehead, engage in the same behaviors listed for preschoolers/young children, or be unable to sleep.

5) Adolescents may localize and verbalize pain, deny pain in the presence of peers, have changes in sleep patterns or appetite, be influenced by cultural beliefs, exhibit muscle tension and body control, display regressive behavior in the presence of the family, or be unable to sleep.

Can you assess pain intensity in children by just looking at their behavior?

As every child has individual strategies of coping with pain, behavior can be very nonspecific for estimation of pain levels. For example, a school-age girl may spend hours playing normally with a toy. At first sight, you may think she is happy and not in pain. But this could be her behavioral expression for coping with pain (by distracting her attention from pain and attempting to enjoy a favorite activity). Though a child's behavior can be useful, it can also be misleading. Using a pain rating scale and looking at physiological indicators of pain (changes in blood pressure, heart rate, and respiratory rate) in addition is recommended.

Are children able to tell you if and where they hurt?

Studies have shown that children as young as 3 years of age are able to express and identify pain with the help of pain assessment scales, accurately. Children are able to point to the body area where they are experiencing pain

or draw a picture illustrating their perception of pain. A widely used and appropriate pain assessment scale is the Faces pain rating scale (recommended for children age 3 years and older) (Fig. 3).

Do children always tell you when they are in pain?

Even when they have adequate communication skills, there are some reasons children may not report pain. Children may be frightened of (1) talking to doctors, (2) finding out they are sick, (3) disappointing or bothering their parents or others, (4) receiving an injection or medication, (5) returning to hospital or delaying discharge from hospital, (6) having more invasive diagnostic procedures, or (7) having medication side effects. And after all, children just may not think it is necessary to tell health professionals about their pain. Thus, parents should always be asked for their observations regarding the child's situation. So even in children whose cognitive development should allow them to report pain, a combination of (1) questioning the child and parents, (2) using a pain rating scale, and (3) evaluating behavioral and physiological changes is recommended.

How can you assess pain in infants and toddlers?

Parents, caregivers, and health professionals are constantly challenged to interpret whether the distressed behaviors of infants and children, who cannot self-report, represent pain, fear, hunger, or a range of other perceptions or emotions. A range of behavioral distress scales for infants and young children have been devised. Facial expression measures appear to be the most useful and specific in neonates. Typical facial signs of pain and physical distress in infants are: (1) eyebrows lowered and drawn together; (2) a bulge between the eyebrows and vertical furrows on the forehead; (3) eyes sightly closed; (4) cheeks raised, nose broadened and bulging, deepened nasolabial fold; and (5) open and squarish mouth (Fig. 4).

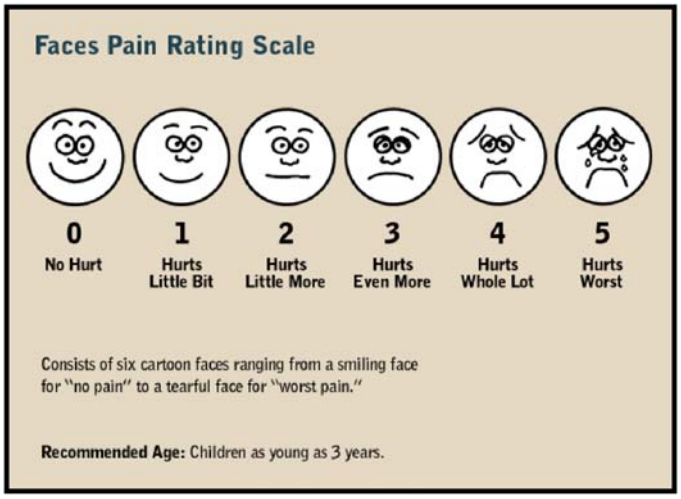

Fig. 3. Faces Pain Rating Scale. Original instructions: Explain to the person that each face is for a person who feels happy because he has no pain (hurt), or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling. Brief word instructions: Point to each face using the words to describe the pain intensity. Ask the child to choose face that best describes their own pain and record the appropriate number. Continuous use of a pain assessment scale for monitoring the effectiveness of pain therapy is recommended. (From: Whaley LF, Wong DL. Nursing care of infants and children, 3rd ed. St Louis: Mosby; 1987. Reprinted with permission.)

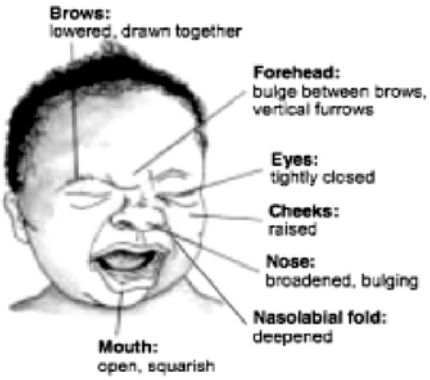

Fig. 4. Facial expression of physical distress and pain in the infant. (From: Wong DL, Hess CS. Wong and Whaley's clinical manual of pediatric nursing, 5th ed. St Louis: Mosby; 2000. Reprinted with permission.)

The FLACC Scale (Fig. 6) is a behavioral pain assessment scale for use in nonverbal patients unable to provide reports of pain. It is used for toddlers from 1 to 3–4 years of age and for cognitively impaired children of any age). Each of the five categories is scored from 0–2, which results in a total score between 0 and 10.

Neonatal/Infant Pain Scale (NIPS)		
Pain Assessment		Score
Facial Expression		
0—Relaxed muscles	Restful face, neutral expression.	
1. Grimace	Tight facial muscles, furrowed brow/chin/jaw (negative facial expression—nose, mouth, and brow).	
Cry		
0. No Cry	Quiet, not crying.	
1. Whimper	Mild moaning, intermittent.	
2. Vigorous Cry	Loud scream; rising, shrill, continuous (note: silent cry may be scored if baby is intubated, as evidenced by obvious mouth and facial movements).	
Breathing Patterns		
0. Relaxed	Usual pattern for this infant.	
1. Change in Breathing	Indrawing, irregular, faster than usual; gagging; breath holding.	
Arms		
0. Relaxed/Restrained	No muscular rigidity; occasional random movements of arms.	
1. Flexed/Extended	Tense, straight arms; rigid and/or rapid extension/flexion.	
Legs		
0. Relaxed/Restrained	No muscular rigidity; occasional random movements of legs.	
1. Flexed/Extended	Tense, straight legs; rigid and/or rapid extension/flexion.	
State of Arousal		
0. Sleeping/Awake	Quiet, peaceful sleeping or alert.	
1. Fussy	Alert, restless and thrashing.	

Fig. 5. Neonatal/Infant Pain Scale (NIPS). An example of an evaluated pain rating scale for neonates and infants. The maximum score is 6; a score greater than 3 indicates pain. (From: Lawrence J, et al. The development of a tool to assess neonatal pain. Neonatal Nets 1993;12:59–66.)

Pain Assessment		Score
Facial Expression		
0–	No particular expression or smile.	
1–	Occasional grimace or frown, withdrawn, disinterested.	
2–	Frequent to constant quivering chin, clenched jaw.	
Legs		
0–	Normal position or relaxed.	
1–	Uneasy, restless, tense.	
2–	Kicking, legs drawn up.	
Activity		
0–	Lying quietly, normal position, moves easily.	
1–	Squirming, shifting back and forth, tense.	
2–	Arched, rigid or jerking.	
Cry		
0–	No cry (awake or asleep).	
1–	Moans or whimpers, occasional complaint.	
2–	Crying steadily, screams or sobs, frequent complaints.	
Consolability		
0–	Content, relaxed.	
1–	Reassured by occasional touching, hugging or being talked to, distractible.	
2–	Difficult to console or comfort.	

Fig. 6. The FLACC scale. (From: Merkel S, et al. The FLACC: a behavioral scale for scoring postoperative pain in young children. Pediatr Nurse 1997;23:293–7. Copyright 1997 by Jannetti Co. University of Michigan Medical Center.)

Table 1
Clinical bedside pain assessment scale

No pain	Child can cough effectively
Mild pain	Child can breathe deeply but cannot cough without distress
Moderate pain	Child can breathe normally but cannot cough or take a deep breath without distress
Severe pain	Child is distressed even during normal breathing

Table 2
Parental assessment scale

No pain	Playful, comfortable in bed, no discomfort in turning over, calm face, when crying easily comforted by parents
Mild	Complains of discomfort at the site of surgery on movement
Moderate	Facial grimace present, pain and discomfort at site of surgery on movement
Severe	Persistent crying and restlessness, pain even without movement

Are simple bedside assessment tools available?

In the clinical practice of the All India Institute of Medical Sciences (AIIMS) in New Delhi, a clinical bedside pain assessment scale and a parental assessment scale have been developed (Tables 1 and 2), which have proven helpful even with illiterate parents.

Pain management

What drugs can be used for effective pain control in children?

Local anesthetics for painful lesions in the skin or mucosa or during painful procedures, e.g., lidocaine, TAC (tetracaine, adrenaline [epinephrine], cocaine) or LET (lidocaine, epinephrine, and tetracaine).

Analgesics for mild to moderate pain (such as post-traumatic pain and pain from spasticity), e.g., paracetamol (acetaminophen) or nonsteroidal anti-inflammatory drugs (e.g., ibuprofen or indomethacin).

Opiates for moderate to severe pain not responding to treatment with analgesics, e.g., codeine (moderate pain, alternatives are dihydrocodeine, hydrocodone, and tramadol) and morphine (moderate to severe pain; alternatives are methadone, hydromorphone, oxycodone, buprenorphine, and fentanyl).

Note: aspirin is not recommended as a first-line analgesic because it has been linked with Reye's syndrome, a rare but serious condition affecting the liver and brain. Especially avoid giving aspirin to children with chicken pox, dengue fever, and other hemorrhagic disorders.

In neonates and infants up to 3 kg body weight, opioids alone have been shown to be effective drugs for treatment of moderate to severe pain. For mild to moderate pain therapy, use nonpharmacological methods, and a formula of 30% sucrose with a pacifier. Local anesthetics can be used for wound care (see Table 7 for frequently used drugs and their dosage regimes.)

What do the pain management terms "by the ladder," "by the clock," "by mouth," and "by the child" mean?

Pain management in children should follow the WHO analgesic stepladder ("by the ladder"), be administered on a scheduled basis ("by the clock," because "on demand" often means "not given"), be given by the least invasive route ("by mouth"; whenever possible give pain medication orally and not by i.v. or i.m. injection), and be tailored to the individual child's circumstance and needs ("by the child").

What nonpharmacological methods can be used to relieve pain, fear, and anxiety in children?

If the child and parents agree and if it helps, the following additional methods (for local adaption) can be combined with pain medications.

- Emotional support (whenever possible allow parents to stay with their child during any painful procedures).
- Physical methods (touch, including stroking, massage, rocking, and vibration; local application of cold or warm; controlled deep breathing).
- Cognitive methods (distraction, such as singing or reading to the child, listening to the radio, play activities, or imagining a pleasant place).

- Prayer (the family's practice must be respected).
- Traditional practices that are helpful and not harmful. (Health professionals should get to know what can help in the local setting.)

Another important point is to give children and family members proper information about the mechanisms and appropriate treatment of pain, to help them better cope with the situation and encourage better compliance with recommended care. For neonates and infants up to 3 months old, oral glucose/sucrose (e.g., 0.5–1 mL glucose 30%) given orally 1–2 minutes before the painful procedure, in combination with pacifiers offered to the baby during the painful procedure, are effective for reducing procedure-related pain from injections or blood sampling. All these methods are "additionals" and should not be used in place of analgesic medications when they are necessary.

What routes of administration are used for pharmacotherapy?

Non-parenteral route

The most commonly used nonopioid analgesic in children is paracetamol (acetaminophen). The traditionally recommended dose is the antipyretic dose, which is too conservative for pain relief. The current recommendation is an oral dose of 20 mg/kg followed by 15–20 mg/kg every 6–8 hours, or a rectal dose of 30–40 mg/kg followed by 15–20 mg/kg every 6 hours. The total daily dose for either route should not exceed 90–100 mg/kg/day in children and 60 mg/kg/day in neonates. This maximum daily dose should not be given longer than 48 hours in infants under 3 months, and not longer than 72 hours in children over 3 months old. If a suppository is used, it should not be cut, because drug distribution might be uneven. Multiple suppositories can be used to obtain the desired dose. The use of paracetamol suppositories given for analgesia has to be seen very critically, because in studies rectal absorption was shown to be slow and erratic with substantial variability, especially in neonates and infants. Often, rectally applied paracetamol does not provide therapeutic drug serum levels. If paracetamol is used, the oral route should be the first choice.

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and ketorolac can be used. Ibuprofen (10–20 mg/kg orally) provides effective relief for mild pain. Ketorolac rectal suppositories have been found to be useful in children with a narrow therapeutic margin for opioids. NSAIDs can affect bleeding time and should be used with caution in adenotonsillectomy.

Tramadol hydrochloride, a mild opioid (with only partial opioid receptor agonist activity), is available for oral and rectal administration in children. It is absorbed rapidly (within less than 30 minutes), and the concentration profile supports an effective clinical duration in the region of 7 hours. Transmucosal, intraoral, or intranasal opioids might become an interesting alternative for breakthrough pain in children, since they generally accept this form of application well.

Parenteral route

The traditional route of parenteral administration used to be intramuscular, which should be avoided nowadays because of the fear, anxiety, and distress it produces in children. A subcutaneous route might be an alternative in those cases where venous access is difficult.

What is the role of opioids?

Opioids are the first line of systemic therapy in moderate to severe pain, with morphine being the most frequently used. Morphine has been intensively studied in children. Serum levels of 10–25 μg/kg have been found to be analgesic after major surgery in children. A steady static serum level of 10 μg/mL can be achieved in children for moderate perioperative pain with a morphine hydrochloride infusion of 5 μg/kg/h in term neonates (8.5 μg/kg/hr at 1 month, 13.5 μg/kg/hr at 3 months, 18.0 μg/kg/hr at 1 year, and 16.0 μg/kg/hr at 1–3 years of age). For the use of morphine and fentanyl in the pediatric patient, and especially in neonates and infants, no strong correlation between dose/serum plasma levels and analgesic effects has been shown, due to the high variability in individual opioid metabolism. For that reason it is advisable not to rely on specific dose recommendations, but use the "WYNIWYG" concept: "what you need is what you get." Titration of the medication is recommended to identify the patient's individual opioid dose for proper pain relief.

Total body morphine clearance is 80% of adult value at 6 months of age. Morphine clearance is higher in infants than adults, primarily because of higher hepatic blood flow and the active alternative sulfation pathway.

Fentanyl can be used as a substitute for morphine in children who have hemodynamic instability and who cannot tolerate histamine release. In neonates, fentanyl has a prolonged elimination half-life compared to morphine. In children older than 1 year, clearance is similar

to adults, but in neonates it is almost twice as long as in adults. An infusion rate of 1–4 μg/kg/hr usually provides adequate analgesia in children.

For remifentanil, which may only be used intraoperatively, adequate analgesia is achieved with a loading dose of 1 μg/kg/hr followed by maintenance infusion of 0.25 μg/kg/min. Alfentanil is effective at a dose of 50 μg/kg followed by an infusion of 1 μg/kg/min. While pethidine (meperidine) has been used clinically for many years, it should not be used in continuous infusions any longer, as it can produce seizures in children.

What are some ways to reduce opioid side effects?

The following methods can be tried by "trial and error" to reduce opioid side effects: (1) dose reduction, (2) change of opioid (e.g., from codeine to morphine), (3) change of route of administration (e.g., from oral to i.v.), and (4) symptomatic therapy (e.g., preventive remedies or a laxative for constipation).

What is the maximum dose of morphine per day?

There is no maximum dose of morphine. If an additional reduction in pain without dangerous medication side effects is possible with an increased dose, it is indicated. Titration of the medication is recommended to identify the patient's individual opioid dose for proper pain relief. If tolerance develops after some time, the dose will need to be increased to maintain the same degree of pain relief.

What are parenteral nonopioid analgesics to consider?

There has been a resurgence of interest in ketamine, an NMDA-receptor antagonist, for its analgesic properties. A dose of 0.1–0.5 mg kg i.v. has been found to provide effective intraoperative pain relief. Ketorolac has sufficient analgesic potency for most day care cases and maybe supplemented initially by parenteral tramadol. No evidence for the effectiveness and safety of these drugs in neonates and infants has been published.

Is it possible to use patient-controlled analgesia (PCA)?

A PCA device is an infusion pump with the facility to deliver a top-up dose whenever the patient feels the need of it. In the pediatric patient, PCA use is possible at beginning school age (over 5 years). In children less than 5 years old, a "parent-controlled" or "nurse-controlled" analgesia could be an alternative to PCA. The pump can be programmed to prevent delivery of toxic doses by using a lockout interval and a maximum hourly dose. Morphine is the usual drug of choice. The patient bolus delivers 10–25 μg/kg. A basal rate of continuous infusion of 10–20 μg/kg maximum might be administered with a lockout interval of 6–12 minutes. In children, a background infusion might be helpful during sleep and it does not seem to increase the total dose. Patient-controlled regional analgesia is also possible. It has been found to be effective in popliteal and fascia iliaca blocks as well as in epidural blocks. One should remember, though, that the lockout interval in these cases should be longer than 30 minutes because the time needed for the bolus dose to be effective is longer.

Regional and local anesthesia

What is the therapeutic value of regional blocks in children?

In recent years, there has been a resurgence in the popularity of regional blocks in children because of their efficacy in providing good pain relief. Regional blocks hold the key to provision of good pain relief in difficult situations as they are simple to use, easy to learn, and cost-effective. They provide profound analgesia, and local anesthetics, such as lidocaine (lignocaine) and bupivacaine, are available even in the least affluent countries. Commonly used blocks in children are given in Table 3.

Table 3
Common regional blocks practiced in children

Caudal epidural	Hernia repair, orchidopexy, urethro plasty, circumcision
Lumbar epidural	All upper and lower abdominal surgery, thoracotomy
Ilioinguinal/iliohypogastric	Hernia repair
Dorsal nerve of penis	Circumcision, advancement of prepuce
Axillary	Surgery of hand and forearm
Femoral/iliac	Thigh and femur surgery

Note: wound infiltration can be as good for a hernia, or caudal block with bilateral drug administration providing complete blockade. Epinephrine-containing local anesthetics should not be used because the penile artery is an end-artery.

Is there a maximum dose of local anesthetics that is safe when the drug is used for local anesthesia?

Yes. No more than 4 mg/kg of lidocaine without epinephrine, or 7 mg/kg with epinephrine, should be used when infiltrating for local anesthesia. Bupivacaine should not exceed 2 mg/kg or 8 mg/day; it is commonly used in concentrations of 0.125–0.25% for caudal epidural block (interestingly, 0.5 mg/kg ketamine by the same route prolongs the action of bupivacaine for up to 12 hours). Maximum doses are generally an issue when suturing large wounds or when using higher concentrations of local anesthetics.

Helpful tips

1) For painful mouth ulcers, apply lidocaine on gauze before feeds (apply with gloves, unless the family member or health worker is HIV-positive and does not need protection from infection; acts in 2–5 minutes).

2) For suturing, apply TAC (tetracaine, adrenalin, cocaine)/LET (lidocaine, epinephrine, and tetracaine) to a gauze pad and place over open wounds.

3) Morphine, when administered through the caudal route, is effective even for upper abdominal and thoracic surgery, and can be effective and safe at a dose of 10 mg/kg through the epidural route.

What regional techniques may be used for continuous analgesia?

Compared to neuraxial blocks, peripheral nerve blocks with or without catheters have the least complications and are popular, especially the axillary, the femoral, and the three-in-one-block. Lumbar epidurals can be used for a single dose administration, especially when caudal block is contraindicated or when the volume needed for the caudal block would be close to toxic levels. A catheter placed in the epidural space can provide continuous analgesia for a long period of time (if tunneled for periods of more than 1 week). The catheter can be placed at the lumbar, caudal, or thoracic level. The thoracic level should be used by experienced and skilled clinicians only. In children, often the caudal route is preferred because it is safest technically due to anatomical differences, and much easier than in adults. The catheters may even be advanced—always without resistance—up to the thoracic segments in infants because their more compact and globular fat makes it easy to pass the catheter. Subcutaneous tunneling of the caudal catheter reduces the rate of bacterial contamination.

Planning an analgesic strategy

It is important to have a plan for pain relief from the beginning of the perioperative period until such time as the pediatric patient is pain free (see Fig. 7). Factors that need to be considered for effective planning are as follows.

Developmental age

The chronologic and neurodevelopmental age of the patient should be considered. A premature or young infant who may have problems with central respiratory drive may benefit from techniques that minimize the use of opioids, which have central respiratory depressant drug effects. In older infants and toddlers, play therapy and the presence of parents have an important role in pain relief. Older children may understand the concept of a PCA.

Surgical considerations

The degree of pain is often associated with the type of surgery. The type of surgery often is the deciding factor in choosing a particular pain relief measure. For surgeries in areas that are moved regularly, such as the chest and upper abdomen, the pain relief measure required would be intense. The patient's ability to take oral medications after surgery is another important factor in planning of care.

Educating nurses and parents

A nurse is the first person who faces a child with pain. She also is the one who takes care of epidural infusions, i.v. infusions, and PCA devices. It is her responsibility to monitor and coordinate with the surgical and the anesthetic team. Her education in pain management is important. If trained nursing personnel is not available or a high-dependency area is not available, more aggressive methods of pain relief may not be safe. Parents provide emotional support to the child, and it is important to discuss the plan with the parents to elicit their support.

Availability of resources

Limited resources can be defined as non-availability of a potent analgesic such as morphine or fentanyl, or equipment for drug delivery such as an infusion pump or a PCA pump or skilled personnel to perform the procedure and monitor the patient postoperatively. In such situations, the strategy should be to devise simple techniques, which do not require precision equipment and intensive monitoring in the postoperative period. These could be as follows:

- Effective use of commonly available oral medications such as paracetamol, NSAIDs, and ketamine. Paracetamol and ketamine have been extensively used in developing countries.
- Optimum utilization of local anesthetics. Local anesthetics can be applied by wound infiltration, prior to incision, before closure, or continuously in the postoperative period.
- The extremely low incidence of complications after peripheral nerve blocks should encourage using them more often when appropriate. In single-injection regional nerve blocks, postoperative analgesia is limited to 12 hours or less. Continuous peripheral nerve blocks provide an effective, safe, and prolonged postoperative pain relief. They have been used even in day-care cases up to the age of 8 years. If all patients received a regional block intraoperatively, that would obviate the need for potent parenteral opioids. The duration of analgesia provided by a caudal block can be prolonged by addition of other adjuvants.
- Alternative therapies such as acupuncture analgesia might prove to be simple, safe, and economical.
- If infusion pumps are not available, a simple pediatric burette can be used for infusion. The author's many years of experience have seen it to be safe, if only 2 hours' worth of the dose is filled up at any time (even with potent opioids like morphine and fentanyl).

Practical treatment plans for a district hospital

Plan 1

A 2 year old child weighing 15 kg is scheduled for hernia repair as a day care procedure. Premedication with paracetamol 300 mg orally or 600 mg rectally, and after induction of anesthesia a caudal or ilioinguinal and iliohypogastric block, followed by wound infiltration at the end of surgery. Two hours after surgery, oral paracetamol 300 mg or a combination of paracetamol and ibuprofen (300 mg) is given 8-hourly until the pain score allows reduction or stopping of the medication.

Plan 2

A newborn baby with an anorectal anomaly is scheduled for an emergency colostomy. No oral medication is possible. The baby can be managed with a spinal subarachnoidal block with bupivacaine alone. In that case no other intraoperative analgesic is needed. In case the baby is administered general anesthesia, ketamine (0.5 mg/kg) and morphine (50 μg/kg) may be administered. For premature babies, opioids should be avoided due to immature respiratory function. Although ketamine is used in many places, there is no good evidence for the effectiveness and safety of this drug in neonates. At the end of surgery, wound infiltration is also used. In the postoperative period, the baby can be given oral paracetamol.

Plan 3

A 5-year-old boy is admitted to the emergency ward with acute burns and severe pain. A child with acute pain should be managed with available i.v. medication such as morphine, ketamine, or tramadol or a combination of these drugs, along with low-dose midazolam to avoid post-traumatic stress, but not for analgesia. Once acute pain subsides, oral medication may be initiated with paracetamol 20 mg/kg. This child will require pain medication for physiotherapy, change of dressings, or even simple bedsheet changes subsequently. The child and his parents should be prepared with an explanation of what is being done. The pain can be managed with oral paracetamol and ketamine (8–10 mg/kg) and i.v. ketamine (1 mg/kg). If it comes to surgery, local infiltration with local anesthetics of the donor area or a regional block would be beneficial.

What monitoring would be necessary for analgesia in the postoperative period?

Resuscitation measures should be available at the bedside for all patients who are receiving opioid infusions. Routine monitoring and recording of pain score, sedation score, and respiratory rate is important in all moderately to severely painful conditions, and for all

patients on infusion. All children on opioid medication should be monitored carefully for at least the first 24 hours, including children on PCA without background infusion. Sedation always precedes respiratory depression in opioid overdose. Therefore, observation of the patient's alertness is the key to safety monitoring. A monitoring frequency of check-ups every 4 hours is considered to be safe to detect increasing sedation. A decrease of respiratory rate below 30% of basal resting value may also be used as an alarm parameter. Oxygen saturation is a better monitor than apnea/respiratory rate monitors as it would detect airway obstruction earlier, but for the average situation and patient outside the intensive care ward, there is no indication that regular sedation control would be inferior to pulse oximetry.

A different story: do children also experience chronic pain?

Yes they do, but little is known about the epidemiology of chronic pain in children, even in the affluent countries. Chronic pain is commonly observed in adolescents. Common conditions are headache, abdominal pain, musculoskeletal pain, pain of sickle cell disease, complex regional pain syndrome, and post-traumatic or postoperative neuropathic pain. Children with cancer or AIDS suffer from varying degrees of pain as the disease progresses. Recurrent pain becomes chronic because of failed attempts to adjust and cope with an uncontrollable, frightening, and adverse experience. Over time it is the weight of this experience that leads the patient to develop concomitant symptoms of chronic physical disability, anxiety, sleep disturbance, school absence, and social withdrawal. Parents report severe parenting stress and dysfunctional family roles. There is a greater psychological element in chronic pain as compared to acute pain as in adults.

How is chronic pain in children treated?

Assessment of chronic pain should establish not only the site, severity, and other characteristics of pain, but also the physical, emotional, and social impact of pain.

Treatment should include specific therapy directed to the cause of pain and associated symptoms such as muscle spasms, sleep disturbance, anxiety, or depression. Standard analgesics such as NSAIDs and opioids may be used, along with antidepressants and anticonvulsants in neuropathic pain. Pharmacological management must be combined with supportive measures and integrative, nonpharmacological treatment modalities such as massage, acupuncture, relaxation, and physiotherapy. Physical methods include a cuddle or hug from the family, massage, transcutaneous electrical nerve stimulation, comfortable positioning, physical or occupational therapy, as well as rehabilitation. Cognitive-behavioral techniques include guided imagery, hypnosis, abdominal breathing, distraction, and storytelling. The treatment plan should include passive, and if possible, active coping skills, to be implemented considering the child's wishes and those of his or her family.

Pearls of wisdom

- For effective pain management in children, it is very important to know how to assess pain in different age groups.
- For perioperative pain management it is necessary to have basic knowledge of the specific pharmacokinetics and pharmacodynamics in this special age group.
- There should be an analgesia plan or algorithm available on the ward for typical therapeutic situations. Nonpharmacological treatment options should be integrated into the analgesia plan.
- Apart from perioperative pain management, a basic ability to diagnose and manage simple chronic pain syndromes should be available. The majority of patients, almost 80–90%, may be managed by simple means, which should be available even in remote or very low-resource environments. Only a small percentage of patients need invasive techniques like epidural analgesia, which might be limited to referral centers.
- With regard to monitoring of analgesia side effects, nothing can substitute for vigilance and frequent clinical assessment.
- No child should be withheld adequate and safe analgesia because of insufficient knowledge.

Table 4
Dose of caudal bupivacaine (0.125–0.25%)

0.5 mL/kg	for penile and anal surgery
0.75 mL/kg	up to lumbar spine
1.00 mL/kg	up to T10
1.25 mL/kg	upper abdominal up to T6

Table 5
Duration of action of caudal bupivacaine with adjuvants

Drug	Duration of Action (hours)
Bupivacaine 0.25%	4–6
Bupivacaine 0.25% with ketamine 0.5 mg/kg	8–12
Bupivacaine 0.25% with clonidine 1–2 μg/kg	8–12
Bupivacaine 0.25% with tramadol 1.5 mg/kg	12
Bupivacaine 0.25% with morphine 30–50 μg/kg	12–24
Bupivacaine 0.25% with ketamine 0.5 mg/kg and morphine 30 μg/kg	24

Table 6
Dosage of epidural infusions

Bupivacaine 0.1% with fentanyl	1–2 μg/mL
Infants under 6 months	0.1 mL/kg/h
Children over 6 months	0.1–0.3 mL/kg/h

Table 7
Frequently used drugs and their dosage regimes

Drug Dosages and Regimens			Dose According to Body Weight				
Drug	Dosage	Form	3–6 kg	6–10 kg	10–15 kg	15– 20 kg	20– 29 kg
Paracetamol (acetaminophen)	10–15 mg/kg, up to 4 times a day	100-mg tablet	-	1	1	2	3
		500-mg tablet	-	¼	¼	½	½
Ibuprofen	5–10 mg/kg orally 6–8 hourly to a maximum of 500 mg/day	200-mg tablet	-	¼	¼	½	¾
		400-mg tablet	-	-	-	¼	½
Codeine	0.5–1 mg/kg orally 6–12 hourly	15-mg tablet	¼	¼	½	1	1½
Morphine	Calculate EXACT dose based on weight of child! Oral: 0.2–0.4 mg/kg 4–6 hourly; increase if necessary for severe pain. Intramuscular: 0.1–0.2 mg/kg 4–6-hourly. Intravenous bolus: 0.05–0.1 mg/kg 4–6-hourly (give slowly!). Intravenous infusion: 0.005–0.01 mg/kg/hour (in neonates only 0.002–0.003!).						
Ketamine	0.04 mg/kg/hr–0.15 mg/kg/hr i.v./s.c. (titrated to effect: usually maximum 0.3 mg/kg/h–0.6 mg/kg/h) OR 0.2 mg/kg/dose–0.4 mg/kg/dose orally t.i.d., q.i.d., and p.r.n.						
Tramadol	1 mg/kg–2 mg/kg 4–6 hourly (max. of 8 mg/kg/day)						
Adapted from: World Health Organization. Pocket book of hospital care for children—guidelines for the management of common illness with limited resources. World Health Organization; 2005.							

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Websites

www.whocancerpain.wisc.edu
Up-to-date information about pain and palliative care published by the WHO Pain & Palliative Care Communications Program

www.whocancerpain.wisc.edu/related.html
Lists of numerous websites related to pain and palliative care

www.ippcweb.org
Online education program for health care professionals by the "Initiative for Pediatric Palliative Care"

International Association for the Study of Pain
IASP
Working together for pain relief

Guide to Pain Management in Low-Resource Settings

Chapter 35
Pain in Old Age and Dementia

Andreas Kopf

What is a geriatric patient?

A geriatric patient is a person of advanced biological age (the age in years being less important), with multiple morbidity, possibly multiple medications, psychosocial deprivation, and an indication for (general) rehabilitation. The treatment of geriatric patients is complicated when dementia is present, because of the patient's impaired communication abilities.

Pain management in geriatric patients

Why is pain management for the geriatric patient a medical challenge for tomorrow?

An important demographic phenomenon of the last few decades in highly industrialized countries is the continuous increase of the higher age groups in relation to the younger generation. Within a few decades, the same demographic change will take place in countries outside the Organization for Economic Co-operation and Development (OECD) as well. For example, in Germany the number of inhabitants in the age group of above 80 years increased from 1.2 million in 1960 to 2.9 million today, and will further increase to 5.3 million by 2020. Therefore, the health care system and health care workers will need to be prepared to be able to cope with this special patient group. With regard to pain problems, the geriatric patient will be a special challenge, since the percentage of patients with chronic pain (pain lasting more than 6 months) increases continuously from 11% to 47% between the ages of 40 to 75 years. Health care workers have to be aware that geriatric patients not only expect the general respect of society but—with increasing life-expectancy—deserve adequate medical treatment, including pain management. Societies have to discuss how they want to cope with this demand.

What do elderly patients expect from their doctor?

In surveys, the older generation has defined a "wish list": being active until death, individual treatment, no pain, autonomous decision making, being able to die "early enough" before needless suffering starts, and addressing reduced social context and contacts.

Why do elderly patients not receive the care they need and deserve?

From the patient's perspective:

- The incidence of dementia increases with age, resulting in impaired communication.
- Elderly patients tend to behave like "good patients".
- They have a traditional "trusting" view of the doctor "who will take care of everything that is necessary."

- They tend to not insist on certain medical interventions.

From the patient's and doctor's perspective:

- Pain in old age is "part of life" and "fate."

From society's perspective:

- Inadequate resources in the health care system restrict adequate treatment.

From the doctor's perspective:

- Elderly patients do not feel pain as intensely as younger patients.
- They cope better with pain and therefore need less analgesia.

What are the opinions and statements of scientific medical organizations?

A wealth of literature shows that geriatric patients are not provided with adequate pain management. Medical societies have made the elderly patient a medical priority. Since pain is frequent, meaningful, underdiagnosed, and undertreated, and since research on this topic is scarce, pain in the elderly has to be declared a medical priority. Consequently, the IASP in September 2006 proclaimed "pain in old age" the main target of the "Global Day of Pain."

Is it true that pain is frequent in elderly patients?

A number of studies document that the incidence of pain is high. In old people's homes, up to three-quarters of interviewed residents reported pain. Half of these had daily pain, but less than one-fifth were taking an analgesic medication. Studies show that unrelieved pain is one of the most important predictive factors for physical disability.

What are the typical pain locations in elderly patients?

The number one cause of pain in elderly patients is degenerative spine disease, followed by osteoarthrosis and osteoarthritis. Other important pain etiologies include polyneuropathy and postherpetic neuralgia. Cancer pain is also a very relevant pain etiology. In highly industrialized countries cancer pain in the elderly is often—at least partially—adequately controlled. But in other countries, management of cancer pain often is not a top priority, although good cancer pain management could be accomplished fairly easy with simple treatment algorithms based mainly on an adequate opioid supply.

If adequate pain medication is provided for elderly patients, why might they still not receive sufficient pain control?

Communication problems and misconceptions of pain are relevant causes of this situation. A number of particularities must be considered in the geriatric patient:

- Compliance: Geriatric patients will have predictable practical problems with their pain medication. Impaired vision and motor skills, combined with xerostomia (dry mouth) and disturbances of memory, may make an adequate treatment a complete failure. It has to be noted that the average geriatric patient in industrialized countries has a prescription for seven different drugs, and only a minority of patients have been prescribed fewer than five daily drugs, making noncompliance and drug interactions highly likely. Noncompliance rates are estimated to be as high as 20%. Apart from that, intellectual, cognitive, and simple manual impairments may interfere with treatment. More than a fifth of geriatric patients fail at the task of opening drug packages and blister packs. Another patient-related compliance factor, compared to younger patients, is reduced "positive thinking": only 20% of geriatric patients expect recovery and healing.
- Availability of opioids and the risks of prescription.
- Comorbidity: Comorbidity may impair physical performance, thereby possibly reducing the effects of rehabilitation efforts.
- Pharmacokinetic changes: One of the main physiological changes in geriatric patients is the reduction of cytochrome P450-dependent metabolization. Also, due to reduced hepatic function, plasma protein levels are generally lower in elderly patients. Both altered mechanisms may cause potential dangerous drug interactions and unpredictable plasma levels. This effect may be most pronounced for drugs that are eliminated through the kidneys, since glomerular filtration rate is generally reduced, too, and for drugs with high plasma protein binding, where unpredictable serum levels of free substance may result.
- Vegetative state: Sympathetic reactions are reduced, causing misunderstanding and underestimation of pain, since the elderly patient appears to be less strained by pain.

With regard to the opioid-receptor population and subjective sensitivity to painful stimuli, there is conflicting evidence. Therefore the conclusion has to be that pain perception and analgesic interactions are unpredictable.

Do patients with impaired communication, such as those with Alzheimer disease, receive insufficient analgesia?

Unfortunately, a number of studies show that patients with Alzheimer disease, and difficult or impossible communication, receive insufficient analgesia. This has been shown both for acute situations such as fractures of the neck of the femur and for chronic pain. This observation is alarming since there is evidence showing that the pain perception of Alzheimer patients is undisturbed.

What is likely to be the most important reason for inadequate pain management?

Much of the problem of inadequate pain management of the geriatric patient is the lack of appropriate assessment. Especially in patients with dementia, failure to assess pain properly results in insufficient analgesia, because less than 3% of these patients will communicate that they need analgesics themselves.

How is pain in the geriatric patient assessed effectively?

The main rule for the geriatric patient is: "ask for pain." The patient may not ask for analgesia spontaneously. All reported pain should be taken seriously; it is the patient who has the pain, and the pain is what the patient tells you it is. Conventional instruments may be used for pain assessment, such as analogue scales or verbal rating scales, if the patient is able to communicate properly. But rating and analogue scales will fail in the noncommunicating patient. Therefore, it will be necessary to use more sophisticated techniques. All these techniques are based on careful observation and interpretation of the patient's behavior. Several scoring systems have been developed for this task. Typical items for observation include facial impression, daily activity, emotional reactions, body position, the chance of consolation, and vegetative reactions. Some scores also include the subjective impression of the therapist. Recent clinical research has tried to interpret various therapeutic interventions to find out more about the patient's pain, with trials called "sequential intervention trials."

Case report: Mr. Ramiz Shehu (prostate cancer)

Mr. Shehu is a 72-year-old farmer from the northern part of Albania, living in the village of Filipoje. He was diagnosed with prostate cancer 3 years ago when he presented himself to the local doctor, Dr. Frasheri, with difficulties with urination. As disease of the prostate was suspected, blood was drawn and send to the district hospital for the prostate-specific antigen (PSA) test. Unfortunately, the PSA was highly positive. After careful evaluation of the individual situation, especially regarding the comorbidity with hypertension and heart insufficiency as well as the patient's advanced age, Dr. Frasheri concluded that there would not be an indication to send Mr. Shehu to the capital Tirana for surgery, chemotherapy, or radiotherapy. Now, after 3 years, Mr. Shehu was still in relatively good general condition, being an important and active member of St. Bartholomew's church in his home village. But in the recent weeks he had developed increasing pain in his left chest and left hip. He described his pain as "drilling," increasing with activity, especially when walking and taking a deep breath. Visitors from Italy had first suspected coronary disease and hip arthritis, since the high PSA had been forgotten by that time. But the local doctor drew the correct conclusions.

1) The options in Filipoje

Local therapy: Use a walking stick, apply a home-made elastic bandage around the chest.
Systemic therapy: The only pain killers available were diclofenac and morphine.

2) The options in the capital, Tirana

At Mother Theresa Hospital, a tertiary care center, the options are:

Local therapy: X-ray or CT for confirmation of bone metastasis, eventually local radiation therapy: fractioned radiation (multiple) for analgesia and bone stabilization, unfractioned radiation (single) for analgesia only.

Systemic therapy: Bisphosphonates (for bone stabilization), radionucleotides such as samarium, or activated phosphates (for patients with multiple painful bone metastasis where radiation is not an option), alternating opioids (for continuing side effects of the first or second opioid, because opioid rotation is the therapy of choice if sedation and/or nausea persists beyond 1 week),

intrathecal catheters (for vertebral metastases where pain at rest is well controlled with opioids but pain on weight bearing is unbearable or only bearable with opioid doses that cause intolerable side effects).

Mr. Shehu's treatment

Due to transportation problems and a long waiting list for treatment in Tirana, Dr. Frasheri decided to treat Mr. Shehu symptomatically at home. In Filipoje, he found a used walking stick and an elastic bandage, which helped with ambulation. Diclofenac was available in local pharmacies, but Dr. Frasheri decided to advise Mr. Shehu to use paracetamol (acetaminophen) instead, since he was not sure about kidney function and it was foreseeable that the need for analgesic therapy would be long-lasting. When Mr. Shehu received piroxicam from the Catholic mission, he also started taking it orally. It was pure luck that Dr. Frasheri found out about the patient taking piroxicam. He stopped this medication and explained to Mr. Shehu that the drug had a number of negative prognostic factors for renal and gastrointestinal side effects: old age, prolonged medication, accumulation of piroxicam because of a long half-life, among other problems. Mr. Shehu was not satisfied with the pain reduction from the paracetamol, since he needed to make his way to and from the church daily, although when sitting or lying down the pain intensity was acceptable. So he insisted at Dr. Frasheri's office that he needed something else.

At first, Dr. Frasheri was reluctant to prescribe opioids, because they are not easy available in Albania. The per-capita amount of morphine and pethidine has been almost unchanged since the time of Enver Hoxha's dictatorship (1970–1980s), and Albania had never signed the Single Convention from 1961. Only recently have prescriptions of fentanyl (mainly for surgery) and methadone (mainly for opioid substitution) increased. Nevertheless, morphine could be obtained—with difficulty. After a lot of education on the pros and cons of morphine (Mr. Shehu was quite sceptical about taking it), Mr. Shehu was started on morphine, starting with 10 mg b.i.d. and gradually increasing the dose over several days. When he found out about the positive effects (especially on walking and standing), Mr. Shehu no longer raised any objections. His steady-state dose was 30 mg morphine sulfate q.i.d. Activity, drinking an extra liter of water, the healthy Mediterranean diet, and milk sugar helped against constipation, but nausea could not be avoided due to the lack of metoclopramide. However, Mr. Shehu had been instructed carefully, so that he was patient enough to wait for nausea (and sedation) to wean off after a week's time. In the educational part of the office visits, family members were included to discuss the patient's wish to stay in Filipoje and his personal attitude toward coping with the disease and its symptoms, finding personal strength in the words of his savior at St. Bartholomew's church.

How did Dr. Frasheri and Mr. Shehu find the optimum dose of morphine?

Since Mr. Shehu was opioid-naive, meaning he had no prior experience with opioids, of advanced age, and with unpredictable cancer pain intensity, the method of choice is titration by the patient. This means that after careful explanation of the pros and cons of morphine, Mr. Shehu was provided with morphine solution (2%), which could be locally produced by the pharmacist. Mr. Shehu was told, with the help of his oldest son Sali, to take 10 drops (ca. 10 mg) of morphine as needed, always waiting for at least 30 minutes after the previous dose, and was told to always write down the time he took extra medication. After two days, Mr. Shehu and his son were told to come back to Dr. Frasheri, and together they looked over the list. It came out that on average every second hour a dose was required, more in the daytime and less in the night. To accomplish stable—and more tolerable—blood levels of morphine, Dr. Frasheri then advised Mr. Shehu to take 30 mg of morphine regularly every 4 hours, since no slow-release version of morphine was available. Of course, Dr. Frasheri did not forget to allow Mr. Shehu to take—as needed—extra doses of 10 mg (roughly 10% of the daily cumulative dose). If Mr. Shehu did not need extra doses, the basic q.i.d. (four times daily) dose would be slightly reduced, e.g., to 20 mg q.i.d.; if he needed 1–4 extra doses the prescription would stay unchanged; and if the extra doses would exceed 4 per day, the basic q.i.d. dose would be increased (e.g., with 6 extra doses per day equal to 60 mg, the regular dose of 30 mg q.i.d. would be increased to 40 mg q.i.d.). The same procedure of titration was used for the time so that the balance between analgesia and side effects was to the benefit of Mr. Shehu.

In conclusion, what should be done?

1) General:
   i) Patients should not be deprived of the benefits of analgesia just because they are elderly.
   ii) Include relatives.

iii) Write down your orders in big letters for patients with impaired vision.
iv) Always provide patients with written information on what to take, when to take it, and eventually, what side effects to expect.
v) Avoid mentally overloading the patient; generally not more than one major topic should be discussed per consultation, and directions should be repeated several times.
vi) Anticipate pain, and treat accordingly.
vii) Use nonpharmacological techniques where applicable, such as positioning, counterirritation (using ice, external alcoholic herbal lotions, etc.).
viii) Use reassurance for anxiety-associated behavior.
ix) Don't use "cookbook dosing schemes," but instead titrate doses individually from very low initial doses.
x) For general assessment of the patient, fitness is a better guideline than chronological age.
xi) Pain management in general may be accomplished in the outpatient setting; inpatient treatment for the sole reason of pain control is indicated only in selected patients.

2) Assessment
i) Ask the patient, who might not reveal information spontaneously for certain reasons.
ii) For patients with impaired communication, one of the suggested scores is the BESD (Beurteilung von Schmerz bei Demenz [Assessment of pain in dementia]). For five observations, 0–2 points may be allocated depending on their nonexistence, medium presence, or strong presence. The observations are:
a) Breathing rate (normal/high/hectic)
b) Vocalizations (none/moaning/crying)
c) Facial expression (smiling, anxious, grimacing)
d) Body position (relaxed/agitated/tonic)
e) Consolation (not necessary, possible, impossible)
iii) Starting with a total of 5 points, this scoring system forces the therapist to start analgesic therapy.

3) Pharmacotherapy. The basic principle of pharmacotherapy in the elderly patient is "start low and go slow," meaning that initial doses of all analgesics should be reduced compared with normal adult doses and that all dose increases should be done slowly and in small stepwise increments.

Pharmacotherapy in older patients

What special considerations are there for analgesic pharmacotherapy in the elderly patient?

NSAIDs have a variety of pharmacological interactions. One of the most relevant is the potential increase of gastrointestinal side effects with the comedication of steroids. Also, blood sugar reduction is increased if the patient is taking oral antidiabetics. Other interactions are the reduction of the comedication's effect, e.g., with diuretics (reduced urine output) or ACE (angiotensin-converting enzyme) inhibitors (less blood pressure reduction). Other interactions with unexpected serum level changes might result from concomitant therapy with NSAIDs and alcohol, beta blockers, methotrexate, selective serotonin reuptake inhibitors (SSRIs), or quinine.

Why are NSAIDs of special importance regarding unwanted effects?

Elderly patients may experience a typical complication spiral with the prescription of long-term NSAID medication. For example, painful arthritis is often the primary cause for prescribing a NSAID. Longer intake (more than 5 days of regular intake), higher doses, and concomitant steroid medication may cause gastrointestinal ulcers. Repetitive ulcer bleeding then may be the cause for anemia. In an older patient with reduced cardiac function, anemia may cause cardiac insufficiency, which is then followed by diuretics as therapy. Although that medication is reasonable in normal instances, the diuretics might cause renal dysfunction and consequently renal failure!

Can opioids have unwanted effects, too?

Opioids may also interact with other medications. Watch out especially for all drugs that have a CYP2D6-inhibiting effect, and expect higher than usual plasma levels, for example cimetidine, quinidine, paroxetine, fluoxetine, methadone, antihistaminic drugs, and haloperidol. Other important direct interactions for morphine with other pharmacotherapies are ranitidine and rifampicin; for fentanyl ketoconazole and clarithromycin; for methadone cimetidine, quinidine, paroxetine, fluoxetine, antihistamines, and haloperidol; and for tramadol quinine and SSRIs.

If organ dysfunction is present, choose—if available—buprenorphine for renal insufficiency and methadone for liver insufficiency. But all other opioids may also be chosen, as long as doses are titrated individually, and dose reductions are made accordingly.

What are some considerations if opioids are chosen?

Opioids have an unbeatable advantage over almost all other drugs available, especially in the elderly patient, since there is no known potential for organ toxicity, even with long-term use. Therefore, all advanced destructive diseases that present with pain (HIV-neuropathy, cancer pain, postherpetic neuralgia, and major degenerative spine disease with vertebral body destruction) are an indication for an opioid trial. Some opioids, like morphine, are cheap (less than the cost of a loaf of bread for a week's dose of morphine) and available in most countries, though local government regulations might prohibit morphine prescription. Morphine and other "simple" opioids like hydromorphone or oxycodone would be fine. Pentazocine, tramadol and pethidine (meperidine) are not the first choice in the older patient because of their specific pharmacodynamics and pharmacokinetics. Although opioids are safe and effective analgesics, some points should be considered when starting an elderly patient on opioids. Because of changes in plasma clearance and fluid distribution, plasma concentrations of opioids may be higher than expected. Especially in long-term treatment, dose adjustments will be necessary. In general, opioid doses have an inverse correlation with age, but the indication for an opioid has a positive (linear) correlation with age, and men on the average need more opioids than women. Elderly female patients need opioids more often, but at a lower dose. As with other age groups, certain rules for opioid therapy must be obeyed, especially structured information about the advantages (no organ toxicity, long-term treatment) and disadvantages (dependency with the need for dose tapering, initial nausea and sedation, and more likely than not continuous constipation).

Is there a "best opioid" for the elderly patient?

In general: "all opioids are equal," but as in the animal farm of George Orwell, "some are more equal": the low plasma-protein-binding of hydromorphone and morphine (8% and 30%, respectively) might be an advantage over others such as oxycodone, fentanyl, or buprenorphine (40%, 80%, or 95%, respectively), since a high rate of plasma-protein binding might provoke drug interactions.

Should coanalgesics be considered in the elderly patient?

The indication for coanalgesics should be determined very carefully to avoid drug interactions and unwanted side effects. For example, the use of tricyclic antidepressants, used often for constant burning pain such as in diabetic polyneuropathy or postherpetic neuralgia, increases the risk of falling down and the incidence of fractures of the neck of the femur. Therefore, in clinical practice, the use of coanalgesics should be restricted to well-tolerated drugs, such as external capsaicin or systemic gabapentin, if available.

Is there anything in addition to analgesics for my elderly patient?

The incidence of depressive disorders is higher compared to younger patients, and older citizens tend to have fewer coping strategies regarding stress. If they have lived through wartime, it is sometimes old age that brings back unpleasant memories. There is evidence that symptoms similar to post-traumatic stress disorder may surface in advanced age. Even if no adequate treatment for this problem is available, asking for such memories and symptoms and an understanding approach may relieve some of the hardships of your elderly patient. Also, religious coping strategies should be used for their healing properties. At times older patients do not dare to mention their beliefs, and the younger medical professional may have separated himself from spiritual thinking. Although spiritual healing may not be used intentionally, if these needs are not already present in the patient, they may be integrated into a holistic approach if careful questioning reveals the patient's disposition. In advanced age, pain may be integrated into life's reality if other factors of general life quality are taken care of. If asked about their "wish-list to the doctor," older patients would appreciate conversations about their biography, encouragement to have hope, integration of religion and family into their treatment, as well as a tender loving environment in the medical setting. The health care system should try to relieve some of the sorrows and anxiousness in the end-of-life situation, so that the patient does not need to quote the famous movie director Woody Allen: "I am not afraid of dying, I just don't want to be around when it happens."

Pearls of wisdom

- There is no evidence that older patients have less pain and need less pain medication than younger patients. Also, the belief that opioid receptor density is reduced has not been confirmed by recent research. Therefore, withholding opioids because the patient is old is not correct.
- Pain is underdiagnosed in the elderly patient. Always ask about pain, and do not rely on analogue scales (e.g., NRS or VAS); instead, use careful observation of the noncommunicating patient for diagnosing unrelieved pain.
- Elderly patients tend to act in a "socially acceptable" manner, meaning that they try to be a good patient ("if I am no burden to anyone, everybody will value me higher" and "the doctor knows what is best for me and will ask me if necessary"), and they tend to suffer through things, especially pain, deprivation, and isolation ("nobody can help me," "it is the destiny of the older person to suffer," "there is no hope for me").
- NSAIDs or paracetamol (acetaminophen) or dipyrone are drugs of first choice for metastatic (bone) pain, depending on the risk profile of the patient (NSAIDs may be used nevertheless in the short term for pain exacerbations). Use the lowest possible dose of NSAIDs, and avoid long-acting NSAIDs that might accumulate (piroxicam and others). Avoid NSAIDs with a history of steroid medication, gastrointestinal bleeding, and kidney dysfunction.
- If no inflammatory pain component is suspected, and the anti-inflammatory activities of NSAIDs are not relevant, than always choose an antipyretic analgesic such as paracetamol or dipyrone.
- Opioids are the analgesics of choice for strong cancer pain unresponsive to NSAIDs. Keep in mind that around four half-lives (for morphine the total time would be about one day) will be necessary before a steady-state situation will be reached in the patient and that women usually need less opioids than men. In most older patients, a longer dosing interval might be a good solution (morphine t.i.d.). If available, combine slow-acting morphine for basic analgesia with fast-acting morphine for on-demand doses.
- Coanalgesics should be used only in individually selected patients. If coanalgesics are unavoidable, calcium-channel-blocking anticonvulsants (gabapentin or pregabalin) should be preferred.
- Nonpharmacological treatment strategies should always be implemented if possible and feasible: education, activity, cognitive techniques, and counterirritation (e.g., acupuncture). Do not forget integration of spiritual beliefs into the treatment plan.
- End-of-life decisions should respect the wishes of the elderly patient to die at home, in dignity, and appreciated, with their pain under control.
- Rule of thumb: Start low, go slow.

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International Association for the Study of Pain
IASP
Working together for pain relief

Guide to Pain Management in Low-Resource Settings

Chapter 36
Breakthrough Pain, the Pain Emergency, and Incident Pain

Gona Ali and Andreas Kopf

The concept of "breakthrough pain" is a relatively new one, and it receives much less attention than "background" pain. As a result, breakthrough pain is much less well understood and managed than background pain. Indeed, breakthrough pain has a number of "unmet needs."

Case report

Tabitha Nadhari, a 66-year-old woman from Basra, Iraq, has a history of breast cancer. Seven years ago, she had a mastectomy with auxiliary clearance, followed by radiotherapy and chemotherapy. She was free of pain up to a year ago, when she started to complain about low back pain, which was mild and misdiagnosed first as "functional." MRI showed, unfortunately, metastasis to cervical, thoracic, and lumbar vertebrae. At that time, Mrs. Nadhari took nonopioid analgesics as needed, such as paracetamol (acetaminophen) or diclofenac. Due to the social problems after the war, neither chemotherapy or radiotherapy was available in the health system.

Recently, her pain became more severe and intolerable. The pain was no longer responding to diclofenac. She found a very caring physician, Dr. Foud, who started her first on the weak opioid tramadol in addition to the diclofenac. After a few days, when it was evident that the tramadol was ineffective, Dr. Foud changed the opioid medication of Mrs. Nadhari to morphine (30 mg q.i.d.).

At rest, the pain was now controlled well, such as when she was in bed or watching television. But Mrs. Nadhari was very disappointed that she was no longer able to do the cooking for her family since longer periods of standing or bending down at the oven had become impossible.

Case report discussion

This patient with breast cancer and auxiliary lymph node involvement complains of severe pain due to multiple bone metastasis. As it is typical in these cases, pain at rest is well controlled by analgesics (according to the World Health Organization [WHO] ladder), but pain on movement is not controlled at all. Since all pain exacerbations did occur in conjunction with physical activity, such pain is called incident pain (as opposed to breakthrough pain, which would appear also spontaneously). The best thing for Dr. Foud to do would be to prescribe 10-mg tablets of morphine for Mrs. Nadhari and to instruct her to use them when physical activity is planned. For example, before starting cooking, Mrs. Nadhari should take a 10-mg tablet (a titration dose), wait approximately 30 minutes, and then start to go to the kitchen. Of course, she should be warned that the extra morphine, especially if she needs more than one titration dose, might produce sedation and nausea, or both. If it is available, metoclopramide should therefore be provided if necessary, and

a family member or friend should be around to help her in case she feels dizzy.

In case Mrs. Nadhari needs more than three or four demand doses of morphine daily, Dr. Foud should consider increasing the background morphine dose accordingly, perhaps to 40 mg morphine q.i.d.

What is breakthrough pain?

The WHO has issued guidelines for matching the potency of analgesics with the intensity of pain. The three-step approach was recommended in 1990 and revised in 1996. The WHO guidelines do not specifically address breakthrough pain.

The transitory exacerbation of pain is described in the medical literature by a number of different terms, such as breakthrough pain, transient pain, exacerbation of pain, episodic pain, transitory pain, or pain flow. An Expert Working Group of the European Association for Palliative Care (EAPC) has suggested that the term "breakthrough pain" should be replaced by the terms "episodic pain" or "transient pain." However, the term "breakthrough pain" is still widely used in the medical literature; therefore, this term will be used in this chapter, too.

Breakthrough pain is usually abrupt, acute, and can be very intense. The characteristics of breakthrough cancer pain vary from person to person, including the onset, duration, frequency of each episode and possible causes.

Breakthrough pain could be described as short-term pain exacerbation which is experienced by a patient who has relatively stable and adequately controlled baseline pain. But currently, there is no universally accepted definition of breakthrough pain. There are diagnostic algorithm and assessment tools for breakthrough pain, although they are not used very often in clinical practice. Breakthrough pain should be assessed in a similar manner to background pain, with a pain history and physical examination.

Why should attention to breakthrough pain be increased?

Breakthrough pain is common in cancer patients, and also in patients with other types of pain. Unfortunately, it is underdiagnosed and under-recognized by health care professionals. An IASP survey on cancer pain characteristics and syndromes found that pain specialists from North America, Australasia, and Western Europe reported more breakthrough pain than did pain specialists from South America, Asia, and Southern and Eastern Europe. Thus, there is a need for specific educational initiatives about breakthrough pain for all groups of health care professionals involved in pain management, since the diagnosis and treatment of breakthrough pain should be independent from the region in which the patient lives. Many patients with cancer-related pain are inadequately managed, and this problem relates to treatment of both background pain and breakthrough pain. Unsatisfactory treatment of breakthrough pain relates to inadequate assessment, inadequate use of available treatments, and, in many instances, inadequate treatments. Health care professionals need to be aware of the different treatment options, and patients need to have access to all of these different treatment options (e.g., anticancer treatment, nonpharmacological interventions, and pharmacological interventions).

What are the causes of breakthrough pain?

Breakthrough pain appears to be more common in patients with

- Advanced disease;
- Poor functional status;
- Pain originating from the vertebral column and to a lesser extent from other weight-bearing bones or joints;
- Pain originating from the nerve plexuses and to a lesser extent from nerve roots.

Other categories include idiopathic breakthrough pain, which occurs spontaneously, and breakthrough pain known as "end of-dose failure," which typically occurs at the end of the dosage interval of pain medication used to control the patient's persistent pain. This transitory increase in pain should be greater than of moderate intensity (e.g., "severe" or "excruciating"). A widely used set of diagnostic criteria for breakthrough pain is by Russell Portenoy, from Memorial Sloan-Kettering Cancer Center, New York. The criteria are:

- The presence of stable analgesia in the previous 48 hours
- The presence of controlled background pain in the previous 24 hours (i.e., average pain intensity of no more than 4 out of 10 on a numeric rating scale [NRS])

- Temporary flares of severe or excruciating pain in the previous 24 hours

How is breakthrough pain assessed?

Currently, there is no validated assessment tool for breakthrough pain, but the assessment of breakthrough pain should involve:

- Taking a pain history
- Examining the painful area
- Appropriate investigations.
- Assessment of pain intensity with well-known tools: e.g., verbal rating scale or numerical or visual analogue scale)

How can breakthrough pain be managed?

As always, the best strategy for treatment of breakthrough pain would seem to be treatment of the cause of the pain, but unfortunately, most of the time, a cause of pain that could be eliminated immediately is not apparent.

Breakthrough pain is a heterogeneous condition, and its management therefore may involve the use of a variety of treatments, rather than the use of a single, standard treatment. The most appropriate treatment(s) will be determined by a number of different factors, including the etiology of the pain (e.g., cancer-related, non-cancer-related), the pathophysiology of the pain (e.g., nociceptive, neuropathic), the characteristics of the pain (e.g., episode duration), the characteristics of the patient (e.g., performance status), the acceptability of different interventions, the availability of different interventions, and the expense of different interventions.

First, you should evaluate whether breakthrough pain may be lessened by nonpharmacological methods, such as repositioning or bed rest, rubbing or massage, application of heat or cold, and distraction and relaxation techniques. Also, never forget to check the fullness of the bladder in cases of acute pain exacerbation in the lower abdominal region, especially in noncommunicating or sedated patients.

Unfortunately, there is relatively little evidence to support the use of these interventions in the treatment of breakthrough pain episodes.

Second, if pharmacological intervention is essential, the drug class of choice in nociceptive pain (described as aching, dull, and drilling) is opioids. Depending on the intensity of pain, the route of application is chosen. In "excruciating" pain (NRS score of 9–10), the time interval between an oral opioid and pain reduction would be considered to be too long (usually 30 to 45 minutes) and intravenous (i.v.) titration of an opioid would be indicated (usually 5–10 minutes). In moderate to high pain (NRS score of 6–8), oral opioids may be used. All immediate-release opioids are suitable as i.v. or oral breakthrough pain medications.

It is a good idea to combine opioids with nonopioid analgesics such as metamizol, ibuprofen, or diclofenac, if the patient is not already taking them regularly.

Practical questions about breakthrough pain

I am afraid of respiratory depression. Is worrying about this typical opioid side effect justified?

Pain is an antagonist for all depressing effects of opioids. As long as the pain and the opioid dose are balanced, there will be only tolerable sedation and no respiratory depression. Since the principle of breakthrough pain management is opioid titration, this balance between pain intensity and opioid side effects can be found easily. The goal of titration is not no pain (NRS score of 0), as at the doses required, side effects would prevail, but a tolerable pain level (NRS score of 3–4). Then respiratory depression should not be a major concern. However, in rare instances, pain intensity may not change, but the patient may become more and more sedated. In these extreme situations, the patient must be woken up to be able to tell you that the pain is still excruciating.

How can a patient be heavily sedated, but still in excruciating pain?

The explanation is that a patient can have pain that is not "opioid sensitive," meaning that because of the type of pain (e.g., neuropathic pain) or tolerance effects (rapid dose escalation with opioids prior to breakthrough pain), the opioids are not working. Therefore, the patient is only experiencing the side effects of the opioids.

Alternative techniques to relieve the pain have to be considered. In neuropathic pain, oral carbamazepine or oral/i.v. phenytoin might work, otherwise i.v. ketamine or S-ketamine in analgesic doses might be indicated (0.2–0.4 mg/kg or 0.05–0.2 mg/kg body

weight per hour, respectively). If an anesthesiologist is available, regional or neuraxial blocks using catheters should be evaluated.

In practical terms, what can I do to help a patient in acute excruciating pain?

In general, we never know what the necessary total dose for pain control will be. Therefore, the basic principle of breakthrough medication application is "titration." A young, male, athletic patient with excruciating pain may need only 2.5 mg i.v. morphine, while a frail elderly lady may need 25 mg of i.v. morphine to get the same pain relief.

If your patient has no prior continuous opioid medication, 2.5 mg of morphine (or 50 mg of tramadol, 0.5 mg of hydromorphone, or 50 mg of meperidine) would be an adequate i.v. titration step. By asking the patient each time, 5–10 minutes after the opioid application, about pain intensity, you can decide whether titration has to be continued.

If your patient has a prior continuous opioid medication, the titration dose should be around 10–15% of the daily cumulative dose of the opioid. If your patient is on 40 mg oral morphine q.i.d. (total daily dose 160 mg orally, which would equal 50 mg of i.v. morphine), the i.v. titration dose would be 5–7.5 mg. The i.v. dose may be repeated about every 8 minutes to allow it to completely take effect before you decide whether further titration is indicated. Breakthrough pain analgesic titration is considered successful when pain intensity is at or below an NRS score of 4.

In practical terms, what do I do in strong, but not excruciating, pain?

Basically, the same rules apply as in the last paragraph, but instead of i.v. titration, oral titration is used. Again, 10–15% of the total daily dose is calculated, and that titration dose is offered to the patient every 30 minutes until pain intensity is under control.

Can I use the acute titration dose to estimate the future opioid needs of my patient?

Yes, in cancer patients you can pretty well foresee the future opioid demand of your patient. If the patient needs 30 mg of oral morphine or 10 mg of i.v. morphine for analgesic titration, he or she will have an estimated daily supplemental demand of 120 mg (oral) or 30 mg (i.v.) morphine (corresponding to the average duration of action of morphine of around 6 hours times four, which would equal the supplemental daily dose).

In what situations may other drugs be indicated for breakthrough pain?

Typical indications for other nonopioid medication in breakthrough pain would be spasmatic pain or neuralgic pain.

Spasmatic pain, e.g., from the renal tract, may be relieved by relatively high doses of metamizol (2.5 g slowly i.v.), which is the first choice of drug.

Neuralgic pain exacerbations, such as in trigeminal neuralgia, are best treated acutely with fast-release carbamazepine (200 mg).

On rare occasions of refractory neuropathic pain, e.g., in Pancoast cancer (superior sulcus tumor with infiltration of the brachial plexus, first described by the American radiologist Henry Pancoast), i.v. titration of phenytoin might be indicated (5 mg/kg body weight over 45 minutes, repeated no more than twice).

However, there is relatively little evidence to support the use of these interventions in the treatment of breakthrough pain episodes.

Should I always wait until my patient has breakthrough pain?

Definitely not! All drug regimes for cancer patients should include a breakthrough pain medication from the start. As a rule of the thumb, the patient should be allowed to use extra ("demand") doses of his regular opioid as needed. In a patient with 40 mg oral morphine q.i.d. (160 mg daily), the patient should be instructed to take an extra dose of 20 mg morphine when needed. The minimum time interval between two demand doses should be 30 minutes to allow the effects of morphine to develop fully.

Can I use the average number of daily demand doses to estimate the true opioid requirement of my patient?

Yes. If your patient needs five demand doses daily, you should add the cumulative daily demand dose to the "background" medication. A patient with 40 mg q.i.d. morphine needing morphine demand doses of 10 mg five times daily should receive from now on 50 mg q.i.d. regularly. A frequency of fewer than four demand doses daily is considered to be "normal," and therefore the dosing scheme may be maintained. If there is no need for demand doses, maybe a (small) reduction of "background" medication may be tried.

What are practical considerations for breakthrough pain in my patient?

- Breakthrough pain refers to a cancer patient who has a chronic pain problem, and is generally taking a long-term analgesic to treat his pain, but still has episodes of increased pain additional to his constant pain.
- Breakthrough pain in noncancer pain is a different story. Usually breakthrough pain has a different etiology than in cancer pain since there is no obvious continuous tissue destruction. Therefore, the patient should not receive "free access" to demand doses to avoid dose escalations in pain etiologies where long-term analgesia by opioids is very rare, e.g., chronic back pain or headache. An exception to the rule would be inflammatory pain, as in advanced rheumatic arthritis or systemic scleroderma.
- Not surprisingly, the pathophysiology of the breakthrough pain is often the same as that of the background pain. Thus, breakthrough pain may be nociceptive, neuropathic, or of mixed origin.
- Breakthrough pain may result in a number of other physical, psychological, and social problems. Indeed, breakthrough pain has a significant negative impact on quality of life. The degree of interference seems to be related to the characteristics of the breakthrough pain. Breakthrough pain is associated with greater pain-related functional impairment, worse mood, and more anxiety.
- The characteristics of breakthrough cancer pain vary from person to person, including the duration of the breakthrough episode and possible causes. Generally, breakthrough pain happens fast, and may last anywhere from seconds to minutes to hours. The average duration of breakthrough pain in some studies was 30 minutes. Breakthrough pain episodes have the following four key features: high frequency, high severity, rapid onset, and short duration.
- Rescue medication should be taken at the first sign of breakthrough pain. Pain that is allowed to build up is much harder to control. It is possible to experience breakthrough pain just before or just after taking the regular pain medication.
- Medications used for treating breakthrough pain are called rescue medications. They are the cornerstone for the management of breakthrough pain episodes. Rescue medication is taken as required, rather than on a regular basis: in the case of spontaneous pain or nonvolitional incident pain, the treatment should be taken at the onset of the breakthrough pain; in the case of volitional incident pain or procedural pain, the treatment should be taken before the relevant precipitant of the pain. In many patients the most appropriate rescue medication will be a normal-release ("immediate-release") opioid analgesic.
- Alternative routes of administration and lipophilic opioids would appear to be appropriate for patients with insufficient breakthrough pain control. Oral transmucosal, sublingual, and intranasal fentanyl, which has become available in some countries, would be a good choice for all patients for whom the onset of effect of oral morphine is too slow and the duration is too long.
- Another type of pain similar to breakthrough pain is incident pain. It may be that certain activities your patient does during the day are going to lead to more pain. Your patient needs to be prescribed medications for this kind of activity, to be taken before engaging in this extra activity. The other type of pain that is somewhat like breakthrough pain, but is a bit different, is called end-of-dose failure. These patients are taking an analgesic that becomes ineffective after a few hours, and then pain returns. The answer to that problem is to choose a different—longer-acting—agent, choose a higher dose of the same agent, or change the dosing interval to avoid low serum levels with consecutive "end-of-dose" failure.

Pearls of wisdom

- About one-half to two thirds of patients with chronic cancer-related pain also experience episodes of breakthrough cancer pain.
- Almost all people experiencing chronic cancer pain should receive pain medications for around-the-clock pain control AND a medication specifically for treatment of breakthrough pain. If you have not offered this option to your patients, always do so from now on.
- Morphine (oral and i.v.) is commonly used and available. Although it has a delayed onset of action, and a prolonged duration of effect, studies

show that the majority of patients have sufficient breakthrough pain control with this approach.

- As patients learn that certain actions cause breakthrough pain, these episodes can be anticipated, which may allow patients and physicians to either prepare a treatment response or to treat prophylactically.
- Raising the continuous "background" analgesia dose moderately may reduce the frequency and intensity of breakthrough pain episodes.
- The management of breakthrough pain is the art of assessment, treatment, and reassessment.

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Guide to Pain Management in Low-Resource Settings

Chapter 37
Pain Management in the Intensive Care Unit

Josephine M. Thorp and Sabu James

Case report

A 52-year-old man, Joe Blogg, was admitted to the intensive care unit (ICU) from the operating room, after undergoing a long surgical procedure. He had been the driver of a car that was involved in a head-on collision, and he was trapped in the car (no seat belt or air bag) for about 30 minutes. When first assessed in the receiving accident and emergency care unit, he was rousable but confused and in considerable pain. His injuries were as follows:

Bilateral pneumothoraces (intercostal drains were inserted in the accident and emergency unit by the resuscitation team). Fractures of the third, fourth, and fifth ribs on the left side. Deep wounds to right knee and right elbow, extending to the joint. An extensive mesenteric tear, for which he underwent a 5-hour laparotomy. Estimated blood loss of about 5 L, coagulopathic, with a platelet count of 50,000 postoperatively. He had several units of blood and blood components in the operating room. He is anuric and hypothermic (with a core temperature of 34°C).

He was transferred to the intensive care unit for elective ventilation and management.

What issues must be considered in this case for intensive care and afterwards?

- Sources of pain (exacerbating factors)
- Effects of untreated pain (advantages of adequate pain relief, disadvantages of excessive analgesics or sedatives)
- Assessment of pain and sedation
- Aims of therapy
- Techniques of pain management (routes for pharmacological agents, analgesics, anxiolytics, and local anesthetic techniques)
- Adjuncts to pharmacological agents (managing the ICU environment, reducing other sources of discomfort, alternative measures, psychological measures)

The majority of patients requiring intensive care will suffer pain, of varying intensity, during their stay. Despite knowledge since the early 1970s that pain is often the worst memory for patients surviving intensive care, in recent multicenter studies up to 64% of patients still said they were often in moderate to severe pain while in the ICU. The experiences of patients who did not survive their ICU stay remain unknown. Patients who were in ICU for longer periods reported greater intensity of pain.

What are the sources of pain?

- Primary pathology, such as burns, traumatic injuries, fractures, wounds (surgical or traumatic)
- Complications of the original condition or new problems, such as bowel perforation or breakdown of bowel anastomosis causing peritonitis, ischemic bowel, pancreatitis

- Other symptoms, such as abscesses, skin inflammation, wound infection, rashes, itches
- Support systems and monitoring—peripheral and central intravenous line insertions and sites, catheters, drains, regular suctioning, physiotherapy, dressing changes
- Tissue hypoxia as a result of low cardiac output, low oxygen saturation, or a sharp fall in hemoglobin may result in myocardial ischemia
- Painful joints, pressure points, pain on changing position in bed

What exacerbating factors may increase pain perception?

- Fear in strange surroundings associated with helplessness and lack of control
- Inability to remember or understand the situation resulting in intensive care
- Anxiety and uncertainty about oneself, one's family, and about the present and the future
- Background aggravations—noise, machine alarms, phones ringing
- Ongoing activity through the night, other patients being admitted or resuscitated
- Inability to communicate, to move, to change position
- Lack of sleep, disturbed sleep patterns
- Other sensations:—thirst, hunger, hot, cold, cramps, itching, nausea
- Fatigue after surgery; even after uncomplicated surgery, fatigue is normal
- Boredom and lack of distraction

Addressing these aspects will make the pain itself more tolerable and manageable.

What are the effects of untreated pain?

- Pain induces increased sympathetic drive, resulting in cardiovascular changes (increased cardiac work and oxygen consumption).
- An increased stress hormone response results in catabolism, with sodium and water retention and hyperglycemia, which in turn leads to immunosuppression and delayed wound healing.
- Ineffective cough and retention of secretions, resulting in reduced oxygenation, infection.
- Chest wounds and abdominal incisions decrease chest wall and abdominal movements, which may delay weaning from ventilation, increase the risk of chest infection, and prolong ICU stay.
- Pain in itself will result in poor-quality sleep.

What are the advantages of adequate pain relief?

- Improved tolerance of endotracheal tube, mechanical ventilation, tracheal suctioning, and other distressing maneuvers.
- During weaning and after extubation, if chest excursion is limited by pain, adequate analgesia will result in larger tidal volumes, better gas exchange, improved sputum clearance, and cooperation with physiotherapy.
- Reduction in the stress response.
- Less disturbing memories of therapy in the ICU.

What is the compromise between too much analgesia and too little?

The middle ground, to gain the benefits without the disadvantages can only be achieved by *regular assessment of pain* along with a "sedation vacation" (a break from sedation) and adjustment of the regime on a daily basis.

How can you assess pain and sedation?

Even under normal circumstances, assessment and quantification of pain are difficult. These difficulties are obviously far greater in the patient in the ICU, with an endotracheal tube often present, preventing speech and empathic discussion. A state of paralysis in an aware patient should be avoided in the ICU just as in the operating room, as this is a terrifying experience for a patient**.** *If the patient is paralysed, it is important to ensure that adequate sedation and analgesics are given to avoid a patient who is awake but unable to move!*

If the patient is able to speak, a routine history about the pain and its severity can be taken. A patient who is able to understand, but unable to speak, may be able to gesture or to indicate severity on a simple evaluation tool such as a visual analogue scale (VAS) or numeric rating scale (NRS). The NRS is a 10-point scale: the patient chooses a number from 0 to 10, with 10 being the worst pain imaginable. Where no communication is possible, signs of sympathetic drive can be noted—tachycardia, hypertension, and lacrimation. Clinical practice guidelines state: "Patients who cannot communicate should be assessed through subjective observation of pain related behaviors (movement, facial expression and posturing) and physiological indicators (heart rate, blood pressure and respiratory rate) and the change in these variables following analgesic therapy."

Pain is exacerbated by movement, which may evoke pain of a quite different character. Moving, turning the patient, and the effects of endotracheal tube suction and physiotherapy give valuable information about the effectiveness of analgesia.

For children, scales have been developed specifically for neonatal and pediatric use, e.g., the Riley Infant Pain Scale:

Score	Facial Expression	Sleep	Movements	Cry	Touch
0	- Neutral - Smiling, calm	- Sleeping quietly	- Moves easily	- None	-
1	- Frowning - Grimaces	- Restless	- Restless body movements	- Whimpering	- Winces with touch
2	- Clenched teeth	- Intermittent	- Moderate agitation	- Crying	- Cries with touch - Difficult to console
3	- Crying expression	- Prolonged, with periods of jerking or no sleep	- Thrashing, flailing	- Screaming, high-pitched	- Screams when touched - Inconsolable

Whatever method of assessment is selected, it should be regular. Both the patient and the response to drugs are constantly changing, so drugs and doses need regular adjustment.

What are the main problems for Joe in the intensive care unit?

- Being heavily sedated and ventilated, and thus unable to communicate
- Being critically ill, with multiple injuries including lung contusions and possible head injury
- Experiencing massive blood loss, massive transfusion, and coagulopathy
- Having hypothermia
- Having anuria
- Experiencing multiple sources of pain: intercostal drains, fractured ribs, elbow and knee wounds, and a laparotomy wound

What are the aims of therapy?

The objective should be a cooperative, pain-free patient, which implies that the patient is not unduly sedated.

The United Kingdom Intensive Care Society guidelines on sedation state the following:

1) All patients must be comfortable and pain free: *Analgesia is thus the first aim.*

2) Anxiety should be minimized. This is difficult as *anxiety is an appropriate emotion*. The most important way to reduce anxiety is to provide compassionate and considerate care; communication is an essential part of care.

3) Patients should be calm, cooperative, and able to sleep when undisturbed. *This does not mean that they must be asleep at all times.*

4) Patients must be able to tolerate appropriate organ system support. Thus, patients with very poor gas exchange, particularly those requiring inverse I:E ratios or the initial stages of permissive hypercapnia, may need neuromuscular blockade. The use of a nerve stimulator to monitor the extent of neuromuscular blockade may be useful in some situations.

5) Patients must *never* be paralysed and awake.

Pain management in the intensive care unit

What techniques of pain management are available?

Most intensive care patients will require analgesia. In 1995, the Society of Critical Care Medicine published practice parameters for intravenous analgesia and sedation in the ICU. Morphine and fentanyl were the preferred analgesic agents, and midazolam or propofol were recommended for short-term sedation, with propofol being the agent of choice for rapid awakening. More recently, sedative and analgesic practice in ICUs in Europe has been surveyed; opioids are the drugs most commonly used for pain relief, usually by infusion, with morphine being the most widely used. Shorter-acting fentanyl and alfentanil, as well as ultra-short-acting remifentanil, are also used, but they are more expensive. Propofol and benzodiazepines are used for sedation, with diazepam, lorazepam, and midazolam all being widely used.

What are the available application routes for pharmacological agents?

The ideal route is intravenous, which is more reliable than the alternatives. Small frequent intravenous bolus

doses or an intravenous infusion are the best routes for analgesics. The latter avoids peaks and troughs but may result in accumulation. Bolus doses should be regular without waiting until another dose is obviously essential. In all situations, it is important to review the requirement regularly, for example daily, by discontinuing the infusion or stopping the boluses. In this way, pain can be assessed, accumulation can be avoided, and the dose can be adjusted accordingly. Another important reason for discontinuing drugs and allowing the patient to recover from the effects is the great variations in drug handling in the critically ill patient. There are a variety of explanations for this variation, but discontinuing drugs allows the effect to wear off and reduces the tendency to accumulation.

Gastrointestinal absorption can be unpredictable, and absorption of opioids is poor. Rectal administration, for drugs that are available in suppository form, may give better absorption, although the side effects of the enteral route remain. Some classes of analgesics have only become available in parenteral form relatively recently. Intravenous nonsteroidal anti-inflammatory agents (NSAIDs) and, more recently, paracetamol (acetaminophen) are available as intravenous formulations.

What would be a good choice of analgesia for Joe?

- Paracetamol/acetaminophen (intravenous, if available, or via nasogastric tube regularly)
- Nonsteroidal analgesics (via nasogastric tube) given regularly (after coagulopathy has resolved), combined with gastric protection agents
- Opioids (preferably as a continuous intravenous infusion)
- Nerve blocks (single-shot nerve blocks or epidural analgesia)

What to bear in mind when using opioid analgesics in the intensive care unit

Morphine and fentanyl are the most commonly used analgesics in Europe according to a survey in 2001; morphine has the advantage of being cheap. It is longer acting than synthetic opioids but also more inclined to accumulate. Elderly patients are more sensitive, as are those with renal or hepatic impairment. The potent active metabolite, morphine-6-glucuronide, can accumulate in renal failure, resulting in continued sedation, failure to breathe, or failure to wake up. This contraindication also applies to diamorphine and papaveretum. In renal impairment, if there is no alternative, the dose and dosing interval should be reduced.

Systemic effects of opioids within the context of intensive care are:

- Central nervous system: morphine, diamorphine, and papaveretum have sedative properties, but excessive doses would be required to achieve sedation.
- Respiratory system: all opiates depress respiration in a manner proportionate to the pain relief obtained. This is not a major issue in a ventilated patient. Some cough-suppressant effect can be an advantage in the intubated patient.
- Cardiovascular system: given in small doses, there is usually little effect on blood pressure.
- Gastrointestinal system: opiates have a gut antimotility effect and so may exacerbate paralytic ileus and constipation. Nausea and vomiting are well-known side effects of morphine.
- Other side effects: pruritis can be a distressing side effect for the patient. Addiction is not a problem with the use of opiates in severe pain and is not a concern in patients who have survived intensive care. However, withdrawal symptoms and signs are possible after several days of continuous therapy or if therapy is stopped suddenly. An initial reduction of 30% followed by a 10% reduction every 12–24 hours thereafter should help to avoid withdrawal phenomena.

The systemic effects of other opiates are similar to those described above. *Diamorphine or papaveretum* could be used instead of morphine if more readily available. *Fentanyl* is a synthetic opioid that was introduced as a short-acting agent, but it can accumulate when given as an infusion in intensive care. It may be useful for short painful procedures. *Alfentanil* has the advantages of fentanyl quoted above. Its onset is faster than that of fentanyl, and even as a prolonged infusion, it is less cumulative; it would be the drug of choice in renal impairment. Like fentanyl, it is particularly useful for additional short-term analgesia, lasting around 10–15 minutes. Unfortunately, it is much more expensive.

Remifentanil, although quite expensive, is currently used in the intensive care arena, especially for weaning and tube tolerance. It is rapidly metabolized and does not accumulate regardless of time or in renal or hepatic dysfunction.

For less severe pain, pethidine and tramadol could be used. *Pethidine/meperidine* could be given by bolus doses for procedural pain relief, but not as an infusion, because its metabolite can accumulate and is associated with twitching and seizures. *Tramadol* has the advantage of two mechanisms of action for pain relief—opiate-like activity by binding to opiate receptors and inhibition of serotonin and norepinephrine reuptake by nerves, mainly in the spinal cord. It is relatively expensive but avoids the problems of respiratory depression and gastrointestinal stasis. Rapid intravenous injection may cause seizures, and it is not advised in pregnancy or breastfeeding.

Buprenorphine and *pentazocine* are unsuited for analgesia in intensive care. If given in a sufficient dose to cause respiratory depression, they are not reliably reversible with naloxone. In addition, these agents antagonize other opioids because of powerful receptor binding, reversing the analgesic effect of other opioids by displacing them from receptors. Thus, they may precipitate opioid withdrawal symptoms and signs. Pentazocine can be associated with bizarre thoughts and hallucinations.

Other opioids include meptazinol and codeine. *Meptazinol* is claimed to cause less respiratory depression, but it can cause nausea. Intravenous injection needs to be slow. *Codeine* is used in mild to moderate pain and might have some effect as a cough suppressant. It is usually given orally, though linctus could be given down a nasogastric tube. Actually, codeine is metabolized in the liver into morphine and other products that cause relatively severe side effects.

How to reverse the effects of opioids if necessary

Naloxone reverses all opioid effects, so both respiratory depression and pain relief are reversed (for buprenorphine and pentazocine, see above). Too much naloxone given too quickly and reversing analgesia may result in restlessness, hypertension, and arrhythmias and has been known to precipitate cardiac arrest in a sensitive patient. If possible, dilute naloxone to 0.1 mg/mL and titrate, giving 0.5 mL of the diluted solution at a time to achieve the required degree of reversal, so that respiration becomes adequate and some analgesia continues. Naloxone has a shorter duration of action than many opiates, and the patient may become renarcotized. Repeat doses of naloxone or an infusion may be required.

What nonopioid analgesics are options for analgesia in the intensive care unit?

Nonopioid analgesics used in combination with an opioid achieve better-quality pain relief. Although some intravenous and intramuscular preparations are available, these agents are mostly given by the enteral route if gastrointestinal function permits adequate absorption. Some are available in suppository form or as a liquid suspension, which can be given down a nasogastric tube.

Paracetamol/acetaminophen is a non-narcotic analgesic with useful antipyretic action as well. It is useful in mild to moderate pain and has an additive effect if given with an opiate. It is available as dispersible tablets, as an oral suspension, and in suppository form. It has no anti-inflammatory activity and so avoids the side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). *Clonidine,* an alpha-2-adrenergic agonist, can be used to augment both the sedative and analgesic effects of opioids. A dramatic reduction in opioid requirements and the attendant side effects has been reported with low-dose clonidine. *Diclofenac, ketoprofen, ibuprofen,* and other NSAIDS are good for bone pain and for soft-tissue pain in young patients without asthma or renal impairment and can reduce opioid requirements. Oral, nasogastric, intravenous, and rectal routes can be used. Regardless of route, they cause gastric irritation. Hence, prophylactic treatment for gastric ulceration should be given. However, the significant side effects of NSAIDs in intensive care have to be considered: they can cause bronchospasm, may precipitate or exacerbate a bleeding tendency, cause gastrointestinal bleeding from mucosal ulceration (exacerbated by platelet inhibition), or lead to development of renal impairment or worsening of renal failure, particularly when other risk factors are present, such as hypotension, hypertension, or diabetes. NSAIDs should be used with caution in older patients due to a higher incidence of gastric complications and renal impairment. Aspirin, indomethacin, and cyclooxygenase (COX)-2 inhibitors are not recommended for use in the ICU due to a plethora of side effects.

What about using ketamine in the intensive care unit?

Good analgesia can be achieved with low-dose ketamine. It tends not to be used for background analgesia in intensive care in the United Kingdom, though it may be used for short procedures. Some studies have shown

that ketamine reduces opioid requirements in surgical intensive care patients. The dose range for avoiding psychomimetic side effects is 0.2 to 0.5 mg/kg body weight. If using S-ketamine, the dose range has to be divided by two. Long-term use is possible. Ketamine could perhaps be the analgesic of choice in patients with a history of bronchospasm to have the benefit of bronchodilator activity without contributing to arrhythmias, if aminophylline is also required. Where expensive analgesics are not available, ketamine may have a slightly greater role as an adjunct in pain relief in intensive care. Also, predominantly neuropathic pain might be an indication, since the "normal" coanalgesics for neuropathic pain, e.g., amitriptyline, carbamazepine, and gabapentin, are not available for parenteral use and have a delayed onset of action.

Can local-anesthetic techniques be used in the intensive care unit?

Intercostal nerve blocks, paravertebral blocks, epidural analgesia, transversus abdominis plane (TAP) blocks, femoral nerve blocks, and interscalene/brachial plexus blocks can be used as single shots or with catheters (not for intercostal blocks) for continuous infusion. To avoid nerve damage, nerve stimulators or ultrasound guidance should be used, if the patient is sedated and paresthesias cannot be communicated. Regular coagulation profile, full blood count, and platelet numbers should be noted before these procedures as regional techniques are contraindicated in patients with a bleeding tendency such as anticoagulation, coagulopathy, and thrombocytopenia. *If a continuous technique with an indwelling catheter is used, this should be clearly labeled.* A filter should be used to minimize or prevent infections.

What to discuss regarding appropriate analgesia for Joe

- Availability of analgesics (both type and form).
- Appropriate analgesic for this situation, since this patient has renal failure and coagulopathy.
- Opioids (preferably as a continuous infusion).
- Nerve block and/or epidural may be appropriate once his renal function improves and he is no longer coagulopathic.

How and when to use anxiolytics and sedatives

Although these drugs have no analgesic properties, they may reduce the dose of analgesia required. In a survey in 2001 in Western Europe, *midazolam* was most frequently used for sedation in the intensive care situation because it has a shorter duration of action than *diazepam* and is less prone to accumulation. *Lorazepam* is a cost-effective drug that is longer acting and can have useful anxiolytic effects for prolonged treatment of anxiety; however, it can result in oversedation. In the American Society of Critical Care Medicine Guidelines, lorazepam was the drug recommended for longer-term sedation. *Propofol* infusion is also frequently used in many countries in Europe; the advantage being that it can be titrated easily and the effect will usually diminish quickly once the infusion is stopped, allowing for a "sedation vacation" in the ICU. In addition to benzodiazepines and propofol, other drugs with sedative properties have been used in the past and are considered obsolete for sedation: phenothiazines, barbiturates, and butyrophenones. *Opioids should not be used to achieve sedation, and some of their side effects can be disturbing in themselves.*

Excessive sedation has negative effects—reduced mobility results in increased risk of deep vein thrombosis and pulmonary thromboembolism. Oversedation may slow the weaning process or delay extubation, when the patient is otherwise ready, and so can prolong ICU stay, with its attendant risks, and increase the cost of care. After several days of continuous therapy with propofol or benzodiazepines, withdrawal phenomena may be precipitated, and reduction in dose should be gradual to avoid them.

What adjuncts to pharmacological agents should be considered in the intensive care unit?

The ICU can be a noisy place with regular monitor alarms, telephones, and pager calls. Much of the monitor alarm noise is avoidable by setting alarm limits around the expected variables of a particular patient at that time. This means that the alarm will still sound if there is a change beyond the expected. Although patients may appear asleep or sedated, their hearing may remain, so discussions about the patient may be better held out of earshot as the patient may misinterpret limited information. This applies perhaps even more to discussion about other patients, because a listening patient may mistakenly believe that the conversation applies to himself.

Adjustment of the lighting to provide nighttime/daytime levels may help. Even if the patient is

tired, it is difficult to sustain sleep with full daytime lighting, and the ICU patient does not have the option of hiding beneath the bedclothes. Feeling thirsty, hungry, hot, or cold is a driving force that normally results in remedial action, but this is beyond the power of the ICU patient.

Good nursing care helps to avoid pressure areas and prevents the patient from lying on a rumpled sheet or tubing, ventilator tubing from dragging on the endotracheal tube, ECG leads pulling across the skin on the chest, drip tubing pulling on cannulae (in addition, dislodgement usually means re-insertion, which may be difficult). Awareness of all such details helps to reduce unnecessary discomfort.

Supportive modes of ventilation such as pressure support and other modes on modern ventilators are associated with greater patient comfort and require less analgesia and sedation compared with full ventilation. Maintaining muscle activity will reduce respiratory muscle wasting.

Other symptoms such as nausea, vomiting, itch, significant pyrexia, and cramps require their own management. Fractures need to be stabilized either surgically, when appropriate, or immobilized. Causes of agitation such as a full bladder or rectum should be excluded.

Are there alternative and psychological measures from which my patient could benefit?

Relaxation techniques require a cooperative patient preferably breathing spontaneously to coordinate deep breathing with sequential relaxation of muscle groups from head to toe. Music can be beneficial, particularly if it is of the patient's choice and appreciated through headphones, rather than being added to background noise of ICU.

Speaking to the patient by name, even though the patient appears sedated, and explaining what is about to happen is always helpful, both for the patient and for visiting relatives or friends. It helps patients to reconnect with who they are and with their family. Telling patients who understand and are recovering that they are making good progress assists positive thinking and can enhance recovery.

Giving patients the opportunity to express their pain or discomforts by some means is helpful so that they know staff are sympathetic and will explain the possible remedies. If the patient can write, the first opportunity will invariably produce squiggles resembling abstract art as opposed to words (reassurance that this is very common is needed). Alternatively, pictures displaying the most common complaints and requests can be used.

For planned admissions to the ICU, such as after major surgery, an explanation of tubes, lines, monitoring and procedures can be made in advance. In this way, common interventions that are not expected by the patient will not interpreted by the patient as "something has gone wrong."

While pain perception may be exaggerated by additional factors, and ameliorating these factors may make pain considerably more tolerable, they will not take pain away. Therefore, appropriate doses of analgesics will still be required.

Case report (cont.)

Still heavily sedated and ventilated, Joe is started on an intravenous infusion of morphine at a rate of 10 mg per hour. He starts struggling, and the ventilator alarm keeps buzzing. He also becomes very tachycardic and hypertensive, causing concern for the staff. A review of sedation and analgesia is necessary in the unit. (Think of infection, fat emboli, inadequate sedation/analgesia, respiratory distress due to pulmonary contusions, etc.). Joe's white cell count is slightly elevated, temperature is on the higher side, platelets are increasing, and coagulation results are encouraging. There is no clinical evidence of fat embolization. There is a concern that Joe's sedation/analgesia might be inadequate. He is started on regular nasogastric paracetamol, his sedation with midazolam is increased, and his morphine dose is raised to 15 mg per hour, after a bolus dose of 5 mg. He settles down, eventually, and there are no immediate concerns.

What should be considered for weaning and preparation for extubation?

The first rule is to outline your strategies for a successful weaning and extubation, from a pain control point of view:

- Continue paracetamol
- Reduce morphine and midazolam
- Review full blood count, coagulation parameters, and renal function
- Does the patient still need the intercostal drains?
- Plan to achieve better analgesic control, such as with nerve blocks, or by adding an NSAID if renal function has improved and platelets are

within normal limits (remember gastric mucosal protection)

Case report (cont.)

Respiratory parameters support adequate weaning, morphine infusion is ongoing, no epidural or paravertebral block has been inserted, and the patient is extubated. He manages to survive off the ventilator for about 2 hours. He complains of severe pain in his chest (from the fractured ribs) and in the laparotomy wound. Progressively he becomes unable to breathe, his saturation drops, and he needs to be re-intubated soon afterward.

Once Joe is settled and stable, inadequate pain control is seen to have been a major factor in the failed extubation, and he gets a thoracic epidural and a left-sided paravertebral block. A bolus dose of local anesthetic is given into the epidural, and a continuous infusion is set up.

What should be done next? Review his analgesia and slowly wind down the morphine infusion, hoping that the epidural and paravertebral blocks are working.

Joe is reviewed next day; sedation and morphine are minimal, and he is wide awake and wants the endotracheal tube out. When queried about pain, he signals that he has none, and is quite comfortable. He is extubated successfully and remains well.

Pearls of wisdom

In general:

- Talk to the patient by name.
- Encourage visitors to talk to the patient.
- Tell recovering patients they are doing well; tell those who are less well about some positive aspects.
- Much can be achieved by reducing additional sources of discomfort.
- An adverse ICU experience can be reduced by better communication with patients.
- As ever, "it's not what you say, but how you say it"—use an empathetic tone of voice.

Regarding pain:

- Ask about pain and irritations at regular intervals.
- Regular assessment of pain and discontinuing boluses or infusions avoids underdosing and overdosing and improves outcome and costs
- Stabilize fractures with a splint, plaster, or surgical fixation as soon as possible.
- As elsewhere, pain on movement is greater than pain at rest.
- Anticipate painful procedures or maneuvers by giving extra analgesia beforehand.
- Bolus doses of opiate are required before an infusion is started.
- An infusion rate increase takes time to become effective; give a bolus first.
- Multimodal therapy can reduce opioid requirements and side effects, but beware the hazards of nonopioid analgesics in this group of patients.
- Older persons have lower analgesic requirements; young adults have higher ones.
- Addiction to opioids is not a problem in patients surviving critical care.
- Underprovision of analgesia in general is a greater problem than overdosing.

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Websites

Bandolier—evidence based web site incorporating the Oxford Pain Internet Site is a free resource

http://www.jr2.ox.ac.uk/Bandolier/booth/painpag/index2.html

Lothian Joint Formulary is freely accessible on the internet. There are both adult and paediatric formularies. Two choices are provided for each group of drugs. Analgesics are under Central Nervous System section 4.7. Detailed drug information is not given

http://www.ljf.scot.nhs.uk/

Lothian Joint Formulary can be downloaded and saved

http://www.ljf.scot.nhs.uk/downloads/ljf_adult_20060524.pdf

Update in Anaesthesia. An educational journal aimed at providing practical advice for those working in isolated or difficult environments. Extremely valuable resource; all twenty-five issues accessible on-line.

http://www.nda.ox.ac.uk/wfsa/index.htm

AnaesthesiaUK is an educational resource for postgraduate exams. As well as instructive material, it provides access to a weekly tutorial

http://www.frca.co.uk/default.aspx

A selection of articles on acute pain topics

http://www.frca.co.uk/SectionContents.aspx?sectionid=148

A selection of articles on chronic pain topics

http://www.frca.co.uk/SectionContents.aspx?sectionid=183

International Association for the Study of Pain
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Guide to Pain Management in Low-Resource Settings

Chapter 38
Diagnostic and Prognostic Nerve Blocks

Steven D. Waldman

What are the assumptions underlying the use of nerve blocks in pain management?

The cornerstone of successful treatment of the patient with pain is a correct diagnosis. As straightforward as this statement is in theory, success may become difficult to achieve in the individual patient. The reason for this difficulty is due to four disparate, but interrelated issues:

Pain is a subjective response that is difficult if not impossible to quantify;

The pain response in humans is made up of a variety of obvious and not-so-obvious factors that may serve to modulate the patient's clinical expression of pain either upward or downward;

Our current understanding of neurophysiological, neuroanatomical, and behavioral components of pain is incomplete and imprecise; and

There is ongoing debate by pain management specialists as to whether pain is best treated as a symptom or as a disease.

The uncertainty introduced by these factors can often make accurate diagnosis very problematic and limit the utility of neural blockade as a prognosticator of the success or failure of subsequent neurodestructive procedures. Given the difficulty in establishing a correct diagnosis of a patient's pain, the clinician often is forced to look for external means to quantify or firm up a shaky clinical impression. Laboratory and radiological testing are often the next place the clinician seeks reassurance, although the lack of readily available diagnostic testing in the low-resource setting may preclude their use.

Fortunately, diagnostic nerve block requires limited resources, and when done properly, it can provide the clinician with useful information to aid in increasing the comfort level of the patient with a tentative diagnosis. However, it cannot be emphasized enough that overreliance on the results of even a properly performed diagnostic nerve block can set in motion a series of events that will, at the very least, provide the patient with little or no pain relief, and at the very worst, result in permanent complications from invasive surgeries or neurodestructive procedures that were justified solely on the basis of a diagnostic nerve block.

What would be a roadmap for the appropriate use of diagnostic nerve blocks?

It must be said at the outset of this discussion, that even the perfectly performed diagnostic nerve block is not without limitations. Table 1 provides the reader with a list of do's and don'ts when performing and interpreting diagnostic nerve blocks.

First and foremost, the clinician should use the information gleaned from diagnostic nerve blocks

Table 1
The do's and don'ts of diagnostic nerve blocks

Do analyze the information obtained from diagnostic nerve blocks in the context of the patient's history, physical, laboratory, neurophysiological, and radiographic testing
Don't over-rely on information obtained from diagnostic nerve blocks
Do view contradictory information obtained from diagnostic nerve blocks with skepticism
Don't rely on information obtained from diagnostic nerve block as the sole justification to proceed with invasive treatments
Do consider the possibility of technical limitations that limit the ability to perform an accurate diagnostic nerve block
Do consider the possibility of patient anatomical variations that may influence the results
Do consider the presence of incidence pain when analyzing the results of diagnostic nerve blocks
Don't perform diagnostic blocks in patients currently not having the pain you are trying to diagnose
Do consider behavioral factors that may influence the results of diagnostic nerve blocks
Do consider that patients may premedicate themselves prior to diagnostic nerve blocks

with caution and only as one piece of the overall diagnostic workup of the patient in pain. Results of a diagnostic nerve block that contradicts the clinical impression that the pain management specialist has formed, as a result of the performance of a targeted history and physical examination and consideration of available confirmatory laboratory radiographic, neurophysiological, and radiographic testing, should be viewed with great skepticism. Such disparate results, when the nerve block is used in a prognostic manner, should never serve as the sole basis for moving ahead with neurodestructive or invasive surgical procedures, which in this situation have little or no hope of helping to alleviate a patient's pain.

In addition to the above admonitions, it must be recognized that the clinical utility of the diagnostic nerve block can be affected by technical limitations. In general, the reliability of data gleaned from a diagnostic nerve block is in direct proportion to the clinician's familiarity with the functional anatomy of the area in which the nerve block resides and the clinician's experience in performing the block being attempted. Even in the best of hands, some nerve blocks are technically more demanding than others, which increases the likelihood of a less-than-perfect result. Furthermore, the proximity of other neural structures to the nerve, ganglion, or plexus being blocked may lead to the inadvertent and often unrecognized block of adjacent nerves, invalidating the results that the clinician sees, e.g., the proximity of the lower cervical nerve roots, phrenic nerve, and brachial plexus to the stellate ganglion. It should also be remembered that the possibility of undetected anatomical abnormality always exists, which may further confuse the results of the diagnostic nerve block, e.g., conjoined nerve roots, the Martin Gruber anastomosis (a median to ulnar nerve connection), etc.

Since each pain experience is unique to the individual patient and the clinician really has no way to quantify it, special care must be taken to be sure that everybody is on the same page regarding what pain the diagnostic block is intended to diagnose. Many patients have more than one type of pain. A patient may have both radicular pain and the pain of diabetic neuropathy. A given diagnostic block may relieve one source of the patient's pain while leaving the other untouched.

Furthermore, if the patient is having incident pain, e.g., pain when walking or sitting, the performance of a diagnostic block in a setting other than one that will provoke the incident pain is of little or no value. This often means that the clinician must tailor the type of nerve block that he or she is to perform to allow the patient to be able to safely perform the activity that incites the pain. Finally, a diagnostic nerve block should never be performed if the patient is not having, or is unable to provoke the pain that the pain management specialist is trying to diagnosis as there will be nothing to quantify.

The accuracy of diagnostic nerve block can be enhanced by assessing the duration of nerve relief relative to the expected pharmacological duration of the agent being used to block the pain. If there is discordance between the duration of pain relief relative to duration of the local anesthetic or opioid being used, extreme caution should be exercised before relying solely on the results of that diagnostic nerve block. Such discordance can be due to technical shortcomings in the performance of the block, anatomical variations, and most commonly, behavioral components of the patient's pain.

Finally, it must be remembered that the pain and anxiety caused by the diagnostic nerve block itself may confuse the results of an otherwise technically perfect block. The clinician should be alert to the fact that many pain patients may premedicate themselves with alcohol or opioids because of the fear of procedural pain. This situation also has the potential to confuse the observed results. Obviously, the use of sedation or anxiolysis prior to the performance of diagnostic nerve block will further cloud the very issues the nerve block is in fact supposed to clarify.

What are important and useful specific diagnostic nerve blocks?

Early proponents of regional anesthesia such as Labat and Pitkin [3] believed it was possible to block just about any nerve in the body. Despite the many technical limitations these pioneers were faced with, these clinicians persevered. They did so, not only because they believed in the clinical utility and safety of regional nerve block, but because the available alternatives to render a patient insensible to surgical pain at their time were much less attractive. The introduction of the muscle relaxant curare in 1942 by Dr. Harold Griffith changed this construct [2], and in a relatively short time, regional anesthesia was relegated to the history of medicine, with its remaining proponents viewed as eccentric at best. Just as the Egyptian embalming techniques were lost to modern man, many regional anesthesia techniques that were in common use were lost to today's pain management specialists.

What we have left are those procedures which have stood the test of time for surgical anesthesia. For the most part, these were the nerve blocks that were not overly demanding from a technical viewpoint and were reasonably safe to perform. Many of these techniques also have clinical utility as diagnostic nerve blocks. These techniques are summarized in Table 2. The more commonly used diagnostic nerve blocks are discussed below.

Table 2
Common diagnostic nerve blocks

Neuroaxial blocks: epidural, subarachnoid
Peripheral nerve blocks: greater and lesser occipital, trigeminal, brachial plexus, median, radial and ulnar, intercostal, selective nerve root, sciatic
Intra-articular nerve blocks: facet
Sympathetic nerve blocks: stellate ganglion, celiac plexus, lumbar, hypogastric plexus and ganglion impar

Neuroaxial diagnostic nerve blocks

Differential spinal and epidural blocks have gained a modicum of popularity as an aid in the diagnosis of pain. Popularized by Winnie [9], differential spinal and epidural blocks have as their basis the varying sensitivity of sympathetic and somatic sensory and motor fibers to blockade by local anesthetics. While sound in principle, these techniques are subject to some serious technical difficulties that limit the reliability of the information obtained. They include:

1) The inability to precisely measure the extent that each type of nerve fiber is blocked;

2) The possibility that more than one nerve fiber type is simultaneously, blocked leading the clinician to attribute the patient's pain to the wrong neuroanatomical structure;

3) The impossibility of "blinding" the patient to the sensation of warmth associated with sympathetic blockade as well as the numbness and weakness that accompany blockade of the somatic sensory and motor fibers;

4) The fact that in clinical practice, the construct of temporal linearity, which holds that the more "sensitive" sympathetic fibers will become blocked first, followed by the less sensitive somatic sensory fibers and lastly by the more resistant motor fibers, breaks down. As a practical matter, it is not uncommon for the patient to experience some sensory block prior to noticing the warmth associated with block of the sympathetic fibers, rendering the test results suspect;

5) The fact that even in the presence of a neuroaxial block dense enough to allow a major surgical procedure, afferent nociceptive input can still be demonstrated in the brain;

6) The fact that the neurophysiological changes associated with pain may increase or decrease the nerves' firing threshold, suggesting that even in the present of sub-blocking concentrations, there is the possibility that the sensitized afferent nerves will stop firing;

7) The fact that modulation of pain transmission at the spinal cord, brainstem, and higher levels is known to exist and may alter the results of even the most carefully performed differential neural blockade; and

8) The fact that there are significant behavioral components to a patient's pain, which may influence the subjective response the patient reports to the clinician performing differential neuroaxial blockade.

In spite of these shortcomings, neuroaxial differential block remains a clinically useful tool to aid in

the diagnosis of unexplained pain. Furthermore, there are some things that the clinician can do to increase the sensitivity of this technique, which include:

1) Using the reverse differential spinal or epidural block, in which the patient is given a high concentration of local anesthetic, which results in a dense motor, sensory, and sympathetic block, and the observation of the patient as the block regresses;

2) Using opioids instead of local anesthetics, which removes the sensory clues that may influence patient responses;

3) Repeating the block on more than one occasion using local anesthetics or opioids of varying durations, e.g., lidocaine versus bupivacaine or morphine versus fentanyl, and comparing the results for consistency.

Whether or not this technique stands the test of time, Winnie's admonition to clinicians that sympathetically mediated pain is often underdiagnosed most certainly will.

Greater and lesser occipital nerve block

The greater occipital nerve arises from fibers of the dorsal primary ramus of the second cervical nerve and to a lesser extent from fibers of the third cervical nerve [4]. The greater occipital nerve pierces the fascia just below the superior nuchal ridge along with the occipital artery. It supplies the medial portion of the posterior scalp as far anterior as the vertex. The lesser occipital nerve arises from the ventral primary rami of the second and third cervical nerves. The lesser occipital nerve passes superiorly along the posterior border of the sternocleidomastoid muscle, dividing into cutaneous branches that innervate the lateral portion of the posterior scalp and the cranial surface of the pinna of the ear.

Selective blockade of greater and lesser occipital nerves can provide the pain management specialist with useful information when trying to determine the cause of cervicogenic headache. By blocking the atlantoaxial, atlanto-occipital, cervical epidural, cervical facet, and greater and lesser occipital nerve blocks on successive visits, the pain management specialist may be able to differentiate the nerves subserving the patient's headache.

Stellate ganglion block

The stellate ganglion is located on the anterior surface of the longus colli muscle. This muscle lies just anterior to the transverse processes of the seventh cervical and first thoracic vertebrae [5]. The stellate ganglion is made up of the fused portion of the seventh cervical and first thoracic sympathetic ganglia. The stellate ganglion lies anteromedial to the vertebral artery and is medial to the common carotid artery and jugular vein. The stellate ganglion is lateral to the trachea and esophagus. The proximity of the exiting cervical nerve roots and brachial plexus to the stellate ganglion makes it easy to inadvertently block these structures when performing stellate ganglion block, making interpretation of the results of the block difficult.

Selective blockade of stellate ganglion can provide the pain management specialist with useful information when trying to determine the cause of upper extremity or facial pain without clear diagnosis. By blocking the brachial plexus(preferably by the axillary approach) and stellate ganglion on successive visits, the pain management specialist may be able to differentiate the nerves subserving the patient's upper extremity pain. Selective differential blockade of the stellate ganglion, trigeminal nerve, and sphenopalatine ganglion on successive visits may elucidate the nerves subserving often difficult-to-diagnose facial pain.

Cervical facet block

The cervical facet joints are formed by the articulations of the superior and inferior articular facets of adjacent vertebrae [6]. Except for the atlanto-occipital and atlantoaxial joints, the remaining cervical facet joints are true joints in that they are lined with synovium and possess a true joint capsule. This capsule is richly innervated and supports the notion of the facet joint as a pain generator. The cervical facet joint is susceptible to arthritic changes and trauma caused by acceleration-deceleration injuries. Such damage to the joint results in pain secondary to synovial joint inflammation and adhesions.

Each facet joint receives innervation from two spinal levels. Each joint receives fibers from the dorsal ramus at the same level as the vertebra as well as fibers from the dorsal ramus of the vertebra above. This fact has clinical importance in that it provides an explanation for the ill-defined nature of facet-mediated pain and explains why the branch of the dorsal ramus arising above the offending level must often also be blocked to provide complete pain relief. At each level, the dorsal ramus provides a medial branch that wraps around the convexity of the articular pillar of its respective vertebra and provides innervation to the facet joint. Selective blockade of cervical facet joints can provide the pain management specialist with useful information when

trying to determine the cause of cervicogenic headache and/or neck pain. By blocking the atlantoaxial, atlantooccipital, cervical epidural, and greater and lesser occipital nerve blocks on successive visits, the pain management specialist may be able to differentiate the nerves subserving the patient's headache and/or neck pain.

Intercostal nerve block

The intercostal nerves arise from the anterior division of the thoracic paravertebral nerve [7]. A typical intercostal nerve has four major branches. The first branch is the unmyelinated postganglionic fibers of the gray rami communicantes, which interface with the sympathetic chain. The second branch is the posterior cutaneous branch, which innervates the muscles and skin of the paraspinal area. The third branch is the lateral cutaneous division, which arises in the anterior axillary line. The lateral cutaneous division provides the majority of the cutaneous innervation of the chest and abdominal wall. The fourth branch is the anterior cutaneous branch supplying innervation to the midline of the chest and abdominal wall. Occasionally, the terminal branches of a given intercostal nerve may actually cross the midline to provide sensory innervation to the contralateral chest and abdominal wall. This fact has specific import when utilizing intercostal block as part of a diagnostic workup for the patient with chest wall and/or abdominal pain. The 12th nerve is called the subcostal nerve and is unique in that it gives off a branch to the first lumbar nerve, thus contributing to the lumbar plexus.

Selective blockade of intercostal and/or subcostal nerves thought to be subserving a patient's pain can provide the pain management specialist with useful information when trying to determine the cause of chest wall and/or abdominal pain. By blocking the intercostal nerves and celiac plexus on successive visits, the pain management specialist may be able to differentiate which nerves are subserving the patient's chest wall and/or abdominal pain.

Celiac plexus block

The sympathetic innervation of the abdominal viscera originates in the anterolateral horn of the spinal cord [8]. Preganglionic fibers from T5–T12 exit the spinal cord in conjunction with the ventral roots to join the white communicating rami on their way to the sympathetic chain. Rather than synapsing with the sympathetic chain, these preganglionic fibers pass through it to ultimately synapse on the celiac ganglia. The greater, lesser, and least splanchnic nerves provide the major preganglionic contribution to the celiac plexus. The greater splanchnic nerve has its origin from the T5–T10 spinal roots. The nerve travels along the thoracic paravertebral border through the crus of the diaphragm into the abdominal cavity, ending on the celiac ganglion of its respective side. The lesser splanchnic nerve arises from the T10–T11 roots and passes with the greater nerve to end at the celiac ganglion. The least splanchnic nerve arises from the T11–T12 spinal roots and passes through the diaphragm to the celiac ganglion.

Interpatient anatomical variability of the celiac ganglia is significant, but the following generalizations can be drawn from anatomical studies of the celiac ganglia. The ganglia vary in number from one to five and range in diameter from 0.5 to 4.5 cm. The ganglia lie anterior and anterolateral to the aorta. The ganglia located on the left are uniformly more inferior than their right-sided counterparts by as much as a vertebral level, but both groups of ganglia lie below the level of the celiac artery. The ganglia usually lie approximately at the level of the first lumbar vertebra.

Postganglionic fibers radiate from the celiac ganglia to follow the course of the blood vessels to innervate the abdominal viscera. These organs include much of the distal esophagus, stomach, duodenum, small intestine, ascending and proximal transverse colon, adrenal glands, pancreas, spleen, liver, and biliary system. It is these postganglionic fibers, the fibers arising from the preganglionic splanchnic nerves, and the celiac ganglion that make up the celiac plexus. The diaphragm separates the thorax from the abdominal cavity while still permitting the passage of the thoracoabdominal structures, including the aorta, vena cava, and splanchnic nerves. The diaphragmatic crura are bilateral structures that arise from the anterolateral surfaces of the upper two or three lumbar vertebrae and disks. The crura of the diaphragm serve as a barrier to effectively separate the splanchnic nerves from the celiac ganglia and plexus below.

The celiac plexus is anterior to the crus of the diaphragm. The plexus extends in front of and around the aorta, with the greatest concentration of fibers anterior to the aorta. With the single-needle transaortic approach to celiac plexus block, the needle is placed close to this concentration of plexus fibers. The relationship of the celiac plexus to the surrounding structures is as

follows: The aorta lies anterior and slightly to the left of the anterior margin of the vertebral body. The inferior vena cava lies to the right, with the kidneys posterolateral to the great vessels. The pancreas lies anterior to the celiac plexus. All of these structures lie within the retroperitoneal space. Selective blockade of the celiac plexus can provide the pain management specialist with useful information when trying to determine the cause of chest wall, flank, and/or abdominal pain. By blocking the intercostal nerves and celiac plexus on successive visits, the pain management specialist may be able to differentiate which nerves are subserving the patient's pain.

Selective nerve root block

Improvements in fluoroscopy and needle technology have led to increased interest in selective nerve root block in the diagnosis of cervical and lumbar radicular pain. Although selective nerve block is technically demanding and requires resources that may not be available in many settings, the technique may help identify the reason behind the patient's pain complaint. The use of selective nerve root block as a diagnostic or prognostic maneuver must be approached with caution because, due to the proximity of the epidural, subdural, and subarachnoid spaces, it is very easy to inadvertently place local anesthetic into these spaces when intending to block a single cervical or lumbar nerve root. This error is not always readily apparent on fluoroscopy, given the small amounts of local anesthetic and contrast medium used.

Pearls

- The use of nerve blocks as part of the evaluation of the patient in pain represents a reasonable next step if a careful targeted history and physical examination and available radiographic, neurophysiological, and laboratory testing fail to provide a clear diagnosis.
- The overreliance on a prognostic nerve block as the sole justification to perform an invasive or neurodestructive procedure can lead to significant patient morbidity and dissatisfaction.
- Do analyze the information obtained from diagnostic nerve blocks in the context of the patient's history, physical, laboratory, neurophysiological, and radiographic testing.
- Don't over-rely on information obtained from diagnostic nerve blocks.
- Do view discordant or contradictory information obtained from diagnostic nerve blocks with skepticism.
- Don't rely on information obtained from diagnostic nerve block as the sole justification to proceed with invasive treatments.
- Do consider the possibility of technical limitations that reduce the ability to perform an accurate diagnostic nerve block.
- Do consider the possibility of patient anatomical variations that may influence the results of diagnotic nerve blocks.
- Do consider the presence of incidence pain when analyzing the results of diagnostic nerve blocks.
- Don't perform diagnostic nerve blocks in patients who are not currently having the pain you are trying to diagnose.
- Do consider behavioral factors that may influence the results of diagnostic nerve blocks.
- Do consider that patients may premedicate themselves prior to diagnostic nerve blocks.

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Chapter 39
Post-Dural Puncture Headache

Winfried Meissner

Case report

Mr. Lehmann, an expatriate, works for Bilfinger & Berger, a large construction company in Nigeria. For a knee arthroscopy, he received an uneventful spinal anesthesia in the company's hospital. He recovered quickly, so he decided to travel to a business meeting the next afternoon, although a light headache occurred at noon. On the way to Kano the headache increased in intensity, and only a reclining position gave Mr. Lehmann any relief.

When Mr. Lehmann arrived in Kano, the headache was so intense that he felt very unwell. He vomited once and was unable to walk. His driver could not contact the doctor at Bilfinger & Berger, so they decided to go to the nearest local hospital. Lehmann was seen by the on-call physician, Dr. Adewale; however, as Lehmann did not know about the possible association between spinal anesthesia and headache, he did not mention it. On the other hand, Dr. Adewale only examined Lehman's head and neck—so he missed the wound dressing (and because Lehmann could not walk due to his headache, Dr. Adewale could not notice his limping).

The following features were documented: Slightly increased body temperature, increase of headache when bending the neck (imitating meningism), otherwise normal neurological status.

Dr. Adewale's differential diagnoses were intracranial hematoma, meningitis, or cerebral malaria.

However, there was no CT available in this hospital. Mr. Lehmann asked for referral back to Abuja, where he was based, but Dr. Adewale recommended referral to the nearest teaching hospital for a CT scan. However, there was no ambulance immediately available, so the patient was kept under observation and clinically monitored. Finally, while admitting the patient to the ward, the head nurse Betty Hazika noticed the dressing on his knee and realized the complete medical history. When she informed Dr. Adewale about her finding, he successfully contacted the anesthesiologist in Abuja, who confirmed that he "might have nicked the dura a touch." They diagnosed a post-dural puncture headache (PDPH) and decided to monitor the patient for 2 days. As per guidelines in the hospital, Mr. Lehmann was given paracetamol, lots of fluid (which was very annoying to the patient because the headache severely restricted walking to the toilet), and Betty added some herbal medicines of her own (the latter not in the hospital guidelines).

By evening next day, the headache decreased, and Mr. Lehmann recovered well. As he was very pleased by the care of the nurse, he associated her herbal treatment with his recovery, and he recommended it to all his colleagues as a treatment for hangover!

Risk factors and diagnosis

What causes a PDPH, and what are its characteristics?

If you perform neuraxial regional anesthesia you will intentionally (e.g., with spinal anesthesia) or may unintentionally (e.g., with epidural anesthesia) cause perforation of the dura mater with your needle. Normally the breach seals by itself in a few hours or days. In some cases, however, it does not close, and cerebrospinal fluid (CSF) continues to leak. If the fluid loss exceeds its production (approximately 0.35 mL/min), intrathecal CSF volume decreases, giving rise to an intracranial hypotension that manifests as a bad headache known as postdural puncture headache (PDPH). Typically, it is postural—the headache increases when the patient is in an upright position and decreases or disappears if he or she reclines or lies down.

In most cases, PDPH develops within 24–48 hours of dural puncture, but it may be delayed by a few days, so often these patients present to somebody other than the anesthetist. It is very important that the incidence of an inadvertent dural puncture (especially while performing an epidural) is documented and the patient warned about the strong possibility of developing a postural headache.

Do any risk factors increase the likelihood of PDPH?

The incidence is higher in young patients, during pregnancy, or with complicated or repeated punctures, and it also depends on the diameter and type of needles (see below). Incidence is decreased if the puncture is performed in a lateral instead of sitting position, and if saline is used instead of air for the loss-of-resistance technique during the epidural. The experience of the anesthetist has also been shown to influence the incidence of PDPH.

What are differential diagnoses of PDPH?

Although the clinical symptoms, together with the history of neuraxial puncture, usually allow a straightforward diagnosis, there are important differential diagnoses such tension headache and migraine, and in the case of postpartum women, eclampsia has to be kept in mind. Other possible, but rare, life-threatening differential diagnoses are intracranial venous thrombosis, meningitis, and subdural hematoma. Symptoms such as focal neurological deficits, headache independent of upright position, neck stiffness, fever, blurred vision, somnolence, photophobia, confusion, or vomiting should always trigger further diagnosis.

Do type and size of needle influence the incidence of PDPH?

Two characteristics of the needle used for neuraxial puncture are known to influence the incidence of postdural puncture headache. One is the diameter of the needle (larger needles produce larger and longer-lasting dural holes, which result in an increased loss of CSF and a higher incidence of headache). The other is the shape of the needle. Pencil-point, Whitacre, and Sprotte needles, and ballpoint needles are associated with a lesser incidence than Quincke needles. After use of a 22-G Quincke needle, the occurrence of headache has been reported to be up to 30%. In contrast, small nontraumatic needles are associated with a PDPH risk of less than 3%. The incidence of postdural puncture headache after dural perforation is said to range from 5% (thin pencil point needles) up to 70% (large Quincke needles).

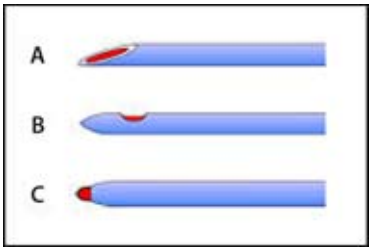

Fig. 1. (A) Quincke needle, (B) pencil-point needle, (C) ballpoint needle.

Natural course and management

What is the natural course of PDPH?

In most cases, PDPH is self-terminating. Normally, patients recover spontaneously after 4–6 days. However, some cases might last longer, with severe symptoms.

How do you manage a case of PDPH?

As PDPH is usually self-terminating, and in most cases a reclining position, oral rehydration, and plenty of patience constitute the best therapy. Overall, clinical guidelines do not offer much, since a number of different approaches to treat PDPH have been suggested and are used in different institutions, but only very few of them may be considered evidence-based.

Bed rest is the most frequent recommendation; however, duration of headache does not seem

to be decreased by bed rest, which could be considered purely a symptomatic treatment. Treatment with nonopioid analgesics such as paracetamol (acetaminophen) or other drugs such as caffeine, sumatriptan, or flunarizine is poorly supported by scientific evidence. The same is true for fluid "therapy." A recent study supported the use intravenous theophylline (200 mg theophylline in 100 mL 5% dextrose over 40 minutes).

The only treatment that has proved to be at least partly effective is the epidural injection of blood known as an "epidural blood patch" (EBP). The best results from studies indicate that with the correct indication, a blood patch might terminate PDPH in one out of five patients. After repeated blood patching, this number might increase to more than a 90% success rate. It is used if symptomatic treatment fails, the intensity of pain is high, and the patient is severely incapacitated. This method is especially relevant in postpartum females if they are unable to breastfeed or bond with their babies. However, there is no consent on the optimal time of neither an EBP nor the amount of blood that should be used. As EBP may cause even more complications (see below) and as a PDPH is unpleasant but very often self-limiting and rarely life-threatening, the indication to perform an EBP should be made with precaution and performed by experienced, senior staff.

How do you perform an epidural blood patch?

Basically, an EBP is performed in the same way as an epidural anesthesia. Instead of injecting a local anesthetic drug, 10–20 mL of the patient's blood, immediately drawn, is used. You need two persons for the procedure itself and, if available, a third person assisting. One person performs the epidural, often one segment below or above the former insertion site. The second person draws the blood immediately after the first person has identified the epidural space under absolute aseptic conditions (surgical skin disinfection, sterile gloves, gown, mask) from an easily accessible vein and passes the syringe with the blood to the first person for epidural injection.

Possible complications include all problems associated with an epidural, such as infection, hematoma, and nerve damage, and, of course, another perforation of the dura and a subsequent CSF leak. Therefore, and because the fact that PDPH has occurred might indicate difficult puncture conditions, blood patching should be performed only by experienced clinicians!

When should you perform an epidural blood patch?

As postdural puncture headache is self-limiting in most cases, and as EBP is not without risks (see above), it is recommended only if headache is very incapacitating and it interferes with the patient's recovery or as in the case of postpartum females, it prevents them from breastfeeding or bonding with their child. Being poorly mobile or bedridden also increases the incidence of a deep vein thrombosis and fatal pulmonary emboli.

Are there any dangerous complications of PDPH if unrelieved by an epidural blood patch?

A rare complication of an untreated PDPH is a subdural hematoma due to traction on cerebral veins. An infrequent, indirect complication is a deep vein thrombosis due to bed rest, as mentioned above.

Pearls of wisdom

- Diagnostic criteria: postural headache shortly after neuraxial puncture (spinal or accidental dural puncture during an epidural).
- Differential diagnoses: any other forms of headache (tension headache, migraine), intracranial hematoma and venous thrombosis, meningitis, and in case of postpartum females, eclampsia. Always check for focal neurological deficits, headache independent of upright position, neck stiffness, fever, blurred vision, confusion, vomiting, and photophobia.
- With a history of neuraxial puncture with typical symptoms, no further laboratory work or radiology examination is necessary.
- Treatment: reclining or supine position, oral fluids (but not too much); consider EBP only if the headache severely interferes with the patient's daily life and an experienced team is available. Balance the risks of EBP and the normal spontaneous relief of postdural puncture headache within 3 to 7 days.
- PDPH persisting for more than 1 week should be an indication for EBP.

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Chapter 40
Cytoreductive Radiation Therapy

Lutz Moser

What is the current status of radiotherapy services in low- and middle-income countries?

External-beam radiotherapy can be delivered by linear accelerators or cobalt teletherapy units. Cobalt units are more robust and less prone to external influences like unstable electricity supply. Even though radiotherapy is one of the most cost-effective forms of cancer treatment, there is an undersupply of radiotherapy facilities especially in Africa and Asia. This problem is due to the high initial capital investment in equipment and specially designed buildings and in technical maintenance, equipment replacement, and permanent access to engineering support. Therefore, radiotherapy facilities are restricted to metropolitan centers such as the capital cities of these countries.

Many countries in Africa do not have radiotherapy facilities at all. The availability of radiotherapy services differs in the other countries from 1 machine per 126,000 people (Egypt) to 1 machine per 70 million people (Ethiopia). West Africa has the poorest supply of radiotherapy equipment, with 1 unit per 24 million people. In Asia the distribution ranges from no facility in some states, to 1 machine per 11 million people (Bangladesh), to 1 machine per 807,000 people (Malaysia).

What is the significance of radiotherapy in pain?

The efficacy of radiotherapy applies mostly to cancer-related pain. Palliative care improves the quality of life of patients by providing pain and symptom relief from diagnosis to the end of life (according to the World Health Organization). The principal aim is to alleviate the patient's symptoms.

Pain control in patients with cancer represents a significant aspect of radiation therapy practice worldwide. Radiation therapy is one of the most effective, and often the only, therapeutic option to relieve pain caused by nerve compression or infiltration by malignant tumor or pain from liver and bone metastases, and it provides successful palliation of dysphagia caused by esophageal carcinoma and of pain due to pancreatic cancer.

What is the efficacy of radiotherapy in pain due to bone metastasis?

In about 50–80% of patients, symptoms from bone metastases manifest as skeletal or neuropathic pain, pathological fractures, hypercalcemia, nerve root damage, and spinal cord compression. The most common symptom of skeletal metastases is pain, present in the majority of patients with metastatic bone lesions. Typically, the pain is slowly progressive over days to weeks and

requires frequently increasing doses of analgesics. Skeletal pain is thought to be induced by a combination of mechanical and biochemical factors that result in activation of pain receptors in local nerves. Increased blood flow to the metastatic lesions promotes an inflammatory response, with release of cytokines by both the tumor cells and the surrounding tissue. Radiotherapy is an effective tool used to control pain due to bone metastasis. Although a complete response will be achieved in only 30% of cases, a partial response results in a sufficient reduction of additional pain medication. Further goals of treatment are preservation of mobility and function, maintenance of skeletal integrity, and preservation of quality of life.

The global response to radiotherapy of bone metastasis in reducing pain is about 80%. About 3 out of 10 people (30%) will have no pain within a month of radiotherapy treatment. For at least another 4 out of 10 (40%) people, the treatment reduces the pain by half. The patient's subjective experience confirms the effectiveness of radiotherapy in reducing pain caused by bone metastases and in improving quality of life. About 6 to 12 weeks after treatment, the bone repairs itself and becomes stronger.

Local palliative efficiency can be expressed as the time to pain progression, the rate of pathological fractures, and the requirement of local retreatment. Depending on the reported time periods for evaluation and how the results were assessed, the documented duration of pain relief is more than 6 months in at least 50% of patients, and the first increase in pain score can be expected after 1 year in 40% of patients.

The reported incidence of pathological fractures following palliative radiotherapy of bone metastases is low, varying between 1% and 10%. Recalcification of osteolytic bone metastases after 6 months, defined as a rise of density in the region of interest of more than 20%, was found in 25–58% of patients.

Studies show that hemibody or wide-field irradiation gives nearly all patients some pain relief. It can relieve pain completely in up to half of the people treated and can help to stop new painful areas developing.

What fractionation schedules are applied for pain control?

Conflicting opinions on low-dose, short-course radiotherapy versus prolonged or higher-dose schedules led to many scientific publications and randomized trials to find the answers. The clinical trials included patients with painful bone metastases of any primary sites, mainly in the prostate, breast, and lung. The radiation doses of the most common schedules are single fractionation treatments with 8 Gy, shorter duration treatments with four times 5 Gy or five times 4 Gy, or more protracted regimens such as 10 times 3 Gy or 20 times 2 Gy. Fractions with single doses of 4 Gy and 5 Gy are applied three to four times a week, 3 and 2 Gy fractions most often five times a week, up to the total doses of 30 Gy and 40 Gy. The maximum relief of pain may be expected after 1 month.

The degree and duration of pain relief do not depend on the fractionation schedules applied. No significant differences in terms of pain relief and analgesic use were found with single fractions, shorter duration treatments, or more protracted regimens. However, the retreatment rate and pathological fracture rates are higher after single-fraction radiotherapy because a relevant recalcification of osteolytic bone metastases following irradiation is related to more protracted schedules.

Is re-irradiation possible?

A second course of palliative radiotherapy of the affected bone is possible and helpful if the first course does not work well or if the pain is initially relieved, but increases again some weeks or months later. The decision for retreatment has to take into account any sensitive structures in the irradiated volume, for example the spinal cord or kidneys. The indication has to be confirmed by a radio-oncologist.

What are the side effects for external palliative radiotherapy?

Palliative radiotherapy has few side effects. Acute toxicity is mild, rarely requiring further supportive care. Irrespective of the fractionation schedule chosen, the incidence of grade 2 or greater acute and late toxicity is low, with a rate of approximately 10–15% (acute) and 4% (late), respectively. Pronounced tiredness and listless are the most common general side effects, but recovery occurs within a few weeks after treatment. Most specific side effects of external palliative radiotherapy depend on the location of treatment. While radiotherapy of the bones of the extremities might affect the skin locally with a light reversible erythema, a predominance of gastrointestinal adverse effects such as emesis and diarrhea

may be noted if the bowels or the stomach are involved. Supportive treatment with antiemetics or antidiarrheal agents might be indicated symptomatically. The side effects tend to come on gradually through the treatment course and may last for a week or two after the treatment has finished.

What about radiotherapy for locally advanced tumors and metastases in soft tissues and organs?

As in the case of pain due to bone metastases, radiotherapy is effective in tumor-related pain due to visceral recurrences and metastases. Besides all direct tumor-associated pain from locally extended and nerve-infiltrating situations, indications include pelvic pain due to recurrent non-operable rectal cancer or cancer of the cervix. In this palliative situations, marked pain relief may be achieved with only minor shrinkage of the pelvic mass. In patients with pelvic pain, 70% had relief after irradiation.

The prescribed dose of palliative radiotherapy has to be adjusted to the individual situation and the organs at risk. Schedules mostly used are single-dose treatments of 8 Gy, or hypofractionated regimens with total doses from 20 to 30 Gy.

For pelvic masses, equal responses are obtained from 30 Gy in 10 fractions and from 20 Gy in five fractions, given at four fractions per week. Opposed portals are used most often; multiple portals should be considered if the anteroposterior diameter is greater than 22 cm and photons of higher energy (10 MV) are unavailable.

Pearls of wisdom

- Painful complications of cancer, such as bone pain, should be amenable to radiotherapy, if the pain is anatomically localized and not diffuse, so that a target for radiotherapy can be defined (e.g., single painful osteolytic metastasis following breast cancer) and if the life expectancy due to the whole tumor situation could be some months or longer.
- Tumor-related pain combined with a short life expectancy should be treated with analgesics only. The time and effort in terms of travel and accommodation for the radiotherapy treatment, the costs, the technical complexity of the radiotherapy must be balanced against the benefit (e.g., osteoblastic metastases of a prostate carcinoma or presacral recurrent rectal carcinoma).
- Radiotherapy has been a mainstay in the palliation of symptomatic metastatic prostate cancer and is most often used for palliation of painful metastatic bone lesions, resulting in a relief of pain in about 80–90% of patients and therefore reduced dependence on analgesics.
- Palliative radiotherapy of bone metastases is very effective and should be applied with a single dose of 8 Gy in most patients as multifraction regimens do not offer relevant better pain relief. More protracted schedules should be used in palliative situations with a life expectancy of more than 6 months as the rates of retreatment and pathological fractures are reduced.

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Guide to Pain Management in Low-Resource Settings

Chapter 41
The Role of Acupuncture in Pain Management

Natalia Samoilova and Andreas Kopf

Case report

Mansur, aged 37, with acute back pain radiating to the left leg, has come to you for medical advice. He has an acute radicular pain syndrome, without evidence of any major neurological deficit (bladder/ bowel incontinence, loss of sensitivity, or muscle paralysis). You explain to Mansur that currently there is no indication for surgery as long as sensation and muscle function are not impaired. A conservative treatment is planned. Because of the etiology of the pain, epidural steroids and systemic anticonvulsants would be the first therapeutic option, but there is no anesthesiologist trained in epidurals, and anticonvulsants are not available. Simple analgesics like diclofenac and tramadol are tried, initially, but they do not relieve the pain, and Mansur comes back complaining about inability to walk and sit for longer periods of time. You decide to try acupuncture. Certain acupuncture points have to be chosen according to the symptoms and the underlying disease:

First, acupuncture points at the site of pain are treated: B40 and B60, then Du-mai 26.

After that painful points are chosen: B2, B24, B52, B54, B36, GB30, and GB34. The needles are left in place for 10–20 minutes every day for a week, then every other day for 2 weeks. Luckily, over the 3 weeks of treatment, the symptoms decline, allowing Mansur almost complete range of motion and mobility.

Basic concepts

Why has acupuncture become so popular for pain management?

Acupuncture, as an alternative treatment for pain management, is becoming popular. The main reason is growing evidence on the effectiveness of acupuncture, even though studies on efficacy (e.g., specificity of standard acupuncture points compared to needling sham points) have shown contradictory results. A low rate of adverse events and a high degree of patient satisfaction are other main arguments for the growing use of acupuncture in Western countries. Another reason could be that the framework of traditional Chinese medicine (TCM) regards the human body as "whole," rather than a complex of individual symptoms. There is a strong tendency toward the biopsychosocial model of pain management, an idea that has become an integral part of modern pain management. Another reason is that in small remote hospitals with a limited supply of drugs, acupuncture sometimes remains one of the few possible methods of treatment to provide pain relief. Also, acupuncture maybe a reasonable alternative in patients with contraindications to various drugs or who are intolerant of side effects, or in situations where drugs are not affordable. When used in a rational way and as part of a comprehensive pain management program, acupuncture can be effective, especially if the patient is receptive toward it. Another advantage

is that acupuncture can be simply applied without technical support or devices. The only preconditions are the presence of a skilled acupuncturist and a supply of sterile acupuncture needles.

What are we trying to manage: pain or disease?

As globalization accelerates, different cultures and philosophies of medicine have started to spread worldwide. It is very tempting to adapt to a new idea quickly, and TCM (including acupuncture)—because of its holistic approach—has a very positive image. Very busy weekend acupuncture courses in Europe and the English-speaking countries show that we are only too willing to incorporate new ideas. While it always makes sense to extend one's own horizon, it has to be doubted whether the cross-cultural transfer of TCM, including acupuncture, is that easy.

To give an example, TCM uses acupuncture not as an isolated single therapy, but as part of a diagnostic and treatment concept including pulse diagnosis, physiotherapy, and dietary treatments. Pulse diagnosis is one of the original set of four diagnostic methods that are described as an essential part of TCM practice. The Chinese term indicating a blood vessel or a meridian is *Mai,* and the same term is used to describe the pulse. Pulse feeling is called *Qiemai,* which is part of the general diagnostic method of palpating or feeling the body. Pulse diagnosis was mentioned in ancient Chinese medical textbooks. A pulse too strong or too weak denotes illness. The aim of pulse diagnosis, like the other methods of diagnosis, has always been to obtain useful information about what goes on inside the body, what has caused disease, what might be done to rectify the problem, and what the chances are for success. "Hotness" and "coldness," or "excess" or "deficiencies," are typical categories used to make a diagnosis in this approach. The physician must feel the pulse under proper conditions—following established procedures—and must then translate the unique pulse that is felt into one or more of the categories of pulse form. The most standard iconography involves 24–28 different pulse forms! In essence, there are nine pulse takings on each wrist: one for each of the three pulse-taking fingers at each of three levels of pressure. This example gives the reader the possibility to understand on the one hand the complexity of TCM and on the other hand its fundamental differences to the Western medical approach.

It has to be remembered that TCM was developed a long time ago when there was only rudimentary knowledge about (patho)physiology. It should therefore not be regarded as detracting from the Western tradition if we promote the use of acupuncture in this chapter, possibly outside the concepts of TCM. The essence should be that TCM promotes the subjectivity of the patient and the therapist, which is an important aspect, sometimes lost in Western technical medicine, which tries to fragment the patient into symptoms. Due to the subjective approach, acupuncture remains a unique therapeutic exchange between patient and doctor. It must be noted, though, that the transfer of acupuncture into Western medicine has caused some confusion. Therefore today's practice of acupuncture does not necessarily reflect traditional acupuncture but a Western interpretation of Chinese texts, which are full of misunderstandings and misinterpretations. Putting acupuncture into an explanatory context of "counterirritation," "gate-controlling," and "endogenous pain inhibition" might on the one hand, save acupuncture from "quackery" and on the other hand may help acupuncture find its place as an accepted complimentary therapy. Since learning acupuncture might this way become much easier, it would also make it possible to spread knowledge and practice of acupuncture in low-resource countries. It will be interesting to see whether and how the new initiative, the "Pan-African Acupuncture Project" in Kenya and Uganda, will be successful integrating acupuncture into routine medical care.

What is the difference between oriental and Western concepts of medicine?

Acupuncture has been a major part of primary health care in China for the last 5,000 years. It is used extensively for a variety of medical purposes, ranging from the prevention and treatment of disease to relieving pain and even anesthetizing patients for surgery. But as in many oriental medicine practices, the emphasis of acupuncture is on prevention. In TCM, the acupuncturist was regarded very highly for enabling his patient to live a long and healthy life (and in case a patient became sick, the doctor had to treat him or her for free!).

In oriental theory, the understanding of the human body is based on the holistic understanding of the universe as described in Daoism, and the treatment of illness is based primarily on the diagnosis and differentiation of syndromes. The oriental approach treats *Zang-Fu* organs as the core of the human body. Tissue and organs are believed to be connected through a network of channels and blood vessels inside the human body.

Medical treatment starts with the analysis of the entire system, and then focuses on the correction of pathological changes through readjusting the functions of the *Zang-Fu* organs. Evaluation of a syndrome not only includes the cause, mechanism, location, and nature of the disease, but also the confrontation between the pathogenic factor and the body's resistance. Therefore, two people with an identical disease might be treated in different ways, and on the other hand, different diseases may result in the same syndrome and be treated in similar ways. This is true for some chronic diseases. Pain can be simply interpreted as a *Qi* stagnation and be treated pragmatically, with Chinese orthopedic acupuncture.

TCM also focuses on the "balance" within the patient. According to this view, an imbalance in a person's body can result from inappropriate emotional responses such as excess anger, overexcitement, self-pity, deep grief, or fear. Environmental factors such as cold, damp/humidity, wind, dryness, and heat can also cause imbalance, as do factors such as wrong diet, too much sex, overwork, and too much exercise. To restore the balance, the acupuncturist stimulates the acupuncture points that will counteract that imbalance. In this way, acupuncture is believed to rebalance the energy system and restore health or prevent the development of disease. The earliest written account of this system is found in the *Nei Jing* (The Yellow Emperor's Classic of Internal Medicine). This document is believed to be from around 200 BCE to 200 CE and is one of the oldest comprehensive medical text books.

What is the idea behind the acupuncture points?

As described, the idea of harmony and balance is very important in acupuncture. The concept that underlies balance is the opposing principles of yin and yang. The principle that each person is governed by opposing, but complementary, forces of yin and yang, is central to all Chinese thought. Yin and yang are the opposites that make the whole. They cannot exist without each other, and a situation or person could neither be 100% yin nor 100% yang. Life is possible only because of a balanced interplay between these forces.

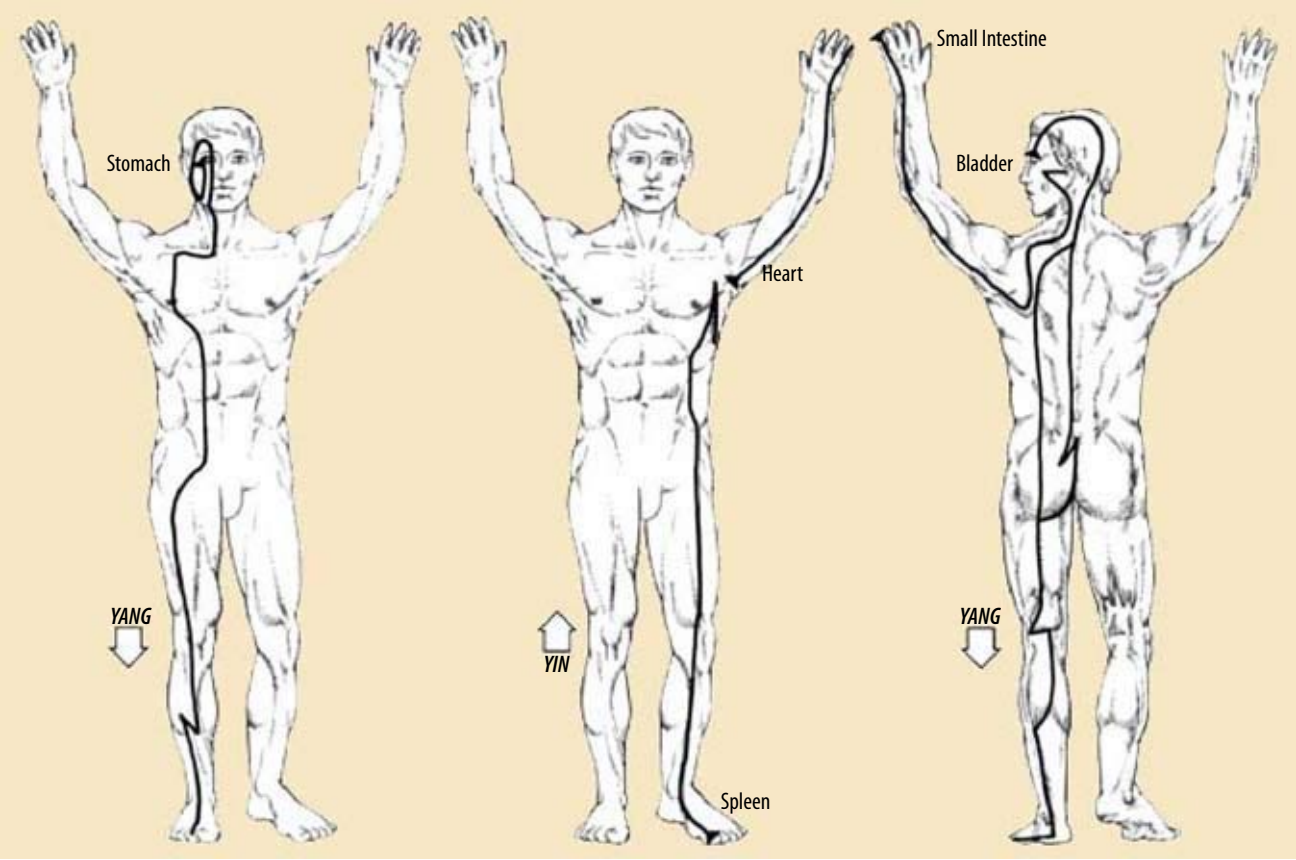
According to TCM, these complementary forces of yin and yang influence the life energy or Qi (pronounced "she"). Qi is thought to circulate throughout the body in invisible channels (other translations of the Chinese term *jing luo* include "conduit" and "meridian"). The acupuncture points (or holes, as the Chinese term *xue* is more aptly translated) are the locations where the Qi of the channels rise close to the surface of the body. Twelve main channels have been described, six of which are yin and six which are yang, and numerous minor channels, which form a network of energy channels throughout the body. Each meridian is related to, and named after, an organ or function. The main meridians are lung, kidney, gallbladder, stomach, spleen, heart, small intestine, large intestine, gallbladder, urinary bladder, san jiao ("triple warmer") and pericardium. It is believed that when Qi flows freely through these meridians, the body is balanced and healthy, but if the energy becomes blocked, stagnant, or weakened, it can result in physical, mental, or emotional ill health.

What does a meridian look like?

A meridian does not follow conventional anatomical structures, and the designation of meridians is only understandable in the context of TCM. The nomenclature follows a certain logic in this context. The localization of meridians (and acupuncture points) may differ depending on the literature resource (which is also true among practitioners in China).

How are the various acupuncture points classified?

Although locations and functions of acupuncture points may vary according to different authors, the main structure of classification is rather uniform. First of all, acupuncture points are situated along 12 "organ-related" meridians; then there are eight extraordinary meridians in acupuncture that are considered to be reservoirs supplying Qi and blood to the 12 regular channels. Dotted along these meridians are more than 400 acupuncture points, which have been also classified by the World Health Organization. These are listed by name, number, and the meridian to which they belong. Besides the classification, we find by experience that points on the same meridian may have common effects. Another type of acupuncture points are the "extra points." They have specific names and definite locations, but are not attributed to the meridians. They may be selected in certain diseases. *Ashi* points ("tender spots") are often used in patients with acute pain syndromes. Local tenderness when manually palpating the patients identifies an *Ashi* point. Therefore, these points have no specific names and definite locations. *Ashi* points are considered to represent the earliest stage of acupuncture point evolution in China and may be also considered as appropriate acupuncture points for a physiological pain approach to



(Image courtesy of John F. Thie, DC, from his book entitled *Touch for Health*)

acupuncture. But in the original (Chinese) approach to acupuncture, the points that the practitioner chooses may not necessarily be at the site of the pain.

How is this very different medical philosophy on disease incorporated into Western medical concepts?

From the frequent use of quotation marks, it should be obvious that acupuncture is not easily transferred or translated into the Western concept of medicine. It should therefore be noted that the oriental definitions and terms do not necessarily reflect a physiological view, but a concept that was developed without the knowledge of modern physiology by observing and describing. A great number of different schools for acupuncture exist, using different point localizations and point selections. Hence it is not possible to interpret acupuncture and redefine it into a pragmatic pain approach.

Recent large-scale studies in Germany have added a lot to this discussion by showing that acupuncture per se, but not the strict following of classical traditional Chinese rules for acupuncture point selection, is effective in treating pain. Therefore, it may be a pragmatic solution to adapt traditional Chinese acupuncture into a simplified acupuncture point selection for practical use. This strategy would allow the clinician to use acupuncture without becoming a specialist with extensive training in clinical practice. The authors are well aware that such an approach will be challenged by traditional acupuncturists, but scientific evidence may allow such a simplified approach to acupuncture.

How are the effects of acupuncture explained with modern (patho)physiological knowledge?

Historically, acupuncture points were believed to be "holes that allow entry" into the meridians or channels to allow alteration of "energy flows." These holes provide, in traditional Chinese acupuncture, a gateway to influence, redirect, increase, or decrease the body's vital substance, Qi, thus correcting many of the imbalances mentioned earlier. These traditional Chinese concepts may be irrelevant to understand the impact of acupuncture, since modern physiological research has been able to demonstrate that acupuncture does have a neuromodulatory effect on parts of the peripheral and central nervous system and on neurotransmitters. These effects do not seem to be acupoint-specific and are at least partly a psychophysiological phenomenon. Some

important analgesic and other effects of acupuncture include central release of endorphins, serotonin, norepinephrine, GABA, and neurokinin A, among other substances. There is some evidence of activation of the descending inhibitory system and activation of segmental and heterosegmental inhibitory systems at the spinal level (diffuse noxious inhibitory controls). Other supraspinal mechanisms involved in acupuncture analgesia have been found in the limbic system (affective processing of pain stimuli), the secondary somatosensory cortex, and the hypothalamus. Local effects of acupuncture include release of substance P and calcitonin gene-related peptide (CGRP), which increases local perfusion, and a local twitch response of the muscles followed by relaxation when trigger points are used for acupuncture. Interestingly, a high proportion of identified muscular trigger points coincide with Chinese acupoints.

Acupuncture in pain management

What is more effective in the management of chronic pain?

As always, specialists are convinced that their own method is superior, and therefore acupuncturists tend to see acupuncture as a panacea (cure-all). Nevertheless, experienced pain therapists who use acupuncture and go through a thorough training would use a more sophisticated view: creating an antagonism between these two approaches of acupuncture and conventional pain management would be counterproductive for acupuncture in the long run, since its effects are considerable but not overwhelming. Therefore, pain specialists are trying to incorporate acupuncture as a complementary technique into regular pain management as one module together with manual therapy, therapeutic exercises, and psycho- and pharmacotherapy within a therapeutic, rehabilitative, and preventive management complex.

What do we use for diagnosing and evaluating pain if we want to use acupuncture?

Using acupuncture does not eliminate the need for thorough history taking, a physical examination of the patient, as well as laboratory and functional diagnostics. Before applying acupuncture, a proper diagnosis should be established, and it should be decided if acupuncture or another mode of therapy is more promising. Pain is assessed, as always, by using the visual analogue scale (VAS) for pain intensity, the duration and character of pain, and the patient's psychological/emotional status and motivation for treatment. Various tests and questionnaires for the definition of the pain may be used if appropriate, as discussed in the respective chapters.

How do we treat the acupuncture points?

Acupuncture needles are extremely thin and can often penetrate the skin with no pain at all. Some areas may be more sensitive and feel like a small pinch as the needle in inserted, but that lasts for less than a second. Once the needles are in place, there should be no pain, but only a sensation of dull pressure (known as a "De Qi feeling") reflecting activation of A-beta fibers. The acupuncturist will simultaneously feel that the needle is "tightened."

Acupuncture is an extremely safe medical procedure when performed by a qualified practitioner. Needles are presterilized, stainless steel, single-use, and disposable. Acupuncture needles are usually 0.3 mm wide (30 Gauge) and 1–2 inches long (3–6 cm). Application of the needle may be done with the patient in any position, as long as the patient feels comfortable and is relaxed, but it would be clearly advisable to use the supine position during treatment because a minority of patients might get a feeling of dizziness. The acupuncture needles are held between thumb, index finger, and middle finger, with the needle parallel to the index finger. The needle should be inserted quickly to minimize painful sensations. The angle of insertion is usually between 60 and 90 degrees. Depending on the region, the depth of insertion is usually between 0.5 and 5 cm. The needles are usually left in situ for 15–30 minutes. During this time the needles may be manipulated to achieve the effect of toning or sedating the Qi, according to the situation. Needle manipulations generally involve lifting, thrusting, twisting, and rotating, according to treatment specifications for the health problem. Thin needles are inserted into these acupoints.

What are the complications and side effects of acupuncture?

If the practitioner is adequately qualified, side effects and complications are rarely observed. Care must be taken in certain regions in the body where vulnerable structures are close to the skin, such as the lung in the thoracic area or superficial blood vessels and nerves, none of which should be needled. Hence, basic knowledge of anatomy is essential.

What about the costs of acupuncture?

Due to the increase in popularity of acupuncture, acupuncture needles are now widely available. Costs may vary, but have to be set in relation to the savings from using less or shorter-lasting pharmacotherapy. Depending on the wholesale merchant, a box of hundred needles may cost around US$5–10.

Is it possible to treat pain with acupuncture in all patients?

Theoretically, all patients may benefit from acupuncture, but studies have only been able to show—so far—evidence for selected syndromes. Acupuncture should never be used—after adequate Western medicine diagnosis—as the exclusive method of treatment, since it might prevent patients, such as cancer patients, from receiving other effective treatments.

Typical syndromes where acupuncture is effectively used are the following:

- Headache (e.g., migraine, tension-type headache
- Low back pain
- Neck pain

Other indications with less proven effectiveness include:

- Osteoarthritis
- Visceral pain syndromes
- Vascular ischemic pain
- Post-amputation pain and causalgia
- Chronic postsurgical and post-traumatic pain syndromes, e.g., post-thoracotomy-syndrome

Does acupuncture also work in acute pain, such as postoperative pain?

There is strong evidence from studies and meta-analysis that acupuncture has a role in reducing opioid-related side-effects like nausea, vomiting and sedation.

How can I perform acupuncture for pain without knowing complicated acupuncture point selection using the meridian system?

This question is difficult to answer. On one hand side, the general view of acupuncture is that it may only be used if it is part of TCM. Therefore, thorough training would be necessary to be able to understand the fundamentally different approach to illness and therapy concepts. The usual approved (basic) training courses for acupuncture involve more than 200 hours of theory and case seminars. On the other hand, recent studies, such as the GERAC studies in Germany, suggest that acupuncture might be worth using in a simplified and pragmatic way, since the true effects of acupuncture may be the result of counterirritation and modulation of central nervous sensitivity and not strictly dependent on the classical concepts of acupuncture point selection. However, this concept is not widely recognized, and existing scientific literature has not evaluated this pragmatic approach.

Since the technique of needle placement is simple and acupuncture needles are widely available and relatively inexpensive, it would be a pity if acupuncture would not be used because of the lack of adequate training facilities. Nevertheless, at least some practical and theoretical training as well as anatomical knowledge are indispensable to make acupuncture an effective and safe pain management technique.

In situations where even the minimum training is not available, it is advisable to replace the needling technique by acupressure with superficial point stimulation, such as by using small wooden sticks. A recent Cochrane review (Furlan et al. [1]) suggests the effectiveness of acupuncture point massage.

Step one:

Always start with "distant" points to activate the different antinociceptive systems, and choose from the following empirical locations for analgesia (ipsi- and contralateral sites):

- ST 36 (stomach): approx. 4 cm below the patella in a depression lateral to the patellar ligament, one finger width lateral from the anterior border of the tibia
- B 40 (urinary bladder): midpoint of the transverse crease of the popliteal fossa, between the tendons of biceps femoris and semitendinosus
- ST 44 (stomach): proximal to the web margin between the 2nd and 3rd metatarsal bones, in a depression distal and lateral to the 2nd metatarsal joint
- LI 4 (large intestine): middle of the 2nd metacarpal bone on the radial side
- PC 6 (pericardium): approx. 3 cm above the wrist crease between the tendons of palmaris longus and flexor carpi radialis (also good for nausea)
- LI 11 (large intestine): at the lateral end of the transverse cubital crease, midway between a line between the radial side of the biceps brachii tendon and the lateral epicondyle of the humerus
- K 6 (kidney): in the depression below the tip of the medial malleolus

- SP 6 (spleen/pancreas): approx. 4 cm directly above the tip of the medial malleolus on the posterior border of the tibia

In headache, use:

- ST 44 (stomach): proximal to the web margin between the 2nd and 3rd metatarsal bones, in a depression distal and lateral to the 2nd metatarsal joint
- GB 34 (gallbladder): in a depression anterior and inferior to the head of the fibula
- ST 44 (stomach): proximal to the web margin between the 2nd and 3rd metatarsal bones, in a depression distal and lateral to the 2nd metatarsal joint

Step two:

Choose 2–4 spots at the site of the pain (*Ashi* points) as acupuncture points.

Step three:

Choose 1 segmental spot corresponding with the dermatomal innervation of the painful region at the corresponding vertebral level and place the needle at the identified vertebral level some centimeters paravertebrally on the affected site.

Step four:

Choose 2–4 mirror-like spots on the contralateral site for segmental modulation.

Pearls of wisdom

- Although there is a centuries-long history of acupuncture, its efficacy has to be proven in evidence-based medicine.
- According to recent literature, there are a number of indications in pain management where acupuncture can be applied successfully.
- However, nowadays it may be more rational to use acupuncture outside the concept of traditional Chinese medicine, according to the concept of an integrative pain management approach within the biopsychosocial concept of pain.
- In particular, in pain management it seems to be a worthwhile concept to combine blockades, pharmacotherapy, and acupuncture, as well as physical and psychological therapy.

Acknowledgment

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Recommended websites

www.acupuncture.com

www.acupuncture.com.au

www.pain-education.com

http://nccam.nih.gov/health/acupuncture/

www.tcmpage.com/index.html

www.panafricanacupuncture.org (the Pan-African Acupuncture Project, Allen Magezi, Uganda coordinator)

Planning and Organizing Pain Management

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Chapter 42
Setting Up a Pain Management Program

M.R. Rajagopal

"I am interested in starting a pain service. But no one seems interested. And there are no resources. What can I do?" is a question that comes up pretty often in developing countries. The questioner is often a kind-hearted person who is interested in relieving human suffering, but feels at a loss about what the next step should be. The absence of a sense of direction often results in the enthusiast burning out and giving up the struggle at some point. This chapter is aimed at providing some useful information to any aspirant who would like to set up a pain management program without burning out.

What are major barriers to access to pain relief?

Lack of awareness is a major barrier to access to pain relief. It needs to be remembered that any change is likely to be resisted anywhere in the world. It will need sustained effort to bring in a new way of thinking. Improving overall awareness is essential for overcoming such resistance.

Professionals: Due to lack of professional education on pain and its treatment, unfortunately, medical and nursing professionals often form the biggest barriers to access to pain relief. The explosion of knowledge in pain physiology and management, at the present time, remains limited to developed countries. Medical education is oriented to diagnosis and cure, and pain relief is not taught in most medical and nursing schools. In general, the approach is disease- or syndrome-oriented and not patient- or symptom-oriented. Professionals, hence, have a poor concept of the need for pain relief and have an unnecessary fear of analgesics, particularly of opioids. Even if they overcome this fear, often they do not know the fundamentals of pain evaluation and its treatment.

Administrators: "Opiophobia" has resulted in stringent narcotic regulations, and this too comes in the way of access to pain relief. Besides, chronic pain is not a "killer disease," and so it is pushed aside in statistics and receives little attention.

The public: The public is not aware that pain relief is possible and tends to accept pain as inevitable. The public too, is generally afraid of the "addiction" potential of opioids.

Drug availability: The widely prevailing fear of opioids has resulted in complicated restrictions on licensing of opioids and on prescription practices. Unaffordability of drugs and other therapeutic measures is also a limiting factor.

Institutional policy: Pain relief services are not often seen as lucrative, and hospitals are often reluctant to invest in them.

What are essential components of service development?

The following suggested scheme of action takes the above common barriers into consideration. It is important to remember that all three sides of the following

triangle need to be addressed if a pain relief program is to succeed. Personnel with the required training, access to affordable essential drugs, and a supportive administrative system are all needed. If one side of these three components is lacking, the whole system fails, naturally.

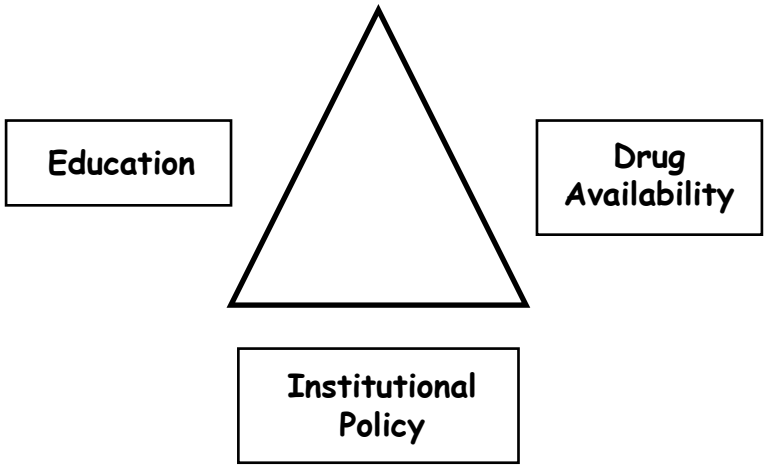
What are the challenges regarding education?

Educational needs of professionals must be considered against a background in which generations of professionals in developing countries have had no exposure to modern pain management. The average doctor in a developing country has not been trained to distinguish between nociceptive pain and neuropathic pain. The average nurse has never seen pain being measured in actual practice. This means that education of professionals must include teaching of fundamentals. It is important that such education be appropriate for the local sociocultural realities. Not uncommonly, it so happens that professionals who are trained in excellent institutions in developed countries try to start pain management facilities in their own developing countries and feel overwhelmed by the scope of problems. Part of the difficulty could be an attempt to transplant the Western system in its entirety. Regional models of pain education that have succeeded in Uganda and in India could be adapted to individual countries. The organization or the individual trying to set up a pain management program needs to identify the most appropriate training program available to them in the region. The professionals involved in patient care should get such training as an essential first step. Ideally such training should include all three domains of knowledge, skill, and attitude.

The following is an attempt to group these programs according to the duration and type of training:

- Distance education programs that can deliver knowledge, but are generally inadequate to impart skills or attitude.
- Short introductory courses of a few hours to one or two days. They offer some new knowledge and are useful for sensitization of the participants to the new field; but are seldom capable of changing practice. They do help in finding some "converts" who may want to study pain medicine more.
- Foundation courses of 1–2 weeks that introduce the subject in greater detail but usually are capable of attending only to the domain of knowledge. On the positive side, they may stimulate the participant to seek more training and to build on the foundation that has been laid.
- Certificate courses of several weeks, which have both didactic and practical (clinical) components. The participants gain enough here in all three domains of knowledge, skills, and attitude to start practicing pain management, but they need continued mentoring.
- Fellowship or diploma courses of 1–2 years, which prepare the participant to be an independent pain practitioner.

It is important to remember that pain management services cannot be really effective if they stand alone isolated from the general medical and nursing community. If they do, referral rates will be poor. Patients' compliance will also be poor because unless other professionals understand what you do, patients may be discouraged from following your treatment. Hence, the following scheme of action would be good for initial practice:



- First, an introductory advocacy program for the general public and professionals is needed. All professionals in the hospital and in the neighborhood should be offered the opportunity to attend such a program. The more people are sensitized, the better the response to your pain management service. All the professionals involved in some way with the pain management program, including nurses, should be able to evaluate pain and should understand the fundamentals of pain management.
- Second, the professionals who deliver pain care should all have at least a few weeks' "hands-on" training such as the certificate course described above.
- Third (and ideally), at least one or two members of the team should, at the earliest opportunity, gain the level of expertise that can be obtained with a fellowship or diploma program.

What are the challenges regarding drug availability?

Matters related to opioid availability, particularly regulatory issues, have been dealt with in detail in a separate chapter. Affordability of drugs is a matter of particular concern in developing countries. Sadly, very often, the most expensive medication would be available in developing countries, while the inexpensive drugs tend to slowly fade away and go off the market. Organizations such as regional chapters of International Association for Study of Pain (IASP) have a big role to play in influencing national or regional drug policy so that affordable essential drugs are available. Such an effort, for example, has resulted in availability of a week's supply of oral morphine for the price of a loaf of bread in Uganda.

What are the challenges regarding institutional policy?

Whether the pain service is part of a hospital or a stand-alone service, some clear policy decisions are needed. If the service is successful, the demand is likely to be enormous, and soon the service will be flooded with patients and the service may find it impossible to reach all the needy. The following points would be useful as guiding principles.

Setting realistic goals: It may be prudent to start with something easily achievable. If the service is part of a large department of anesthesiology that already has a considerable role in postoperative management, it may be easiest to start a postoperative pain management program. A cancer hospital may find it easiest to start with an outpatient facility for cancer pain management. A stand-alone service may find it easiest to start a chronic pain service.

Multidisciplinary approach: Ideally, pain management should be a multidisciplinary effort. Volunteers, social workers, nurses, general practitioners, anesthetists, oncologists, neurologists, psychiatrists, and other specialists all have their roles to play. However, all these people sitting around a table to care for one patient is an ideal that can never be achieved. It would make better sense to have a system for consultations when necessary. At the same time, the better the interaction is between the social worker, the nurse, and the pain therapist, the better the outcome is likely to be.

What are the challenges regarding the goal of pain management?

Quality of life as the objective: The goal of management should be improved quality of life rather than just treatment of pain as a sensation. All the symptoms of the patient must be treated. Given that anxiety and depression form part of the pain problem, there should be routine screening of patients for psychosocial problems.

Partnership with the patient and family: Successful pain management would mean an essential partnership between the patient, the family, and the therapist. The nature of the problem and treatment options must be discussed with the patient and family and a joint plan arrived at. In developing countries, lack of literacy is often pointed out as the reason for not giving enough explanations to the patient. Professionals need to remember that formal education and intelligence are not synonymous. The illiterate villager, with his experience of a hard life, is usually able to understand problems very well if we remember to avoid jargon and speak in his language. And often he will be more capable of making difficult decisions than a more sophisticated, educated patient.

Affordability of treatment: Affordability of a treatment modality should be taken into consideration when treatment options are discussed.

Incorporation of principles of palliative care: What is the objective of pain management? If pain is relieved, but other symptoms such as breathlessness or intractable vomiting persist and hence quality of life does not improve, the purpose of treatment fails. Hence, the objective should be improvement of quality of life, and not just pain relief. In developed countries, two parallel streams of care have evolved—one managing pain as a symptom and the other providing "total care." But in the absence of such a system, the pain therapist in the developing country has to play the role of a family physician too; he needs to be ready to offer general symptom control, and his team should be able to offer psycho-socio-spiritual support. In many occasions, the involvement of a spiritual person close to the family would help decision making and make patient compliance easier.

Treatment at home: The majority of people in pain in developing countries may have little access to transportation. Hospitals seldom have enough space to take in such patients, even if the patients could afford to do so, except for short periods of time. Most patients will need to stay in their homes. The service will have to be geared to care in the home setting. As in developed countries, patients are opting to stay at home to be treated, especially when they are terminally ill. Successful models of care using "roadside clinics" and nurse-based home care services have been developed in countries like Uganda and India.

Pearls of wisdom

In conclusion, three foundation measures are necessary for an effective national program.

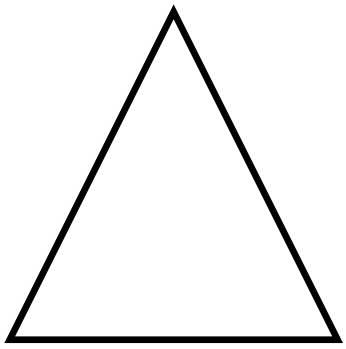
Governmental policy

National or state policy emphasizing the need to alleviate chronic cancer pain through education, drug availability, and governmental support/endorsement.

The policy can stand alone, be part of an overall national/state cancer control program, be part of an overall policy on care of the terminally ill, or be part of a policy on chronic intractable pain.

Education

Public health-care professionals (doctors, nurses, pharmacists), others (health care policy makers/administrators, drug regulators)



Drug availability

Changes in health care regulations/legislation to improve drug availability (especially opioids)

Improvements in the area of prescribing, distributing, dispensing, and administering drugs

Chapter 43
Resources for Ensuring Opioid Availability

David E. Joranson

The purpose of this chapter is to provide perspective and tools that you can use to make opioid analgesics more available and accessible for the treatment of your patients' pain.

The availability of opioid analgesics depends on the system of drug control laws, regulations, and distribution in your country. Unless this system is able to safely distribute controlled medicines according to medical needs, clinicians will be unable to use opioid analgesics to relieve moderate to severe pain according to international health and regulatory guidelines and standards of modern medicine.

This chapter poses a number of questions that are relevant to a better understanding of how the system is supposed to function, and to identify and remove impediments to availability of opioids and patient access to pain relief. This is of utmost importance, since pain management of postoperative, cancer, and HIV/AIDS pain is virtually impossible without the availability of opioids. This does not imply that opioids are indicated for every type of pain. Opioids can be useful to treat patients with chronic pain from noncancer conditions, but the choice of therapies needs to be made on an individual basis, governed by a careful consideration of risks and benefits of treatment.

Case examples

Several real cases are offered to focus this chapter on the critical importance of availability and access to opioid analgesics for the relief of pain.

Case 1

A patient was initially given radiotherapy for her pain, but it was not effective as the disease progressed. Next she was given a weak pain-relieving medication, but her pain continued to worsen. Finally, she returned to the doctor in excruciating pain requesting medication that would end her life. She was given another weak pain medication along with antidepressants and sent home. She committed suicide. [Pain & Policy Studies Group]

Case 2

XX is a referral hospital for cancer management. The annual requirement of morphine is approximately 10,000 tablets of 20 mg. But the Institute has not been able to procure a single tablet ... primarily due to the stringent state laws and multiplicity of licenses. After a lot of effort, the Institute had been able to obtain the licenses... and had approached a [manufacturer] for a supply of tablets ... the [manufacturer] did not have tablets in stock and by the time the tablets could be arranged, the licenses had expired. The doctors at the Institute and the associated pain clinic have stopped prescribing morphine tablets because they would not be available. [Joranson et al. 2002]

Case 3

[T]here were several occasions when no morphine was available. Such situations normally arose as a result of the difficulties encountered when trying to obtain the required licences. At other times, manufacturers of the

drugs simply did not have any stock to sell … a direct result of low and unpredictable demand. During these times, morphine stocks … would run out. In these emergencies, the clinic would resort to otherwise unethical and unacceptable cutback measures, implemented in such a way so as to minimize the effect on patients and families. … When these alternative treatments failed to achieve adequate pain relief, as was usually the case, the staff would share in the helplessness, anger, and frustration of the patients and their families. To communicate the intensity of the dread felt by staff and patients when a morphine shipment was delayed, and the joy when the morphine finally arrived, is not possible. [Rajagopal et al. 2001]

What do these cases illustrate?

These cases demonstrate some of the causes and the human impact of unrelieved severe pain when access to opioid analgesics is blocked. Such situations are tragic and never should be allowed to happen, but they do set the stage for this chapter that will describe a number of resources that can be used by health professionals and government in low-resource settings, or anywhere else, to improve availability and patient access to opioid analgesics such as oral morphine.

This chapter is based on the international studies and experience of the University of Wisconsin Pain and Policy Studies Group (PPSG) and many collaborators. Since 1996, the PPSG has been a World Health Organization Collaborating Center (WHOCC) with terms of reference to develop methods and resources that can be used to improve availability and access to essential opioid pain medicines.

The following questions and responses are intended to assist clinicians and advocates in their efforts to improve patient access to pain relief. Readers are encouraged to consult the resource materials referenced in the text and at the end, refer to other chapters in this book, and seek expert professional guidance on specific questions relating to clinical pharmacology, medicine, and law.

What is the principle of balance?

Efforts to improve opioid availability should be guided by the drug regulatory principle of "balance." Balance is an internationally accepted medical, ethical, and legal principle stating that opioids are indispensable for relief of pain and suffering and that they also have a potential for abuse. The principle recognizes that efforts to prevent illegal activities and abuse should not interfere with the adequate availability of opioid analgesics to relieve pain and suffering. International agreements that are binding on governments have recognized for decades that narcotic drugs, i.e. opioids, are indispensable for the relief of pain and suffering and that governments are obligated to ensure their adequate availability for medical and scientific purposes.

What is the world situation regarding the availability of opioids such as oral morphine for people in pain?

Throughout the world every day, millions of people including older adults and children experience pain from surgery, trauma, cancer, AIDS, sickle cell anemia, and a range of other diseases that may include severe pain. The incidence of cancer and HIV/AIDS is shifting to low- and middle-income countries. Clinicians understand only too well how unrelieved severe pain can destroy quality of life and sometimes even the will to live.

Some—but not all—of the wealthier countries have fairly good opioid availability, and therefore patients have access to opioid analgesics. However, the reality is that most of the world's population lacks access to these indispensable medicines. Lack of access is especially serious in settings with limited resources and an inadequate health care infrastructure. A number of organizations with an interest in pain, palliative care, cancer, and HIV/AIDS are working to address these problems.

Why are controlled drugs such as oral morphine important?

While other chapters address this question in more detail, it is important to note that a variety of drug and nondrug therapies, including surgical procedures, radiation, and behavioral techniques, can be useful in treating pain and providing palliative care. Pain is treated with a combination of drug and nondrug measures. The WHO has determined that pharmacological treatment, including opioids and nonopioids, is the mainstay for relieving pain due to cancer and HIV/AIDS.

Opioids block the transmission of pain in the pathways of the nervous system. Some opioids, such as fentanyl, morphine, hydromorphone, and oxycodone can relieve moderate to severe and escalating pain. These opioid agonists lack a "ceiling effect" so that the dose can be increased to relieve increasing pain, keeping in mind side effects. International health and regulatory bodies do not recommend a maximum dose for opioid analgesics. Some other opioids and nonopioid analgesics do have a ceiling effect and, especially in the absence of opioid agonists, may be overused to try to achieve an effect of which they are not capable.

There is agreement that several opioid agonists in different dosage forms should be available to allow clinicians to change opioids, doses, and routes of administration to maximize efficacy and minimize side effects. The goal is to ensure the availability of these important pain relief medicines at an affordable cost, when and where needed by patients. A number of opioids are listed on the WHO and International Association for Hospice and Palliative Care (IAHPC) lists of essential medicines.

Do opioids have a potential for abuse?

Yes, opioids do have an abuse potential and therefore are "controlled" under international, national, and state laws and regulations. Many controlled opioids are also designated as essential medicines; they are safe and effective—indeed indispensable—for the relief of severe pain.

There is a legal tradition to classify opioids as "narcotic drugs," "dangerous substances," and even as "poisons." "Controlled substances" is a less stigmatizing term. The movement of controlled substances is subject to government regulatory controls such as licensing, secure storage, inventory, recordkeeping, and reporting of procurement, storage, distribution, and dispensing. A medical prescription is required to provide patients with lawful access to controlled medicines.

The manner in which regulatory requirements are administered differs greatly from country to country, and even from state to state and among institutions. But it should be understood that the purpose of opioid regulations should not only be to prevent unauthorized use and diversion from the supply chain. The purpose is also to ensure medical and patient access. However, it has been well documented that some national and provincial/state regulations are more restrictive than is necessary and impede or completely block access, hampering the ability of pain and palliative care clinicians to practice modern medicine.

Although international agreements recognize that national governments may be more restrictive, regulatory controls over opioid analgesics are not balanced if they interfere in legitimate medical treatment of patients. Tools for assessing balance in national laws and regulations and for bringing about change are discussed later in this chapter.

How should prescription opioid analgesics be handled safely?

Safe handling of controlled substances can prevent diversion, misuse, and injury. All those who handle controlled opioid analgesics, including manufacturers, distributors, physicians, pharmacists, nurses, patients, and family members, should know and respect that opioids are to be distributed, prescribed and dispensed only for a medical purpose such as relief of pain or medical treatment of opioid dependence/addiction. Controlled medicines should be used only by the person for whom they are prescribed and according to the physician's instructions.

It is important to keep prescribed medicines in the original container because the label has the prescription information that establishes in the eyes of the law the patient's right to possess a controlled drug. The label on the original container should have the instructions for use, as well safety-related warnings. Controlled medicines should always be stored out of sight to prevent theft, and kept out of reach of children to avoid accidental ingestion.

National requirements vary for returning or disposing of unused or "leftover" medicines. Additional information about requirements for secure disposal and ways to avoid harm to others and the environment should be obtained from the relevant government authorities.

What should be done if pain medicines are diverted?

In some cases, opioid analgesics are unlawfully stolen or "diverted" from various points along the drug distribution system, and then sold for nonmedical purposes, including to abusers. Abuse of essential medicines, especially if publicity is sensational and unbalanced, can

lead to overreactions and more restrictions on essential medicines that can undermine confidence in their therapeutic use. When diversion occurs, the response should be quick and balanced, i.e., the person or persons responsible should be held accountable, without interrupting patient access to pain relief. National leaders in pain management and palliative care should discuss balanced approaches to diversion with the government before it happens.

How can I find out about the opioids that are used in my country?

The PPSG has posted on its website extensive information about the consumption trends of selected opioids in each country. Governments are required to report consumption statistics to the U.N. International Narcotics Control Board (INCB). The INCB in turn provides the data to the PPSG/WHOCC. "Consumption" means the amount of opioids that are distributed by manufacturers or distributors to the retail level in the country, such as to physicians, pharmacies, hospitals, hospices, pain clinics, and palliative care programs. Opioid consumption statistics are an indicator of the capacity of a country to relieve moderate to severe pain.

The opioid consumption trend graphs include information for fentanyl, hydromorphone, methadone (also considered essential for the treatment of opioid dependence), morphine, oxycodone, and pethidine (meperidine). These data do not tell us which dosage forms of the opioid are being consumed in a particular country.

If the graphs for a country show no consumption of a particular opioid, this is an indicator that the drug may not available, or it could be a problem in reporting. The consumption statistics are updated annually by the PPSG as new data are received. These statistics can be used to study the consumption trends for the strong opioids in the world, a region, your country, or any country. Opioid consumption statistics can be used in the evaluation of long-term outcomes of efforts to improve availability.

Consumption statistics can be found in the Country Profiles on the PPSG website. Users can download the graphs and tables of data and use them for presentations without special permission, with appropriate citation. Examples of slide presentations relevant to international and national pain policy are available at http://www.painpolicy.wisc.edu/internat/conferences.htm.

What are the reasons for inadequate availability and access?

The lack of opioid analgesics in a country is not a "supply side" problem. According to the INCB, the United Nations' principal regulatory body for narcotic drugs, there is no insufficiency of raw materials for manufacturing opioid medicines. Instead, the problem is the result of system barriers within countries that result in a low or sometimes nonexistent demand for opioids.

The INCB periodically surveys national governments, in consultation with the WHO, to explore the status of opioid availability and the reasons why they are not adequately available. Governments have reported that the following barriers contribute to the lack of availability of opioids in their countries:

- Concerns about addiction;
- Insufficient training of health care professionals;
- Regulatory restrictions on opioid manufacture, distribution, prescribing, or dispensing;
- Health care professionals' reluctance to stock opioids because of concerns about legal sanctions.

These factors and interaction among them can act as a vicious circle—low national availability can lead to low medical use, resulting in weak demand, which in turn fosters continued low availability. Insufficient medical education about pain, combined with regulatory restrictions and exaggerated concerns about opioid analgesics and addiction, may conspire to maintain the status quo. However, it is possible to break out of this cycle if there is leadership both from health professionals and government.

What can the "National Competent Authority" do to improve availability and access?

Key to breaking the cycle and improving availability and access is the National Competent Authority (NCA). This is an agency in every country, often located in the Ministry of Health. It is intended to be responsible for implementing the government's international narcotics treaty obligations to ensure adequate availability of narcotic drugs for medical and scientific purposes. The Country Profiles on the PPSG website provide contact information for the NCA for each country.

The NCAs have been asked by the INCB to work with health professionals to determine and anticipate adequately future medical needs for opioid analgesics so that the necessary amounts can be imported and

manufactured. The "estimates system" administered by the NCA and the INCB is designed to estimate unmet needs for opioids and then authorize their acquisition. Each year, the NCA prepares and submits to the INCB the estimated requirements of the quantities of each opioid that will be needed in the country.

Only when the national estimate is increased or expanded to include other opioids can there be a change in the overall amounts that are imported, manufactured, distributed, and dispensed to patients. However, if there is little public interest in obtaining pain relief or medical interest in providing it, there may be little justification for increasing availability.

When controlled drugs are needed for humanitarian emergencies, the usual time-consuming regulatory procedures governing exports and imports can be abbreviated to expedite increased availability and access; further information is available from the INCB and the WHO.

Are there recommendations for educators and professional organizations to address opioid availability problems?

Yes. The INCB, in consultation with the WHO, has recommended a strong role for educational institutions and nongovernmental health care organizations—including the International Association for the Study of Pain (IASP)—to teach students in health care professions and licensed practitioners about the use of opioid analgesics, their control, and *correct* use of terms related to dependence. Furthermore, health care professionals and their organizations have been requested to establish ongoing communication with their governments about unmet needs for opioid analgesics and to help identify impediments to availability and access.

Where can a clinician find information about how to improve opioid availability and access?

Although there are numerous guidelines and educational curricula that address pain and palliative care, clinical training materials often do not describe the drug control system and the steps necessary to obtain and distribute opioid analgesics. Obtaining and *sustaining* access to opioid analgesics in any country depends on learning about the context of international and national drug control laws and regulations, how these are implemented in the distribution system, how they can be evaluated, and then working with government to make necessary changes in policy and administration.

With support from the National Hospice and Palliative Care Organization and the Foundation for Hospices in Sub-Saharan Africa, the PPSG developed an Internet course titled "Increasing patient access to pain medicines around the world: a framework to improve national policies that govern drug distribution." The course was developed to make available this specialized information to clinicians, government administrators, drug regulatory personnel, national health policy advisors, health policy scholars, and to those who develop clinical guidelines and training materials for pain management and palliative care.

The course has seven lessons, each with required readings and extensive citations (see Table 1). The course explains why patients and clinicians have a right to expect that their national drug regulatory system should make opioids available, and explains how this goal can be accomplished.

Do health professionals already have skills that can be used to address opioid availability?

If you have medical training, you already have relevant medical knowledge that can be applied in the drug regulatory policy and systems arena. For example, you may appreciate the need for pain relief among patients with various diseases and conditions. You may know about the drugs and their uses. The medical model is also a solid problem-solving approach that can be applied to the diagnosis of barriers to opioid availability and access, and to formulating action strategies, or treatments, as if the opioid distribution system in your country is your patient. Using this knowledge and skill, you can become an effective leader to work with government to examine, diagnose, and then decide on and implement the treatments necessary to correct the problems.

What tools are available to help diagnose regulatory problems in my country?

Information about drug control policy and systems barriers is often new to the health professional, so the WHO has published *Cancer Pain Relief with a Guide*

Table 1
Lessons in the PPSG Internet Course*

Lesson 1:	Understanding the Relationship between Pain and Drug Control Policy
Lesson 2:	The Role of International and National Law and Organizations
Lesson 3:	Barriers to Opioid Availability and Access
Lesson 4:	WHO Guidelines to Evaluate National Opioids Control Policy
Lesson 5:	WHO Guidelines to Evaluate National Administrative Systems for Estimating Opioid Requirements and Reporting Consumption Statistics
Lesson 6:	WHO Guidelines on Procurement and Distribution Systems for Opioid Analgesics
Lesson 7:	How to Make Change in Your Country

* This is a self-paced noncredit course that can be taken at any one time or over a period of time. It may take between 10 and 12 hours to complete. Each lesson has a pre-test and post-test; links to background reading and many authoritative resources are provided. A certificate is issued upon successful completion. The welcome and sign-in page is found at http://www.painpolicy.wisc.edu/on-line_course/welcome.htm. The course is available only in English at present.

to Opioid Availability, which explains basics of policy, as well as *Guidelines for Achieving Balance in National Opioids Control Policy.* The WHO *Guidelines for Achieving Balance* provides a framework for diagnosis of impediments in national drug control laws that has been used extensively around the world. These guidelines and the diagnostic checklist are available in 22 languages on the PPSG website at http://www.painpolicy.wisc.edu/publicat/00whoabi/00whoabi.htm.

From a practical point of view, what can clinicians and government regulators do to improve cooperation?

Table 2 presents recommendations from the WHO *Guidelines for Achieving Balance* about how health professionals and drug regulators can cooperate through exchange of information and perspectives and establishment of mechanisms of communications and engagement.

Do health professionals have beliefs or attitudes that might interfere with addressing opioid availability?

Possibly. Misinformation about the addictive potential of opioids and confusing terminology have led to exaggerated concerns about the use of opioid analgesics and overly strict regulations that impede efforts to improve access to appropriate treatment for moderate to severe pain.

Decades ago, experts said that mere exposure to morphine would inevitably result in "addiction." At that time, addiction researchers studied the withdrawal syndrome that occurs when opioid use is stopped abruptly. Today in the field of pain management, we know that physical dependence is an expected adaptation of the body to the presence of an opioid analgesic, and that the withdrawal syndrome can be managed if the opioid is stopped. The WHO no longer uses the term "addiction." The current terminology is "dependence syndrome," which is a biopsychosocial condition, the markers of which are maladaptive behavior, compulsive use, and continued use despite harm. However, in referring to dependence syndrome, use of the term "dependence" by itself has the possibility of being confused with physical dependence. Under these circumstances, it is important to be clear in clinical and scientific communications whether one is referring to a diagnosis characterized by maladaptive behavior, or to physiological adaptation.

The notion that morphine should only be used as a last resort is based on an outdated view of opioids and addiction. Indeed, efforts to prevent dependence/addiction that were based on this now outdated understanding have led to excessively strict prescribing restrictions that impede access. Examples include strict limits on patient diagnoses that are eligible for opioid analgesics, restrictions on dosing and prescription amount, and complex prescription forms that require multiple approvals and are difficult to obtain. These matters are discussed more fully in the PPSG Internet course; articles about progress to remove barriers in a number of countries appear on the PPSG website.

If I want to assume more of a leadership role in my country, is specialized training available?

Yes. In addition to the Internet course, the PPSG sponsors an International Pain Policy Fellowship (IPPF), with support from the International Palliative Care

Initiative of the Open Society Institute and the Lance Armstrong Foundation. The purpose of the IPPF is to prepare leaders from low- and middle-income countries to become change agents, and to develop plans to improve patient access to opioid pain medicines in their countries. Fellows are selected through a competitive application process and spend a week in training with the PPSG and other international experts. In some cases, a representative of the NCA accompanies the Fellow to facilitate cooperation with the government drug regulators.

The Fellows study the Internet course, diagram and diagnose impediments in their country's drug distribution system, learn to use WHO tools to assess national drug control laws, and develop their own action plans to improve opioid availability and access. During the 2-year fellowship, the Fellows implement their action plans with technical assistance from the PPSG. Please visit the PPSG website for announcements, or go to http://www.painpolicy.wisc.edu/newslist.htm to sign up for email announcements from the PPSG.

Pearls of wisdom

- Today's regulatory requirements for "narcotic drugs" were developed long ago, well before pain relief became a priority, before opioids were designated essential medicines by the WHO, and at a time when morphine was thought to cause addiction in anyone exposed to it.
- More recently, the WHO and the INCB have encouraged governments to provide patients with trouble-free access to oral opioid analgesics, and the WHO has updated its definition of dependence syndrome. Still, opioid analgesics continue to be inaccessible to most of the world's population.
- The U.N. drug regulatory and health authorities have recognized the lack of availability of opioid analgesics, have urged governments to examine national laws and regulations for barriers to opioid availability, and have asked health professionals and the IASP to work together to cooperate to

Table 2
Examples of cooperation between government and health care professionals

Government regulatory authorities can:
Inform health professionals about trends in drug trafficking and abuse.
Explain the framework of drug control policy and administration in the country including how the estimated requirements for opioid analgesics are prepared.
Create mechanisms such as a task force or commission to examine ways that national drug control policy and its administration could help to improve availability and access while maintaining adequate control.
Endorse World Health Organization guidelines for management of pain.
Support national guidelines for pain management.
Inform health professionals about legal requirements and discuss any concerns.
Explore ways to provide an adequate number of outlets to maximize patient access.
Collaborate with other government organizations, e.g., in cancer and AIDS planning for services, and to support medical education, education of patients and the general public.
Health professionals can:
Provide the government with information about the needs for various opioids for pain management and palliative care in the country.
Identify needs to address any barriers in the regulatory system.
Provide information about modern pain management, current knowledge about opioid analgesics in treating pain, and knowledge and attitudinal barriers to their optimal use.
Demonstrate understanding of the international narcotic conventions and the obligation of governments to ensure adequate availability of opioid analgesics, while also preventing abuse and diversion.
Provide information about WHO guidelines that can be used in self-assessment of the national opioids control policy.
Assist in providing information to estimate the amounts of various opioids that are needed to satisfy actual needs.
Identify impediments and weaknesses in the distribution system that lead to shortages.
Support the government's efforts to obtain adequate personnel to administer drug control functions under the Single Convention.
Explain health professionals' concerns about prescription requirements and the possibility of investigation.

educate health workers and to ensure adequate patient access to pain relief.

- Pain and palliative care experts report that the absence of a clear statement about the governmental obligation under international agreements to ensure adequate opioid availability in national laws makes it difficult to convince regulators. PPSG studies show that the U.N. model drug control laws that should provide balanced guidance to governments also lack such language.
- Traditionally, most countries have used pethidine (meperidine) for pain relief, with the thought that such a short-acting opioid would be less addictive. But since the regulatory controls for morphine and other strong opioids are the same as for pethidine, it should be possible for health professionals and the NCA to figure out how to make available other opioids where they are needed.
- The resources provided in this chapter offer a starting point as well as encouragement to work with colleagues, professional organizations, and government to correct the conditions that block efforts to relieve pain and suffering.

In closing, here are a few tips:

Be alert to new opportunities and resources. There may be opportunities in your country for synergistic partnerships with government and nongovernment public health organizations that advocate the use of methadone for treatment of intravenous drug users to reduce the spread of HIV/AIDS. The international controls on morphine and methadone are the same, and the regulatory steps to make them available and accessible in a country should be similar to those for opioid analgesics.

The WHO is developing an Access to Controlled Medicines Program to provide additional support for efforts to improve medical access to opioid analgesics as well as other essential medicines that are controlled drugs.

Pain relief is becoming recognized as a human right. As the right to pain relief becomes more widely recognized, there may be additional opportunities for collaboration with human rights advocates. Human rights advocates understand that working with government is necessary. The work outlined here to evaluate and reform outdated drug control policies is an integral part of making the human right to pain relief a reality.

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Recommended websites

Pain & Policy Studies Group: www.painpolicy.wisc.edu/

World Health Organization: www.who.int/medicines/

International Narcotics Control Board: www.incb.org

International Association for Hospice and Palliative Care: www.hospicecare.com/

International Association for the Study of Pain
IASP
Working together for pain relief

Chapter 44
Setting up Guidelines for Local Requirements

Uriah Guevara-Lopez and Alfredo Covarrubias-Gomez

Case report

A 65-year-old Mexican woman reported generalized abdominal pain. She went to a rural medical practitioner in San Juan de Bautista, who prescribed 30 mg of ketorolac t.i.d. After 2 days the pain had not stopped, and she returned for medical assistance; this time, the physician added to his prescription 90 mg of etoricoxib per day. After two more days, the pain continued, and the woman went to a regional hospital located 10 miles from her home in Lloredo. In the hospital a uterine cancer with omental and liver metastasis was diagnosed, and adequate pain management was provided.

The prescription from the rural practitioner drew the attention of local health authorities. They asked the clinician about his prescription and about his knowledge about Mexican practice guidelines for cancer pain management. The physician responded that he had heard of them but he did not know about their content or recommendations, although he had received education on Mexican practice guidelines for pain management: he had attended a 1-month fellowship in the regional hospital, and was also encouraged to promote education to local organizations about the guidelines and their benefits. A follow-up program for pain management evaluation in his community was established.

So what went wrong?

What are practice guidelines?

The original concept of *practice guidelines* (PGs) was described as "a recommendation for patient management that identifies one or more strategies for treatment". However, in 1990, the *Institute of Medicine* in the United States defined PGs as "systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances" (see Table 1). This definition had been generally accepted.

Guidelines are not rules or standards; they are helpful, flexible syntheses of all the available, relevant, good-quality information applicable to a particular clinical situation that the clinician and patient need to make a good decision. Since medical knowledge, techniques, and technology are in constant development; PG must be actualized and improved in certain time intervals.

Why do we need practice guidelines?

Medical knowledge is under a continuous evolution. Assume, that a physician knows everything about a disease or its treatment on the basis of training and clinical judgement, but continuing medical education was not available. Since there is a great chance, that medical concepts have changed meanwhile, the physician's

Table 1
Definition of practice guidelines and other terms that are confused with practice guidelines

Concept	Definition
Practice guidelines	A systematically developed statement to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances. "Protocol" is often used interchangeably with "guideline," although some view "practice protocols" as a more specific (procedure- or specialty-specific) form of practice guidelines.
Clinical pathways	An optimal sequencing and timing of interventions for a particular diagnosis or procedure. A "care map" or multidisciplinary action plan extends the concept of a clinical pathway by including an outcome index, which allows for the evaluation of the interventions.
Clinical algorithms	A more complex set of instructions containing conditional logic, usually expressed in branching trees.
Information extracted from: Henning [4].	

diagnostic and therapeutic approaches are outdated meaning either impaired efficacy or decreased safety.

The speed of medical evolution has complicated medical decision making; for that reason, PG may be used as an instrument to assist the clinician. This objective is possible because PG summarizes the collective experience and establishes grades to scientific knowledge.

Are there different types of practice guidelines?

Attempts to regulate PG had been made since the early 1980s. Nowadays, different types of practice guidelines can be identified: (i) for the diagnosis and management of specific clinical circumstances, (ii) for risk management, (iii) for the improvement of quality systems, (iv) for medical regulation, (v) for education, and (vi) for preventive care.

Why do we need practice guidelines for pain management?

Pain is considered a health problem in few countries, but the number of countries where pain management becomes a health care priority is increasing. The development of PG in pain medicine is supported by the following issues: (i) the number of surgical interventions is increasing in many low-resource countries without any concept to control postoperative pain; (ii) the demographic change (increase of older population) worldwide will be associated with a growing prevalence of cancer pain; (iii) the frequency of chronic non cancer pain is recognized more today, for which it has been estimated, that the annual treatment costs equal or exceed exceeds those for coronary disease, cancer and AIDS.

Additionally, pain has a significant impact on physical function and activity, return-to-work-quota, social and family relations as well as the general psychoaffective state of the affected patient. This may prove to be a burden for the family of the patient, but also to the society as a whole, since insufficient pain management is a major cause for increased use of health care resources. Therefore, health care policies need the implementation of rationalized instruments that can optimize and improve the quality of medical attention for the most relevant diseases including pain syndromes.

How are practice guidelines developed?

There is a general agreement, that PG must be submitted to public scrutiny, revised regularly in response to medical advances, and derived from high quality scientific evidence. PG must be easy to comprehend, inclusive, and manageable. The method for evidence selection must be explained and the criteria used to grade each recommendation must be explained.

Protocols for developing guidelines have many common features: (i) Reviews of existing research findings are conducted, often with the aid of the National Library of Medicine. (ii) Studies are selected according to predetermined criteria and findings are summarized using techniques such as meta-analysis or systematic reviews. (iii) Panels of experts are convened and guidelines are revised according to feedback received. (iv) Consensus is achieved in some areas; and where disagreement or uncertainty remains and more research is needed, the developers describe this deficiency.

Strategies for developing PG have been proposed by diverse groups worldwide, a summary of those is described in Table 2.

Table 2
Strategies used for developing practice guidelines

Strategy	Description
Identification of a regional medical problem	A regional health problem is identified. The impact of this problem on the population and the usefulness of practice guidelines is analyzed. If needed, a consensus group for the development of guidelines (for management, care, diagnosis, etc.) is formed.
Selection of a group of experts	Formed by specialists from areas related to the guideline topic. Selection criteria include experience (more than 5 years) in this particular field, in clinical research, in grading the evidence for recommendations, and/or an academic profile. Clinical practitioners recommended from the national medical associations related to this specific area are also included. Experts must not have any conflict of interest.
Identifying medical tendencies	A questionnaire to evaluate the medical tendencies (for diagnosis, management, care, etc.) is developed by the group of experts. Items on the questionnaire are based on the statements made by other consensus groups, clinical guidelines, clinical pathways, or clinical algorithms. Results from questionnaires are sent to the selected experts.
Review of the literature	From the selected guideline topic, a focused review of the literature is made. This process is achieved using diverse electronic medical databases (PubMed, EMBASE, LILACS, and others). Cross-reference of selected documents is made. Resources to obtain references are provided by the national institutes of health, national medical associations, and nonprofit organizations.
Sending evidence to the selected experts	Results from the review of the literature are send to the group of selected experts. The objective is that every participant have the opportunity to analyze the literature before the consensus meeting.
Elaborating recommendations	A consensus meeting is held to analyze the results obtained from the questionnaire and to develop specific recommendations (for management, diagnosis, education, care, etc.). Every recommendation is considered for further review based on the group's expertise and the results from the review of the literature.
Preliminary results	From the consensus meeting a preliminary report is obtained. Each of the recommendations is submitted to a focused review of the scientific evidence. Meta-analysis, systematic reviews, randomized controlled trials, randomized uncontrolled trials, and case reports for each specific recommendation are analyzed. If there are no studies, the recommendation is "based on consensus group expertise." Results from this search are sent to the group of experts.
Grading recommendations	Feedback from the group of experts about the evidence to endorse a recommendation is analyzed. The method for grading for every recommendation is described in Table 3.
Preliminary practice guidelines	A preliminary document is sent to the consensus group. Final notes from the participants are considered, and a final document is elaborated.
Review of the final document	The final document is sent to the participants for approval (as many times as needed). After this process is completed, the document is sent for publication in a peer-reviewed journal.
Implementation of guidelines	Extensive education among clinicians, health care administrators, policy makers, benefit managers, and patients and their families is performed in every filiation center from each consensus participant. Conferences at regional congresses or medical meetings are provided. Local efforts to implement guidelines require the commitment of the participants.
Follow-up and evaluation of the guidelines	A questionnaire designed to evaluate clinicians' knowledge of the guidelines or their outcome is performed. Evaluation is obtained by the method developed by the AGREE Collaboration Group.

Information extracted from: Frances [ref. 2], Guevara-López et al. [ref. 3]. AGREE Collaboration Group: www.agreecollaboration.org; National Institute for Health and Clinical Excellence (UK): www.nice.org.uk.

How does the scientific evidence grade the recommendations of practice guidelines?

In 1979, the Canadian Task Force on Periodic Health Examination made the first efforts to characterize the level of evidence underlying health care recommendations and their strength. Since then, a wide variety of methods have been developed for "grading" the strength of the evidence on which recommendations are made.

Grading methods take into account the study design, benefits and harms, and outcome (Canadian Task Force, U.S. Preventive Services Task Force, GRADE working group, SIGN method, SORT taxonomy, etc.). A description of a strategy for grading the evidence according to the methodology of the study is described here:

- Level 1: Evidence is extracted from systematic reviews of relevant controlled clinical trials (with meta-analysis when possible)

- Level 2: Evidence is extracted from one or more well-designed randomized controlled clinical trials
- Level 3: Evidence is extracted from well-designed nonrandomized clinical trials or well-designed cohort studies or analytic case reports (if possible multicenter or performed at different times)
- Level 4: Evidence is extracted from expert opinions and/or opinion leaders (supported if possible by the reports from other consensus statements)

The evidence can be converted into recommendations (type A, B, or C) and the "strength of evidence and maximum benefit" (Class A to Class E), depending on how advisable the use of a specific treatment or intervention is (Class A = highly advisable and Class E = insufficient evidence).

How are practice guidelines evaluated?

The quality of clinical practice guidelines must be evaluated and diverse methods to achieve this propose have been reported. There are three basic stages of evaluation: (i) evaluation during the development of guidelines and before their full dissemination and implementation (inception evaluation); (ii) evaluation of health care programs within which guidelines play a central role (guidelines-program evaluation); and (iii) evaluation of the effects of guidelines within defined health care environments (scientific evaluation).

The evaluation of PGs also includes the identification of potential biases of guideline development, and the assurance that recommendations are valid and feasible for practice. This evaluation process takes into account the benefits, harms, and costs of the recommendations, as well as the practical issues attached to them. Therefore, the assessment of PGs includes judgments about the methods used for its development, the content of the final recommendations, and the factors linked to their uptake.

How can practice guidelines be implemented?

The fact that most PGs have been published and then forgotten has to do with the lack of efforts for their implementation. The acceptance of PGs requires extensive education among clinicians, health care administrators, policy makers, benefit managers, and patients and their families. Therefore, PGs must introduce a comprehensive and integrative strategy for their implementation.

An implementation strategy relies on informing and educating physicians about the content of guidelines. Impersonal approaches that use the dissemination of written material alone or presentations to large audiences have not been very successful. Education of a specific PG must be personalized, involve respected physician leaders and incorporate a high degree of interaction between the target audience and those presenting the information.

Comparison of actual performance with the performance that would be expected if the guidelines were followed may be used as a feedback strategy to achieve PG implementation. Feedback can occur either as the service is being provided (concurrent feedback) or after that service has been provided (retrospective feedback).

A physician's knowledge of PGs to obtain board recertification has been described as an useful strategy for guideline implementation. For that reason, medical associations or medical boards should be part of PG implementation strategies. Their role could be to generate distance learning programs and continuing medical education (CME) certification on the PG contents. To add (and receive) the support from health care administrators and policy makers, it is advisable to stress the economical impact of PGs (which usually attracts their attention!).

Finally, education of patients and their families as well as the public about the potential benefits obtained by PG must be part of the implementation process. These educational efforts may be extended to nongovernmental organizations.

How do clinicians respond to practice guidelines?

The impact of guidelines on the behavior of physicians has been poorly documented, although some reports documented a considerable disappointment with PGs. Other studies show that physicians are generally positive about guidelines but that they do not integrate them into their practices to a large extent. The reason for this ambivalent behavior lies in problems associated with their production, dissemination, and use. However, little is known about physicians' (and patients') attitudes and suspicions toward PGs, as well as

regarding the motives for encouraging their use or as to their credibility. This has been recognized as a deficit, since certain motives could cause practitioners and their patients to resist PGs.

Some studies indicate that the physician's adherence to guidelines may be hindered by a variety of barriers. Identified were: (i) awareness, (ii) familiarity, (iii) agreement, (iv) self-efficacy, (v) outcome expectancy, (vi) ability to overcome the inertia of previous practice, and (vii) absence of external barriers to perform recommendations.

Another factor that may slow down adherence by physicians to PGs may be the dogmatic educational background. For example, Canadian family physicians show little resistance to guidelines and appear to need less threat of external control to incorporate them into their practice. On the other hand, American internists are less supportive of PGs. It is possible that information acquired from medical training may play a role in PG support from practitioners. Therefore, the development of PGs must include lecturers and opinion leaders at medical schools and respected organizations to foster dissemination.

The clarity and readability and the clinical applicability of a guideline are other elements that contribute to the acceptance of guidelines by clinicians. In conclusion, PGs must be written in a user-friendly way, adapted to the practical needs of the clinician's daily practice, and advocated thoroughly by medical boards, opinion leaders, and medical societies. If the implementation of a PG is successful, the results for patient safety are encouraging.

Why must practice guidelines consider regional resources?

Developing countries have limited access to expensive drugs or procedures. Therefore, PGs must consider regional resources for their feasibility and routine application, often making it impossible to simply copy international PGs. It may be inevitable to make certain evidence-based approaches to diagnosis and treatment optional, e.g., by including phrases like "if available." Existing PGs have to be adapted if possible according to the national "essential drug list." If no reasonable alternative drug choice is available, no further compromise for a national PG is recommended. Instead, the essential drug list should be targeted. The effort should be made to encourage all stakeholders to change the drug list accordingly. To give an example, the introduction of basic palliative care in East African Uganda was only possible when the essential drug list was amended by adding morphine.

Another fact to be respected when introducing PGs in low-resource settings is the disparity regarding access to medical services depending on geographic factors, such as the difference between the capital and rural regions or the difference between underfunded national health system institutions and high-standard private ones.

On the one hand, PGs have to be adapted in a stepwise structure to be used depending on the resources available, and on the other hand, PGs may be used as an instrument to optimize resources and the quality of delivery of health care.

Also, certain national differences exist, due to cultural, ethnic/genetic, and traditional reasons, regarding the use of certain drugs and procedures. In Mexico, for example, 80% of the population use herbal medicine, and 3,500 registered medical plants with medicinal properties are available. For that reason, phytotherapy or other complementary medicine could be considered for inclusion in locally adapted PGs.

Finally, potentially effective dissemination and education techniques developed in high-resource settings may also have to undergo some changes to be feasible in a specific low-resource setting. It is understood that such an initiative will mean a considerable effort, although the work of local PGs could at least be based on international accepted PGs. It will be necessary to get all stakeholders at one table: rural and academic practitioners, other health providers, patients and their families, local organizations, and academic institutions. This sounds like a lot of work, but the gain in safety and economy following the publication and implementation of (adapted) PGs will justify the effort.

Pearls of wisdom

- Practice guidelines (PGs) are "a systematically developed statement to assist the practitioner's and patient's decisions about appropriate health care for specific clinical circumstances." Guidelines are not rules or standards, but they are a helpful, flexible synthesis of all the available, relevant, high-quality information applicable to a particular clinical situation, so that the clinician and patient may make a good decision.

- The evolution of medicine has complicated medical decision making; for that reason, PGs may be used as an instrument to assist the clinician in medical decision making. This objective is possible because PGs summarize the collective experience and establish easy access to scientific knowledge.
- PGs must be easy to comprehend, inclusive, and manageable. The method for evidence selection must be explained, and the criteria used to grade each recommendation must be included.
- A wide variety of methods for "grading" the strength of the evidence on which recommendations are made have been developed. Grading methods take into account the study design, benefits and harms, and outcome.
- The acceptance of PGs requires extensive education among clinicians, health care administration, policy makers, benefit managers, and patients and their families. Therefore, PG must introduce a comprehensive and integrating strategy for its implementation.
- Physician adherence to guidelines may be hindered by a variety of barriers, which include: (i) awareness, (ii) familiarity, (iii) agreement, (iv) self-efficacy, (v) outcome expectancy, (vi) ability to overcome the inertia of previous practice, and (vii) absence of external barriers to perform recommendations.
- Developing countries may have limited access to (expensive) drugs or procedures. Therefore, PGs must consider regional resources for their feasibility and routine application.
- PGs must take into account local resources and traditions and make available the evidence regarding the risk-benefit ratio and the cost-effectiveness. If local resources lack proper evidence or local resources ignore essential evidence, PGs may be used as an instrument to draw the attention of policy makers and health administrators to provide the most beneficial management or intervention to the affected population.

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Websites

NICE: National Institute for Health and Clinical Excellence (UK). www.nice.org.uk

AGREE: Appraisal of Guidelines Research and Evaluation Collaboration. www.agreecollaboration.org

Pearls of Wisdom

Chapter 45
Techniques for Commonly Used Nerve Blocks

Corrie Avenant

Why recommend regional anesthesia?

- The patient remains conscious or mildly sedated.
- Airways and respiration are not affected.
- The incidence of postoperative thromboembolism is reduced.
- Regional anesthesia techniques are less expensive compared to general anesthesia.

What are the disadvantages of regional anesthesia?

- Special skills are required to do a nerve block successfully.
- Analgesia may not always be effective, so conversion to general anesthesia might be necessary.
- Immediate complications can occur, such as toxicity or hypotension.

What assessment must be done before performing a block?

There are no differences regarding the assessment of a patient between a general anesthesia or a regional anesthesia technique. The same care and considerations must be taken into account, with a history and relevant clinical examination. Special drug history is necessary with regards to anticoagulant and antiplatelet drugs, such as the type, dose, and the time when the anticoagulants were taken.

It is necessary to explain to the patient what he/she will experience:

- Some paresthesias and involuntary movements during needle insertion.
- Intraoperatively, the patient may feel movement, touch, and pressure while having adequate analgesia, and he or she will have to be reassured that if the analgesia is inadequate, there is a strong possibility of being given general anesthesia.
- Postoperatively the patient will have to wait for a few hours for movement and sensation to return completely, but he or she can eat a meal straight away.

What are the contraindications for regional anesthesia?

- Patient refusal
- Coagulation disorders
- Infections at the site of injection
- Pre-existing neurological deficits: check previous documentation and make your own brief examination before planning regional anesthesia to avoid being blamed for any undocumented neurological deficits

What is the structure and characteristics of a typical local anesthetic drug?

- Local anesthetics have a three-part structure
- The three parts of the structure consist of an aromatic ring, an intermediate chain, and an amino-group
- The intermediate chain has either a ester or an amide linkage
- The ester linkage gets broken down by hydrolysis, has a short shelf-life, and is relatively nontoxic
- The amide linkage is metabolized by the liver
- The mode of action is a reversible block of nerve conduction by blocking the sodium channels (from the intracellular site)

How is toxicity avoided when using local anesthetics?

- Always respect maximum doses: for bupivacaine the maximum dose is 2 mg/kg for a single injection technique (daily maximum 8 mg/kg for continuous techniques).
- In case of toxicity symptoms (slurred speech, tingling in the ear, loss of consciousness, convulsions, or arrhythmias), stop the injection, and administer oxygen and support ventilation to avoid acidosis.
- Stop seizures with intravenous pentothal, benzodiazepines, or propofol.
- If cardiac symptoms are present, give circulatory support (antiarrhythmics such as amiodarone or amrinone); if arrhythmias persist, use direct-current (DC) cardioversion and cardiopulmonary resuscitation (CPR) for as long as needed (which may be much longer than for other causes of arrest).
- If available, use lipid infusion (Intralipid) to "antagonize" local anesthetic toxicity (a bolus of 1.5 mL/kg body weight of Intralipid 20%, followed by 0.25 mL/kg body weight/minute for 1 hour).

What types of nerve blocks are easy to perform?

Finger block

Indications are fractures and lacerations. The two digital nerves run on each side of the finger. Therefore, the technique would be as follows:

- The landmark is the base of the finger.
- Insert the needle and make contact with the bone (the proximal phalanx at its lateral point).
- Withdraw the needle a bit and deposit 0.5–1 mL of 0.5% bupivacaine.
- Redirect the needle dorsally and inject another 1 mL.
- Repeat this on the other side as well.

Toe block

Indications would be fractures and amputations. As in the finger, two nerves run on either side of each toe. Therefore the technique is the same as in finger blocks.

Always use plain local anesthetics for digital blocks; NEVER use mixtures with epinephrine (adrenaline).

Intravenous regional anesthesia (Bier's block)

Bier's block may be a very effective block for upper and lower limb manipulation, such as manipulation of simple fractures and suturing of lacerations.

The method is as follows:

- Secure venous access on both sides.
- Have a full resuscitation trolley available (in case of cuff failure).
- The inflatable tourniquet is placed around the upper arm over a wool bandage to protect the skin.
- A double cuff may be used for prolonged surgery (>15 minutes).
- Drain venous blood from the affected limb.
- Inflate the blood pressure cuff to 100 mm Hg above systolic blood pressure.
- Inject local anesthetic.
- Anesthesia is achieved after 10–15 minutes (the blood pressure cuff should not be deflated within 20 minutes).
- Use 0.5 mL/kg of 0.5% lidocaine (plain) solution

Intercostal nerve block

A typical indication would be postoperative pain relief after cholecystectomy or thoracotomy, as well as pain relief from fractured ribs. Remember that the intercostal nerves derive from the ventral ramus of the spinal nerves and that they run along the inferior border of the ribs. To block the intercostal nerves, use the following technique:

- Position the patient in a supine position.

- Have the patient's arm raised with the hand behind the head.
- Confirm the rib by palpation or adequate landmarks.
- Identify the midaxillary line.
- To avoid pneumothorax, the needle point should be in close proximity to the rib.
- The rib is held between the second and third fingers.
- Insert the needle between the second and third finger and advance to make contact with the rib.
- Direct the needle downward (caudally) and walk the needle until it slides off.
- Advance the needle not more than 5 mm to prevent pneumothorax.
- Finally, inject 2–3 mL of 0.5% bupivacaine at each level, after careful aspiration, as the intercostal artery and nerve are very close by.

Wrist block

Wrist blocks may be used if a plexus block is incomplete, as a diagnostic block, or for pain therapy. Be familiar with the anatomy. The median nerve is located on the radial site of the palmaris longus tendon (better visible when flexing the wrist), and the ulnar nerve is located on its other (ulnar) side. The radial nerve is superficially located at the lateral aspect of the wrist.

To block the median nerve:

- Insert the needle on the flexor side between the tendons of the flexor carpi radialis and palmaris longus tendon.
- After eliciting paresthesias, withdraw slightly and inject 3–5 mL.

To block the ulnar nerve:

- Have the arm stretched out and the hand supinated.
- Insert the needle approx 3–4 cm proximal to the crease between the flexor carpi ulnaris tendon and the ulnar artery.
- After eliciting a light paresthesia, withdraw the needle slightly and inject 3–5 mL of the local anesthetic.

To block the radial nerve:

- Have the arm stretched out and the hand supinated.
- Infiltrate subcutaneously on the radial side of the wrist 3–5 cm proximal to the radial head point.

Ankle block

Indications would be all kinds of foot surgery, including amputations. For an effective ankle block, proceed as follows:

- Position the patient supine.
- Block the superficial peroneal nerve with subcutaneous infiltration between the anterior edge of the tibia and the upper edge of the lateral malleolus with 5–10 mL anesthetic solution.
- Block the sural nerve by subcutaneous infiltration of 5 mL local anesthetic between the Achilles tendon and the lateral malleolus.
- Infiltrate the saphenous nerve with of 5 mL of subcutaneous local anesthetic from the anterior edge of the tibia to the Achilles tendon.
- Block the deep peroneal nerve by inserting the needle between the tendon of the extensor pollicis muscle and the dorsalis pedis artery on the dorsum of the foot. The needle is inserted perpendicularly to the skin and advanced slightly under the artery. Following negative aspiration inject 5 mL local anesthetic.
- Tibial nerve block can be obtained with the needle inserted directly dorsal to the posterior tibial artery on the medial side of the joint, or alternatively, directly anterior to the Achilles tendon behind the medial malleolus.

Pearls of wisdom

- Some peripheral nerve blocks are very easy to perform and very effective.
- They can be performed with minimum training.
- Nevertheless, anatomical details have to be known and memorized (see webpage).
- Peripheral nerve blocks will work better if there is no local inflammation.
- Toxicity of local anesthetics can be prevented (almost always) by respecting maximum doses and avoiding intravascular injection with careful aspiration.
- In case of local anesthetic toxicity have all necessary instruments and drugs ready for treatment, otherwise refrain from performing blocks.
- In case of paresthesias, withdraw the needle to avoid injury to the nerve.
- Do not use blocks if the patient is not willing.

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Websites

http://www.painclinic.org/treatment-peripheralnerveblocks.htm (including anatomical images for each block)

http://www.nysora.com/ (including real life photos for all relevant blocks)

http://www.nda.ox.ac.uk/wfsa (World Anaesthesia Online educational material on different relevant blocks to be used in low-resource settings)

International Association for the Study of Pain
IASP
Working together for pain relief

Guide to Pain Management in Low-Resource Settings

Chapter 46
Psychological Principles in Pain Management

Claudia Schulz-Gibbins

What can we use for acute pain?

Acute pain occurs mainly in connection with an illness or injury or as an effect of a treatment of an illness (e.g., postsurgical pain). In contrast to chronic pain, acute pain is an alarm signal to the body. Normally, the cause is noticeable, and the treatment is mostly rest and management of the cause of pain. The psychological effect is the hope that the treatment will be successful and the pain will be over soon. It is possible that anxiety and apprehension may appear within the period of acute pain, for example, the fear of surgery and anesthesia that could form part of the treatment.

Practical consequences

As part of preparation for surgery, interventions such as relaxation techniques, a good explanation of the procedure and possible outcomes, and an optimistic outlook have been proven to be helpful. It is possible to reduce postoperative pain experience through such knowledge. Knowledge about the treatment can often reduce one's anxiety. Relaxation techniques can minimize psychological agitation patterns such as a high heart rate and inner restlessness.

What can we use for cancer and HIV/AIDS pain?

In the treatment of chronic pain, it is important to differentiate between benign and malignant pain. However, for cancer pain as well as for pain caused by HIV, there is the same relationship, in the framework of the biopsychosocial concept, as with other chronic pain models.

The prevalence of comorbidities such as anxiety and depression is common, as in other pain syndromes, and should be taken into consideration and treated. Often these disorders are ignored. Additionally, patients have to cope with pain due to a tumor, as well as pain that may arise during the course of the treatment. Overcoming the consequences of chronic diseases differs significantly in developed countries in contrast to developing countries. Caring for the ill person is often very difficult for the family because of financial problems. A difficult financial situation and poor access to medical, nursing, or other social services can affect the process of healing negatively. At the time of diagnosis, there is often a loss of control and helplessness in the face of possible physical disfigurement, accompanying pain, and possible financial implications for adequate treatment, not least the fear and uncertainty surrounding the prospect of an untimely death. Additionally, questions of guilt can lead to psychological strain because of trying to own up to one's own responsibility for a disease, for example: "It's my own fault that I have a tumor, because I have been smoking too much," or "Being infected by HIV is because of my irresponsible sex life."

Practical consequences

Adequate counseling and emotional support should be integrated in the provision of health care for these

patients. Good communication and explanations about the existing possibilities of therapy and about the prognosis can reduce fears and helplessness, and enable patients to cope better with the disease and its accompanying challenges. Particularly in Kenya, religious support has been reported as being helpful.

What are the options in chronic noncancer pain?

In the context of chronic abdominal pain, which is quite often difficult for the patient to locate and come to terms with, often together with the threat of incurability and looming death. Commonly, the physician wonders, "Why is the patient coming now?" Possible reasons for the patient can be a fear of serious diseases after deaths in the family, psychological comorbidities, emotional distress because of sexual abuse, but also trouble within the actual context of life and poor coping strategies, which may lead to an increase in the pain.

Practical consequences

Indicators of stress mentioned above should be looked for, which can affect the development and maintenance of pain. Therapeutic interventions including a good explanation of the disease, continuing psychological support, advice on balanced nutrition, and so on should be added over time.

How can we tackle chronic headache?

Most headaches have no organic cause. Very often we find interactions between headache and dysfunctional patterns of the muscles, such as increased tension, which can then, by itself, become a trigger for headache. Social stress factors such as excessive demands at the workplace or poor coping strategies with stress, can make headaches intense and chronic.

Practical consequences

Important in the treatment of headache is describing to the patient that stress can lead to an increase in the intensity and frequency of the headache. The most important psychological interventions are education in coping skills and in the importance of stress management, and the reduction of hyperactivity with lessons in cognitive behavioral therapy, relaxation techniques, and so on.

What can we use for chronic back pain?

Chronic back pain, in most cases, is musculoskeletal in origin, accompanied by poor coping skills along with other "yellow flags." A special problem in coping with back pain is the fact that sometimes no sufficient explanation can be given to the patient regarding the cause and origin of the pain. For example, a diagnosis of "nonspecific back pain" leads to an extreme uncertainty on the part of the patient, often leading to increased fear of serious pathology and the desire for repeated diagnostic procedures. Often there is an iatrogenic component when repeated investigations are ordered—partly because the patient insists on it, and partly because the physician may be uncertain: "Is there a tumor or a serious disk prolapse causing the pain?" There may be a reluctance "to miss something."

Practical consequences

A comprehensive compilation of all available findings, as well as discussion with colleagues about previous diagnosis and treatment, can be useful to get a complete picture about the patient. The patient should be advised against unnecessary and often very expensive invasive diagnostic procedures.

After considering all possible factors including psychiatric comorbidity or risks of chronification, a treatment plan can be developed. Good models on interactions, for example between depression and chronic pain, can help the patient to cope successfully with pain.

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Websites

www. immpact.org (Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)

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Guide to Pain Management in Low-Resource Settings

Chapter 47
Insights from Clinical Physiology

Rolf-Detlef Treede

Insights on acute pain

Aside from alleviating suffering, one of the major aims of postoperative pain management is to facilitate and speed up recovery, reestablish mobility, and ultimately favor a rapid discharge. One of the fundamental mechanisms in the nociceptive system is interfering with these aims is called *central sensitization*. Sensitization is a basic learning mechanism that describes an increased neural response when stimuli of constant intensity are simply repeated. (Its counterpart, habituation, a decrease in response upon repetitive stimulation, is less prominent in the nociceptive system). In central sensitization, the increased neural response is due to enhanced efficacy of the synaptic connections within the nociceptive system. Central sensitization mostly enhances pain to *mechanical stimuli*, whereas peripheral sensitization almost exclusively increases heat pain sensitivity. This makes central sensitization highly relevant in the postoperative setting.

When sensitization occurs in the nociceptive system, the patient perceives more pain in response to relatively mild stimuli such as moving around in bed or coughing. As a consequence, the *patient will move less and breathe less deeply*, in order to titrate the pain down to a tolerable level. Fortunately, effective pain treatment (e.g., with opioids or local anesthesia) also reduces central sensitization.

Practical consequences

Ask each patient about movement-evoked pain, and treat with effective, multimodal analgesics.

Insights on cancer pain

One of the most painful conditions in a patient with advanced cancer is bone metastasis. This well-known clinical reality is in conflict with traditional basic science teaching: according to standard textbooks, only the periosteum is innervated, but not the bone itself. If this were true, only large bone metastases that extend into the periosteum should be painful. But experience teaches otherwise: fortunately, painful bone metastases usually have not yet destroyed the compacta. Thus, when they are treated causally by radiation or chemotherapy, the stability of the bone is still preserved. It is also well known that aspiration of bone marrow is very painful, in spite of local anesthesia of the periosteum.

Thus, the bone's interior structures are densely innervated by nociceptive afferents, probably very similar to the innervation of teeth. Only recently have anatomists been able to demonstrate nociceptive nerve fibres within the bone using the marker CGRP (calcitonin gene-related peptide), where they appear to have contacts with both the bone trabecula and the osteoclasts. Physiologically, there is also some recent evidence that

the spinal cord receives nociceptive input from within the bone.

Practical consequences

Tissue damage restricted to the bone marrow can be a source of intense nociceptive input. Hence, patients with pain in such conditions do need treatment. However, treatment here does not necessarily have to be by analgesics; instead, radiation or chemotherapy may actually eliminate the cause of this pain.

Insights on neuropathic pain

There has been a long-standing debate on how to define "neuropathic pain." The concept, however, is quite simple: consider the nociceptive system as the body's alarm system. Pain is perceived when this system rings an alarm. As with any other alarm system, there are two possible ways the alarm can be activated: (a) it is a true alarm signaling an actual event; (b) it is a false alarm, caused by a defect in the alarm system. The usual pain after tissue damage is a case of true alarm by the nociceptive system. In case of neuropathic pain, it is a false alarm caused by some kind of damage to the nociceptive system.

Practical consequences

If a patient reports pain in a part of the body that is not damaged, consider neuropathic pain as a possibility. To verify this clinical hypothesis, evidence should be sought to demonstrate the underlying damage to the nociceptive system. The patient's history may reveal a possible etiology such as diabetes, peripheral nerve damage, HIV, or previous shingles. The sensory examination is of utmost importance: the distribution of pain and the distribution of negative or positive sensory signs should closely match. Sensory testing must include either a painful test stimulus such as pinprick, or a thermal stimulus such as contact with a cold object (thermoreceptive pathways are very similar to nociceptive pathways and hence are an excellent surrogate). To be able to diagnose neuropathic pain correctly, pain specialists need to have some level of neurological training.

Insights on chronic pain

Migraine is a frequent headache syndrome that has a major impact on quality of life. In spite of major research, its pathophysiology is still not fully understood. In the aura phase, many patients are hypersensitive to external stimuli such as light, sound, smell, or touch. This increased sensitivity appears to be related to a deficiency in habituation. For example, evoked cerebral potential studies have shown that the normal response decrement upon repetitive application of visual stimuli is absent in migraine sufferers. More recently, such deficits have also been shown for pain habituation, by using laser-evoked potentials (here an infrared laser applies very brief heat pulses of a few milliseconds' duration). There is some evidence that deficits in pain habituation occur in other chronic pain conditions as well, such as in cardiac syndrome X.

Practical consequences

Currently none, but in the future it may be possible to alleviate chronic pain conditions by treatment modalities that enhance habituation without being directly analgesic.

Insights on pain in infants and children

Skin innervation occurs at about 7–15 weeks' gestation, and simple reflex arcs appear as early as 8 weeks. Thalamocortical connections are established much later (from week 20 onwards), and EEG signals and somatosensory evoked potentials start to be present at week 29–30. These electrical brain signals suggest that conscious perceptions such as pain may be present before birth. However, the nervous system is immature at birth and undergoes substantial changes postnatally. Immediately after birth, cutaneous withdrawal reflexes are lively and occur with very low threshold, such as mild touch by a pointed object. GABAergic synapses are excitatory at early developmental stages and become inhibitory only with maturation. After birth, reflexes decrease, whereas cortical stimulus responses increase (detectable by near-infrared spectroscopy, for example). Myelination in peripheral nerves is complete within about 1 year, but it takes 5–8 years in the central nervous system. As soon as a child is able to understand verbal instructions, faces pain scales can be used in a similar fashion as visual analogue scales in adults.

Practical consequences

It is difficult to judge the level of pain and discomfort in infants due to their strong reflex responses that may or may not run parallel to conscious perception. To be on the safe side, adequate anesthesia and analgesia

are considered the standard of care at all ages. Special regimens apply, and most medications are being used off-label.

Insights on pain in old age and dementia

Pain thresholds and pain-evoked brain potentials have been studied in healthy volunteers up to the age of 100 years. Pain thresholds and evoked potential latencies slightly increase and evoked potential amplitudes decrease at ages above 80 years. In many cases, however, verbal communication skills may deteriorate in old age, with large individual variations. In this situation, pain assessment becomes difficult. For demented people, special observer-based scales have been developed and validated to allow assessment of pain and suffering in this vulnerable group. There is some evidence that the placebo effect is less efficacious in demented people. Decline in liver and kidney function, on the other hand, makes dosage adjustments necessary for many medications.

Practical consequences

Many people maintain normal functions of their nociceptive system way into old age. When dementia is present, pain assessment relies increasingly on the observation of pain-related behavior. It is currently assumed that the level of pain in demented patients is underestimated substantially.

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Chapter 48
Herbal and Other Supplements

Joel Gagnier

What is the definition of natural health products?

Natural health products include vitamins, minerals, herbal medicines, homeopathics and other naturally derived substances (e.g., glucosamine, bee pollen) to prevent or treat various health conditions.

In the developing world, it would be advisable to consult local elders or healers to determine local plants or foods that may be used. You should get instructions on how to use them safely. Traditional knowledge from a respected elder, healer, or tribal chief may be reliable information. Always think about the risk/benefit ratio, since natural health products might contain "unnatural" ingredients, such as heavy metals or other contaminants. Therefore, the use of natural health products depends on mutual trust between the caregiver and the healer, since there are few evidence-based data and standardized products available.

It is advisable to seek cooperation between the "official" and "unofficial" medical sector, both to broaden therapeutic options and to avoid counterproductive interactions. Some initiatives have undertaken this task. For example, in 1998 a task force was set up by the Ministry of Health in Ghana to identify the credible National Healer Associations. Six such healer associations were identified. These associations came together to form the nucleus of the Ghana Federation of Traditional Medicine Practitioners' Associations (GHAFTRAM). Other activities followed, including international conferences and research exchanges.

What supplements are best for acute pain?

Surgical procedures and acute trauma may be addressed by several natural health products. For example, the homeopathic remedies Arnica and Hypericum may be useful prior to and after surgery. Arnica is particularly useful for decreasing pain, bruising discoloration, and discomfort in the patient. Homeopathic Hypericum is very useful to heal incisions and eliminate pain. These remedies can be given orally at 200C potencies every 2–4 hours on the day prior to surgery and after surgery until the incision is healed. For acute trauma to muscles, ligaments, and tendons, topical creams or ointments containing *Harpagophytum procumbens* (Devil's claw), *Capsicum frutescens* (cayenne), homeopathic Arnica, or methylsulfonylmethane (MSM) may be applied 3–4 times per day on the affected site as long as the skin is intact.

What supplements are best for neuropathic pain?

Peripheral neuralgias, if caused by malnutrition, may be treated by supplementation with vitamins. Vitamins E, B_1, B_3, B_6, and B_{12} are essential for adequate nerve

function. A diet with regular fruit and vegetable intake would include these vitamins, or alternatively a simple multivitamin mineral formula would be sufficient. In patients with diabetic neuropathy, besides adequately controlling blood sugar, vitamin B_6 at 150 mg or vitamin E at 800 IU per day may be effective. These supplements may be used together. A simple dietary intervention to aid in blood sugar control is the regular consumption of beans and legumes.

What supplements are best for chronic pain?

Chronic unspecified back pain may be treated with oral *Harpagophytum procumbens* (Devil's claw) at 2000–3000 mg per day, delivering 50–100 mg of the active constituent harpagoside; oral willow bark (*Salix alba, Salix daphnoides,* or *Salix purpurea)* at 1200 mg per day, delivering 120–240 mg of the active constituent salicin; or topical capsicum cream. Dysmenorrhea may be treated with oral calcium at 1000–1500 mg per day, magnesium at 300–400 mg per day, vitamin B6 at 100 mg per day, vitamin E at 400–800 IU per day, or *Vitex agnus-castus* (chaste berry) at 20–40 mg per day. For migraine headaches the following are effective: vitamin B_2 400 mg per day, *Tanacetum parthenium* (feverfew) 100 mg per day, magnesium 500 mg per day, or *Petasites hybridus* (Butterbur) 150 mg per day. These can be used individually or in combination. Rheumatic pain in the form of osteoarthritis (OA) may be successfully treated with oral glucosamine sulfate at 1500 mg per day together with oral chondroitin sulfate at 1200 mg per day; oral unsaponifiable fractions of avocado and soybean oils at 300 mg per day; oral *Harpagophytum procumbens* (Devil's claw) 2400 mg per day; and topical creams containing a combination of camphor, glucosamine sulfate, and chondroitin sulfate. Mild to moderate OA may respond to a treatment starting with glucosamine sulfate (1500 mg/day) and chondroitin sulfate (1200 mg per day) for 4–6 weeks, and if there is a limited effect adding oral unsaponifiable fractions of avocado and soybean oils and Devil's claw. Rheumatoid arthritis may be treated with oral borage seed oil at 1–1.5 grams per day, oral fish oil providing eicosapentaenoic acid (EPA) and docosahexanoic acid (DHA) at 2 grams/day, oral vitamin E at 800 IU per day, or oral *Tripterygium wilfordii* (thunder god vine) at 200–600 mg per day.

What supplements are best for special therapeutic situations?

Dementia of the Alzheimer's type may be effectively treated with oral *Ginkgo biloba* (Ginkgo) at 120–240 mg per day, oral *Melissa officinalis* (lemon balm) at 60 drops of a 45% alcohol extract, oral *Salvia officinalis* (sage) at 1000 mg per day, or oral vitamin E at 2000 IU per day. These supplements may be used in isolation or in combination. It may take 3–4 months before any effects of these interventions are seen.

Chapter 49
Profiles, Doses, and Side Effects of Drugs Used in Pain Management

Barbara Schlisio

The following drug list is a selection of commonly used drugs for pain management. The selection reflects recommendations of the "Essential Drug List for Cancer" from Makarere University and the health ministry in Uganda for the treatment of cancer patients, which appear to be a reasonable drug selection for treatment of the most common pain syndromes encountered by nonspecialists in a low-resource setting.

This overview explains the mode of action as well as typical side effects of drugs. "Typical side effects" means that other side effects have been described, but I have selected from the lengthy lists of side effects mentioned in desk references the ones that are most important for the therapist and the patient to know about.

Pharmacological therapy in pain management is often selected because of positive empirical knowledge, because most of the time there are no controlled studies of high methodological quality. This means that safety is an issue to be considered when selecting a drug: the possible positive effects must always be balanced against possible side effects. A good recommendation would be to think, when prescribing a drug, whether you would prefer the same drug when in a comparable situation, since it is your decision to select pharmacological treatment.

Pharmacological treatment should be explained thoroughly to the patient, and "informed consent" should be obtained in the same way as for a surgical intervention. A valuable tool to avoid misunderstandings and "incompliance" by the patient is the use of a simple (makeshift) "information sheet" to be given to patients when they leave the office with their prescription.

Here is an example of an information sheet to give to patients:

Name of Drug	How to Take It	What Is It For ?	Important Information
Morphine	1 tablet of 20 mg: 6–12–18–24 o'clock	Strong painkiller for continuous pain control	Nausea and tiredness are possible the first week. Never change the dose on your own!
Morphine	1 tablet of 10 mg as needed	Strong painkiller to be taken if pain increases	See above. Minimum time between extra morphine tablets: 30 minutes.
Metoclopramide	40 droplets: 6–12–18–24 o'clock	Prevents nausea caused by morphine	Should be taken for 10 days. After that, try to go without it.
Carbamazepine	1 tablet of 200 mg: 8–16–24 o'clock	Helps against shooting nerve pain	Dizziness and tiredness in the first few days or weeks. Remember to come to the office to have a blood sample taken in one week.

Nonopioid analgesics

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Despite their chemically differences, NSAIDs have a common mode of action, the inhibition of prostaglandin synthesis by the cyclooxygenase isoenzymes COX-1–3. Remember that prostaglandins sensitize peripheral nociceptor nerve endings to mechanically and other stimuli, thus provoking a decreased pain threshold. Centrally active prostaglandins enhance the perception and transmission of peripheral pain signals. But NSAIDs do interfere with a number of other physiological functions as well, which explains most of their side effects. These unwanted effects include the release of gastric acid, the aggregation of platelets, the activity of vascular endothelium, the initiation of labor, and an influence on the ductus arteriosus of neonates.

NSAIDs are usually indicated for the treatment of acute or chronic pain conditions, especially where inflammation is present. In pain of low to moderate intensity, they may give sufficient pain control as a single therapy, but in moderate to severe pain they should only be used in combination with opioids. In the postoperative situation it makes especially good sense to combine opioids and NSAIDs because the reduction in the dose of opioids will reduce any opioid side effects. Different NSAIDs are available in different countries. Diclofenac and ibuprofen are used most frequently, but other NSAIDs have been shown to be comparable. To avoid unintended drug accumulation, certain long-acting NSAIDs should be avoided (e.g., piroxicam), and to avoid gastrointestinal and renal side-effects, all NSAIDs should be used short-term only. Most NSAIDs cause ulcers and other upper gastric symptoms such as dyspepsia and epigastric pain or discomfort if used long-term (>7–10 days). A less common but serious side effect is anaphylactic reaction with development of severe bronchospasm and/or cardiovascular depression. Renal failure is a more frequent and serious complication and is mostly associated with long-term use, especially in patients with a history of previous renal impairment and hypovolemia.

Note the contraindications: gastrointestinal ulceration, hemophilia, hypersensitivity to aspirin, young children because of the possibility of developing Reye's syndrome, pregnancy especially the last trimester, breastfeeding, and advanced renal impairment.

The standard dose of diclofenac is 50–75 mg t.i.d. (three times a day), of ibuprofen 400–800 mg t.i.d., and of aspirin 500–1000 mg q.i.d. (four times a day).

Acetaminophen (paracetamol)

The exact mechanism of action is unclear. Acetaminophen might inhibit a central cyclooxygenase isoenzyme (COX-3) and act as a central and spinal substance P inhibitor. Even though acetaminophen is classified as an antipyretic drug, it has mild anti-inflammatory properties. Acetaminophen is a safe alternative medication when NSAIDs are contraindicated or not well tolerated by the patient.

Acetaminophen is well tolerated in therapeutic doses, but it is hepatotoxic at high doses (approximately 6–15 g per day), when its metabolites can produce fatal liver necrosis. Alcohol-dependent and undernourished patients are at especially high risk. Renal tubular necrosis may also occur. However, and rightly so, acetaminophen is often used for minor to moderate pain postoperatively, as well as in headache and cancer patients, because it is free of any gastrointestinal and renal side effects when the dose recommendations are observed.

Note the contraindications: severe hepatic and renal impairment, alcohol-dependent patients, undernourished patients, and patients with glucose 6-phosphate dehydrogenase deficiency.

The standard dose of paracetamol is 500–1000 mg t.i.d., and postoperatively the initial oral or rectal dose should be 2000 mg.

Dipyrone (metamizol)

Dipyrone is supposed to be a central cyclooxygenase inhibitor. It acts as an antipyretic. It differs from other nonsteroid drugs in respect to its spasmolytic effects, since dipyrone inhibits the release of intracellular calcium. The benefits of dipyrone are that you do not have to worry about renal function and gastrointestinal side effects and that it is generally cheap. Like acetaminophen, dipyrone may also be used for long-term treatment. Its indications are acute and chronic pain of mild to moderate intensity, as well as colicky pain.

A number of patients will complain about sweating, for which there is no tolerance. The topic of idiosyncratic drug reactions has been reopened after some Scandinavian publications, and a number of countries have therefore made dipyrone unavailable. But several countries, including Germany, Spain, and most Latin American countries, consider the risk low, compared to

the side effects of NSAIDs. Rapid intravenous application may be associated with hypotension, which should not be mistaken for a allergic response, which in fact occurs only rarely. Contraindications include porphyria, glucose-6-phosphate dehydrogenase deficiency, pregnancy (especially the last trimester), and breastfeeding.

The standard dose of dipyrone is 500–1000 mg q.i.d.

Opioid analgesics

For legal reasons, opioids may be classified into weak and strong ones. The World Health Organization (WHO) three-step ladder for cancer pain management also follows this distinction, advocating first the use of a "weak" opioid (e.g., tramadol or codeine) followed by a "strong" opioid (e.g., morphine or hydromorphone). For clinical practice, this distinction is probably irrelevant, because there are no data indicating that equianalgesic doses of "weak" and "strong" opioids have a different side-effect or effectivity profile. Therefore, opioid therapy may be started with low doses of a "strong" opioid, if "weak" opioids are not available.

Opioids may also be classified according to their receptor affinity. The analgesic effect of opioids is mediated through binding to μ, κ, and δ receptors. With the exception of pentazocine, tramadol, and buprenorphine, all commonly available opioids are more or less pure μ-agonists with a linear dose-effect function. Tramadol, pentazocine, and buprenorphine on the other hand have a ceiling effect, and they bind to different or additional receptors. Opioid receptors are found in several areas of the brain, the spinal cord and—contrary to common belief—in the peripheral tissues, especially if inflammation is present. The analgesic effect is a result of the reduced presynaptic opening of calcium channels and glutamate liberation as well as the increase of postsynaptic potassium outflow and hyperpolarization of the cell membrane, which reduces excitability.

Treatment with opioids involves a balance between sufficient analgesia and the typical side effects. Luckily, the most frequent side effects—nausea, respiratory depression, and sedation—diminish over time because of tolerance, and constipation may be prophylactically treated with good results.

The best clinical indications for opioids are the symptomatic treatment of moderate to severe acute pain, especially postoperative pain and cancer pain. Neuropathic pain may be an indication, too, especially in HIV/AIDS patients. Unfortunately, chronic noncancer pain, like chronic nonspecific back pain or headache, is only rarely a good indication for opioids. In palliative care, opioids may also be used to control dyspnea very effectively.

Drug abuse with opioids is extremely rare in patients who do not have a history of alcohol, benzodiazepine, or opioid abuse! The reason is that when opioids are used for control of pain, the regular dosing avoids major changes in serum levels, therefore preventing the activation of our dopaminergic reward system (as opposed to drug addicts experiencing a "high" after sudden blood level increases after the intravenous push-injection of an opioid and a "craving" in the time interval before the next injection). Do not confuse drug addiction with physical dependence. As a matter of fact, all opioids cause physical dependence (as with a number of other classes of drugs, such as beta blockers or anticonvulsants), and patients will develop symptoms of withdrawal if they discontinue opioids without tapering down the dose.

"Weak" opioids

According to the three-step ladder of the WHO for cancer pain, weak opioids should be used first, if nonopioid analgesics are insufficient to control the pain. Tramadol, codeine, and dihydrocodeine are examples of this group. Tramadol has affinity to the μ-opioid-receptor, as well as reuptake inhibiting activities for norepinephrine and serotonin in the descending inhibitory nervous system. Tramadol is also thought to have some NMDA-receptor antagonist effects. Weak opioids are sometimes available in fixed combinations with NSAIDs or acetaminophen/paracetamol.

Weak opioids, unlike strong opioids, have a ceiling effect, meaning that there is a maximum dose above which there is no further increase of analgesia. The risk for respiratory depression is very low with weak opioids. Depending on the region of the world where tramadol or codeine are used, certain genetic polymorphisms may exist that can result in the need for unexpectedly high or low doses. For example, in Eastern Asia and Northern Africa, hepatic metabolism of codeine and tramadol may be impaired in a considerable proportion of the population. Otherwise, the drugs are considered very safe, even in patients with impaired organ function.

The standard dose for tramadol is 50 to 100 mg t.i.d., which is sufficient for postoperative analgesia after most surgical interventions. Tramadol is also available in an intravenous application formulation.

"Strong" opioids

Strong opioids are the medication of the first choice in severe pain in cancer and postoperative pain as well as in cancer-related dyspnea. They may also work to a lesser extent in neuropathic pain, but they are generally not indicated for use in chronic nonspecific pain, such as headache, chronic back pain, fibromyalgia, or chronic irritable bowel syndrome. Do not hesitate to use strong opioids early enough in cancer pain, because they can improve the patient's quality of life remarkably. There is no maximum dose for morphine and its derivates. As a result of progress of the illness, patients often—but not always—require an increase of the dose over the course of the disease. Dose increases do not mean tolerance or addiction, but reflect progressive tissue damage most of the time. Other causes of increasing dose demands are a change in pain quality (development of neuropathic pain instead of nociceptive pain) or concomitant anxiety or depressive disorders. The other causes mentioned have to be diagnosed correctly to be able to treat them specifically with coanalgesics or nonpharmacological interventions.

Nausea and vomiting, drowsiness, dry mouth, miosis, and constipation occur very frequently in patients taking strong opioids. If nausea and vomiting persist, or delirious symptoms develop, a change to another opioid ("opioid rotation") usually controls the problem. Constipation will occur in all opioids and requires therefore constant prophylaxis, while antiemetic drugs should be used prophylactically for only a short period of time (7–10 days), until tolerance has developed. Consider, and explain to the patient, that opioids are not toxic to any organ. Hence there are no contraindications, except in patients with a history of allergic reactions (very rare). Other contraindications such as chronic obstructive pulmonary disease or renal function impairment do not mean that opioids should be withheld, but that their dose must be titrated slowly and carefully to effect.

Strong opioids may even be used in pregnancy, but close cooperation with the pediatrician or neonatologist is necessary to cope with respiratory depression and/or opioid dependency in the neonate.

Dependency occurs in most patients when more than about 100 mg of morphine is given daily for more than 3 weeks. To avoid withdrawal syndrome, the patient must be instructed never to just stop taking the opioid medication but to follow the physician's instructions. A safe protocol would be to taper down the dose in several steps over about 10 days, which safely prevents withdrawal syndromes (tearing, restlessness, tachycardia, and hypertension, among other symptoms).

The starting dose for morphine is approximately 20–40 mg orally per day, four times a day (q.i.d.). If slow-release formulations are available, once- or twice-daily doses may be chosen. When only immediate-release and slow-release formulations are available, a fixed schedule of opioid medication should be combined with an on-demand dose, which should be approximately 10–20% of the cumulative daily opioid dose. For example, in a patient taking 20 mg morphine q.i.d. (80 mg daily consumption), 10 mg of morphine should be allowed as an extra dose to be taken on demand in situations of increased pain ("breakthrough pain"). The patient should observe a minimum time interval of 30 to 45 minutes before using another demand dose. According to the number of daily demand doses, the caregiver may change the constant basal dose of morphine. In a patient needing no demand doses at all, the basal dose may be reduced by 25%, in a patient requiring one to four doses the scheme should stay unchanged, and in a patient requiring more than four demand doses the basal opioid dose should be increased. For example, in a patient with a basal morphine dose of 4 times 20 mg of morphine requiring on average daily 6 times 10 mg of morphine on demand, the basal dose of morphine should be increased to 4 times 30 mg (and the demand dose should be increased to 20 mg).

The same approach should be used for the treatment of dyspnea (even in patients not suffering from pain). Opioids decrease the "breathing force" by a rightward shift of the CO_2 response curve, effectively reducing the subjective "air hunger."

All pure μ-opioid agonists are interchangeable and combinable and differ only in their subjective side-effect profile (which is not predictable individually) and in their relative potency (not their absolute potency). The equianalgesic doses for 10 mg morphine orally are 2 mg hydromorphone, 5 mg oxycodone, 100 mg of tramadol, and 1.5 mg of levomethadone.

The equianalgesic doses of all opioids depending on the application route must be known. In morphine, these are:

Equianalgesic doses of morphine	
Intravenous (i.v.) Subcutaneous (s.c.) Intramuscular (i.m.)	10 mg
Oral	30 mg
Epidural	2–3 mg
Intraspinal	0.1–0.3 mg

Transdermal opioids

Two patches are now available for the delivery of opioids—the fentanyl patch and the buprenorphine patch. These drugs are strongly lipophilic, allowing good passage through the skin into the circulation and avoiding first-pass metabolism in the liver. Consider that analgesia and side- effect profile do not change by using the transdermal route. Therefore, only patients with swallowing problems or recurrent vomiting would benefit from this route of application. If transdermal systems are used, remember that they are indicated only in patients with stable opioid requirements and that it takes around half to one day for the patch to produce a steady state of opioid delivery to the patient (and the same time for blood levels to decrease if the patch is taken off). In conclusion, the vast majority of patients in cancer and palliative care may be treated well with opioids without the use of transdermal systems (which are also considerably more expensive!).

Adjuvant medications for opioid-related side effects

Nausea, vomiting, and constipation associated with opioids need a concomitant "adjuvant" medication. Without one, your patients' compliance will be low! For the first week of opioid therapy, metoclopramide 10 to 30 mg q.i.d. should always accompany the opioid. As mentioned above, earlier tolerance to the nauseating side effects of opioids will then develop. Sedation must to be explained to the patient, since there is no effective adjuvant medication to counteract it. For constipation, a constant prophylactic laxative therapy must be initiated immediately with the start of an opioid. Milk sugar or bisacodyl are good choices. See the chapter on constipation for further details on this therapeutic problem.

Coanalgesics

Coanalgesics are drugs that were originally developed for purposes other than analgesia, but were then found to be useful in certain pain states. Their use is common in neuropathic pain, where NSAIDs and antipyretics are ineffective most of the time and opioids often fail to be effective.

Although a number of substances have shown to have "coanalgesic" properties (among others: capsaicin, mexiletine, amantadine, ketamine, and cannabis), only antidepressants, anticonvulsants, and steroids are used regularly and are most likely to be available in low-resource settings. The use of coanalgesics necessitates knowledge of how to balance benefits and risks and avoid side serious side effects.

As with opioids the doses of most coanalgesics have to be titrated to the effect, meaning, that the dose recommendations for their original indications cannot be transferred to the indication "pain". As always when treating pain, use thorough patient education to gain good patient compliance and adjust and readjust doses and drug selection to gain the best results for your patients. Don´t forget to give a message of hope to your patient but be honest with him and set realistic goals: coanalgesics will not take away the pain, but will only be able to give some relief!

Anticonvulsants

They reduce neuronal excitability and suppress paroxysmal discharge of the neurons by stabilizing neural membranes. Anticonvulsants work by interacting with different mechanisms, e.g., the voltage dependent sodium channel or by the high voltage calcium channels. Anticonvulsants of the sodium channel blocking type (carbamazepine, oxcarbazepine or lamotrigine) show best results in attack like shooting pain, e.g., in patients, where the cancer has infiltrated nerve plexus or in trigeminal neuralgia. Anticonvulsants of the calcium channel blocking type (gabapentin, pregabalin) are indicated above all for continuous burning pain, e.g., in patients with polyneuropathies or postherpetic neuralgia. The latter seem to have a synergistic effect on the calcium channels with opioids. Phenytoin can be used as a "rescue" substance for severe and therapy resistant neuropathic pain. All anticonvulsants should be titrated according to the rule "start low, go slow". Recommended dose ranges for the most common anticonvulsants in pain management are:

Substance	Starting Dose	Maximum Dose	Remarks
Carbamazepine	3 × 100 mg	1600 mg/day	A low dose is often effective
Oxcarbazepine	3 × 150 mg	2250 mg/day	There is less dizziness and sedation
Gabapentin	3 × 100–300 mg	3600 mg/day	A high dose is often required
Pregabalin	2 × 25 mg	300 mg/day	Has anxiolytic effects
Phenytoin	1 × 100 mg	400 mg/day	Avoid long-term use

All anticonvulsants produce drowsiness and dizziness, although this problem can be minimized by increasing the dose slowly, every 4 to 8 days depending on the individual side-effect tolerance. In carbamazepine and oxcarbazepine, regular blood tests (e.g., weekly for 4 weeks, then monthly for 3 months, and then once every 3 months) are necessary to identify patients with elevation of liver enzymes, idiosyncratic drug reactions, and hyponatremia. Idiosyncratic drug reactions denote a non-immunological hypersensitivity to a substance, without any connection to pharmacological toxicity. The medication has to be stopped in all cases of idiosyncratic reaction, if liver transaminases are above ca. 200 and if sodium is below 125. The same applies to phenytoin (with the exception of the danger of developing hyponatremia), for which a normal ECG (look especially for AV-conduction abnormalities) should also be a prerequisite. For gabapentin and pregabalin, no blood tests or ECG controls are necessary. Contraindications for all anticonvulsants include porphyria, lactation, myasthenia gravis, glaucoma, and chronic renal or hepatic failure.

Antidepressants

Antidepressants were the first coanalgesics used after it was found that they effectively reduced pain in polyneuropathy, even in patients who were not depressed. They have been found to be effective in the treatment of constant burning neuropathic pain of different origins. Furthermore, antidepressants are also useful in treating tension type headache and as a prophylactic treatment in migraine headache. Contrary to common belief, there is no "general pain-distancing" effect, so antidepressants should only be used for the indications named above. As a general rule, the "classical" tricyclic antidepressants are the most effective in pain management. Although the best evidence exists for amitriptyline, all tricyclic antidepressants are considered equally effective. The newer and more tolerable selective serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are less potent or not effective, unfortunately. The only SNRIs considered to be effective in the latest meta-analysis are venlafaxine and duloxetine.

Antidepressants induce analgesia by increasing the neurotransmitters serotonin and norepinephrine in the descending inhibitory nervous system (e.g., in the periaqueductal gray). Additionally, antidepressants modulate the opioid system in the central nervous system. Some side effects can be used for the benefit of the patient, such as the sedating effect of amitriptyline for better sleep and the anxiolytic effect of clomipramine for relaxation. If the patient is in an advanced stage of disease with impaired general condition or comorbidities, nortriptyline and desipramine seem to be safer alternatives to use within the class of tricyclic antidepressants.

As with anticonvulsants, the effective dose has to be titrated individually using the rule "start low, go slow" to avoid debilitating side effects. All tricyclic antidepressants should be started with a dose of 10 mg at nighttime, and the dose should be increased every 4–8 days by only 10–25 mg daily.

Elderly patients should not be medicated with tricyclic antidepressants because of multiple drug interactions and an increased rate of falls. For all other patients it has to be remembered that the analgesic effect often starts after a delay, and therefore the caregiver as well as the patient have to have some patience before deciding whether the treatment is effective.

The most frequent side effects are due to the anticholinergic properties of antidepressants (mostly of the tricyclic class) via the muscarinic receptors. Such anticholinergic effects include xerostomia (dry mouth), constipation, urinary retention, blurred vision and impaired accommodation, tachycardia, and slowed gastric emptying. Explain to patients that they are receiving the medication for pain, since they might read the package explanation, where "depression" is the only indication. Also let the patient know that sedation and most other side effects usually wear off over several weeks. Explain that these medications relieve pain but do not resolve it.

Because tricyclic antidepressants may impair liver function, it is advisable to check the liver enzymes regularly (e.g., once a month for 3 months and than once every 3 months). Before initiating tricyclic antidepressant medication, check the ECG for major AV node irregularities and polytope extrasystoles.

Up to 20% of cancer patients develop episodes of depression, and in this case antidepressants with the lowest side effects should be used (SNRIs and SSRIs).

Steroids

Steroids are widely used in cancer pain therapy, especially in patients with an advanced stage of disease. These agents reduce perineural edema and may inhibit spontaneous activity in excitable, damaged nerves due to cancerous infiltration or compression of nerval structures. Because of their anti-inflammatory effects, steroids may be also used in chronic inflammatory diseases, such as rheumatoid arthritis. In cancer patients the drug of choice is dexamethasone, which provides only glucocorticoid properties, causing less fluid retention and potassium loss as compared to hydrocortisone or prednisolone. There is no evidence-based dosing scheme, but in acute pain exacerbation because of massive cancer progression, a common approach would be to use a loading dose of approximately 24 mg the first day and then reduce the dose subsequently over the following days to a maintenance dose of 2 mg daily.

Side effects can prove to be beneficial for the patient, such as euphoria and an increased appetite in cachectic patients. "Negative" uncommon side effects may include psychotic episodes and myopathies. Other typical side effects such as osteoporosis, skin thinning, diabetes, and adrenal suppression are of less importance in the target patient with limited life expectancy. To limit the risk of gastric ulcers, do not combine NSAIDs and steroids, and do not use steroids unless critical in the noncancer patient.

Neuroleptics

Neuroleptics are psychoactive drugs that are commonly used to treat psychotic episodes and nausea. Patients with advanced cancer often suffer from delirium. Do not underestimate the distress for the patient and family in the presence of delirium. Try to identify the reason for the delirium. Most of the time it is the first sign of infection, renal failure, dehydration, or electrolyte imbalances. In rare instances, it may also be a side effect of opioid therapy (in which case, opioid rotation will solve the problem). Always identify and treat the underlying cause along with giving symptomatic treatment with neuroleptics (titrate in increments of 2.5 mg to effect with haloperidol with a "normal" daily dose of 2.5 to 5 mg t.i.d.). In advanced cancer patients, delirium may also be a sign of reaching the terminal stage ("terminal disorientation"). Even at the final stage of illness, delirium should be treated, to reduce the stress of the patient and family.

Neuroleptics (like benzodiazepines) have no analgesic efficacy and therefore should never be used for the indication of pain. Pain needs analgesics and not sedation, with the exception of terminal sedation, when all available alternatives for pain control fail.

Note also that neuroleptics are potent blockers of D_2 receptors in the dopamine pathways of the brain. Therefore, they have direct effects on opioid-induced nausea and are very valuable antiemetics (a dose of 0.5 to 1 mg of haloperidol t.i.d. is sufficient for that purpose and is without psychomimetic effects).

Other neuroleptics that may be available include thioridazine (25 to 50 mg daily), chlorpromazine, and levopromazine. They all have a low neuroleptic potency, but a good sedating effect, and therefore may be used as sleeping pills in cancer patients. The new "atypical" neuroleptics such as olanzapine or risperidone are not the first choice for cancer patients and should be reserved for patients with psychiatric disorders.

Antipsychotics are associated with a wide range of side effects. Extrapyramidal reactions include acute dystonia, tardive dyskinesia, and Parkinson-like symptoms (rigidity and tremor) due to blockage of dopamine receptors. Tachycardia, prolonged QT interval, hypotension, impotence, lethargy, seizures, and nightmares are possible. Another serious side effect is neuroleptic malignant syndrome. In this case the temperature regulation centers fail, resulting in a medical emergency, as the patient's temperature suddenly increases to dangerous levels. Most of the above-mentioned side effects are fortunately rare and not of relevance in the period of the end of life.

Benzodiazepines

Benzodiazepines are a group of drugs with varying sedative, anxiolytic, anticonvulsant, and muscle relaxant properties. The main indication for these drugs in pain management and the palliative care management is the treatment of anxiety and intractable dyspnea. Do not hesitate to prescribe these drugs for terminal

ill patients, who suffer from panic attacks, dyspnea and insomnia. Benzodiazepines are highly beneficial in the palliative care setting.

Benzodiazepines bind at the interface of the α and γ subunits on the γ-aminobutyric acid (GABA) receptor, the most prevalent inhibitory receptor within the entire brain. The anticonvulsant properties of benzodiazepines may be in part or entirely due to binding to voltage-dependent sodium channels.

Benzodiazepines are well-tolerated and safe. If you want to treat panic attacks, use benzodiazepines with shorter half-lives, such as lorazepam. Diazepam has a long half-life. Diazepam can be administered orally, intravenously, intramuscularly, or as a suppository. The dose is between 2 and 10 mg as a single dose or twice daily. Sometimes it is necessary to increase the dose extensively without negative consequences. Diazepam, in combination with morphine, is the drug of first choice for palliative sedation. For trait anxiety in terminal illness, flunitrazepam subcutaneously once daily is a very effective choice (normally in a dose range between 0.5 and 5 mg).

During the course of therapy with benzodiazepines, tolerance to the sedative effects usually develops, but not to the anxiolytic effects. Diazepam does not increase or decrease hepatic enzyme activity. There is no real contraindication in the palliative setting if used with care, titrated to effect, and used where indicated.

Appendix: Glossary

Andreas Kopf

Introduction

A list of pain terms was first published in 1979 (*PAIN* 1979;6:249–52). Many of the terms were already established in the literature. One, "allodynia," quickly came into use in the columns of *PAIN* and other journals. The terms have been translated into Portuguese (*Revista Brasiliera de Anestesiologia* 1980;30:349–51), into French (H. Dehen, "Lexique de la douleur," *La Presse Médicale* 1983;12:1459–60), and into Turkish (as "Agri Teriml," translated by T. Aldemir, *Journal of the Turkish Society of Algology* 1989;1:45–6). A supplementary note was added to these pain terms in *PAIN* (1982;14:205–6).

The original list was adopted by the first Subcommittee on Taxonomy of IASP. Subsequent revisions and additions were prepared by a subgroup of the Committee, particularly Drs. U. Lindblom, P.W. Nathan, W. Noordenbos, and H. Merskey. In 1984, in particular response to some observations by Dr. M. Devor, a further review was undertaken both by correspondence and during IASP's 4th World Congress on Pain. Those taking part in that review included Dr. Devor, the other colleagues just mentioned, and Dr. J.M. Mumford, Sir Sydney Sunderland, and Dr. P.W. Wall. Following that review, these experts agreed to take advantage of the publication of the draft collection of syndromes and their system for classification, to issue an updated list of terms with definitions and notes on usage. Edited by H. Merskey and N. Bogduk, the updated list was published in 1994 by IASP as *Classification of Chronic Pain, Second Edition.*

The usage of individual terms in medicine often varies widely. That need not be a cause of distress, provided that each author makes it clear precisely how he is using a word. Nevertheless, it is convenient and helpful to others if words can be used that have agreed technical meanings. The definitions provided in this Appendix are intended to be specific and explanatory and to serve as an operational framework, not as a constraint on future development. They represent agreement among diverse specialties including anesthesiology, dentistry, neurology, neurosurgery, neurophysiology, psychiatry, and psychology.

The terms and definitions are not meant to provide a comprehensive glossary, but rather a minimum standard vocabulary for members of different disciplines who work in the field of pain.

Acupuncture

Acupuncture is a procedure involving the stimulation or inhibition of anatomical locations on or in the skin by a variety of techniques. A number of effects on pain physiology have been identified, the most important being the activation of the endogenous opioid system and the spinal modulation of pain signalling through activation of touch fibers (Aβ fibers). There are a number of different approaches to diagnosis and treatment in modern acupuncture that incorporate medical traditions from China, Japan, Korea, and other countries. Acupuncture was originally part of traditional Chinese medicine. In the 1950s, French military physicians from Vietnam "exported" the technique to Europe, where it was used mostly as a complementary treatment to mainstream medicine. A few indications in pain medicine, such as certain types of joint pain, back pain, and headache syndromes may benefit from acupuncture.

Addiction

Addiction is a chronic relapsing condition characterized by compulsive drug-seeking and drug abuse and by long-lasting chemical changes in the brain. Addiction is the same irrespective of whether the drug is alcohol, amphetamines, cocaine, heroin, marijuana, or nicotine. Every addictive substance induces pleasant states or relieves distress. Continued use of the addictive substance induces adaptive changes in the brain that lead to tolerance, physical dependence, uncontrollable craving, and, all too often, relapse. The genetic factors predisposing to addiction are not yet fully understood. Addiction has to be separated from dependence. For example, in long-term opioid therapy, dependence is a normal result, and the only clinical implication is that dose reduction has to be stepwise. Addiction to opioids is very rare in pain patients without preexisting addiction problems. Therefore, asking the patient about alcohol, opioid, and benzodiazepine consumption is a prerequisite before starting an opioid medication.

Allodynia

Allodynia is pain due to a stimulus that does not normally provoke pain. The term "allodynia" was originally introduced to distinguish such pain from hyperalgesia and hyperesthesia, the conditions seen in patients with lesions of the nervous system where touch, light pressure, or moderate cold or warmth evoke pain when applied to apparently normal skin. "Allo-" means "other" in Greek and is a common prefix for medical conditions that diverge from the expected. "Odynia" is derived from the Greek word "odune" or "odyne," which is used in "pleurodynia" and "coccydynia" and is similar in meaning to the root from which we derive words with "algia" or "algesia" in them. It is important to recognize that allodynia involves a change in the quality of a sensation, whether tactile, thermal, or of any other sort. The original modality is normally nonpainful, but the response is painful. There is thus a loss of specificity of a sensory modality. By contrast, hyperalgesia represents an augmented response in a specific mode. With other cutaneous modalities, hyperesthesia is the term that corresponds to hyperalgesia, and as with hyperalgesia, the quality is not altered. In allodynia the stimulus mode and the response mode differ, unlike the situation with hyperalgesia. This distinction should not be confused by the fact that allodynia and hyperalgesia can be plotted with overlap along the same continuum of physical intensity in certain circumstances, for example, with pressure or temperature. Allodynia might be provoked by the touch of clothes, such as in patients with postherpetic neuralgia. Its management may be difficult. Apart from coanalgesics, local treatment with local anesthetics and/or capsaicin might be of help.

Anesthesia dolorosa

Pain in an area or region that is anesthetic. Therefore, neurodestructive techniques in pain management should be limited to the few indications where anesthesia dolorosa has not been observed.

Analgesia

Absence of pain in response to stimulation that would normally be painful. As with allodynia, the stimulus is defined by its usual subjective effects. Analgesics are used in both acute and chronic pain. Whereas acute (e.g., postoperative, post-traumatic) pain is generally amenable to drug therapy, chronic pain is a complex disease in its own right and needs to be differentiated into malignant (cancer-related) and nonmalignant (e.g., musculoskeletal, neuropathic, or inflammatory) pain. Acute and cancer-related pain are commonly treatable with opioids, NSAIDs, and/or local anesthetic blocks. Chronic nonmalignant pain requires a multidisciplinary approach encompassing various pharmacological and nonpharmacological (e.g., psychological, physiotherapeutic) treatment strategies. Various routes of drug administration (e.g., oral, intravenous, subcutaneous, intrathecal, epidural, topical, intra-articular, and

transnasal) are used depending on the clinical circumstances and available substances. Local anesthetics are used topically and in regional (e.g., epidural) anesthetic techniques for the treatment of acute pain (e.g., associated with surgery, childbirth) and some selected chronic pain syndromes. In general, the oral route of application is preferred, but in emergency situations and perioperatively the parenteral route is preferred. The use of transdermal, oral transmucosal, and intranasal applications may be beneficial to selected patients if available, but in general, high-quality pain management is possible without them.

Analgesics

Analgesics interfere with the generation and/or transmission of impulses following noxious stimulation (nociception) in the nervous system. This interference can occur at peripheral and/or central levels of the neuraxis. The therapeutic aim is to diminish the perception of pain. Analgesics can be roughly discriminated by their mechanisms of action: opioids, nonsteroidal antiinflammatory drugs (NSAIDs), serotoninergic compounds, antiepileptics, and antidepressants. Adrenergic agonists, excitatory amino acid (e.g., *N*-methyl-D-aspartate [NMDA]) receptor antagonists, neurokinin receptor antagonists, neurotrophin (e.g., nerve growth factor) antagonists, cannabinoids, and ion channel blockers are currently under intense investigation but are not yet used routinely. Local anesthetics are used for local and regional anesthetic techniques. Some drugs (e.g., tramadol) combine various mechanisms.

Antiepileptics (anticonvulsants)

Various antiepileptics (carbamazepine, phenytoin, valproate, gabapentin, lamotrigine, and pregabalin) have been used for neuropathic pain and more recently for migraine prophylaxis as well. Together with antidepressants, they are the most effective coanalgesics. The most common adverse effects are impaired mental function (somnolence, dizziness, cognitive impairment, and fatigue) and motor function (ataxia), which may limit clinical use, particularly in elderly patients. Serious side effects have been reported, including hepatotoxicity, thrombocytopenia, and life-threatening dermatological and hematological reactions. Plasma drug concentrations should be monitored to avoid toxic blood levels. A number of antiepileptics are used in neuropathic pain. Different neuropathic pain syndromes have been attributed to certain common mechanisms, including ectopic activity in sensitized nociceptors from regenerating nerve sprouts, recruitment of previously "silent" nociceptors and Aβ fibers, and spontaneous activity in dorsal root ganglion cells. The increase of peripheral neuronal activity is transmitted centrally and results in sensitization of second- and third-order ascending neurons. Among the best studied mechanisms of peripheral and central sensitization are the increased novel expression of sodium channels, and increased activity at glutamate (NMDA) receptor sites. The mechanisms of action of antiepileptics include neuronal membrane stabilization by blockage of pathologically active voltage-sensitive sodium channels (carbamazepine, phenytoin, valproate, lamotrigine), blockage of voltage-dependent calcium channels (gabapentin, lamotrigine), inhibition of presynaptic release of excitatory amino acids (lamotrigine), activation of GABA receptors (valproate, gabapentin), opening of K_{ATP} channels (gabapentin), potential enhancement of GABA turnover/synthesis (gabapentin), increased nonvesicular GABA release (gabapentin), and inhibition of carbonic anhydrase in neurons (topiramate).

Antidepressants

Antidepressants are used—in the same manner as antiepileptics—in neuropathic pain and migraine prophylaxis. Tricyclic antidepressants have the highest effectivity. They are titrated to effect. The purpose of monitoring plasma drug concentrations is not to achieve optimal effect, but to avoid toxicity and control patient compliance. In most patients, pain reduction may be achieved with a low dose (e.g., 50 to 75 mg/day of imipramine or amitriptyline). As with all coanalgesic treatment options for neuropathic pain, patients should be told before the start of therapy that the treatment goal may only be a 50% pain reduction. Studies have demonstrated that even with optimized treatment, only half of all patients with neuropathic pain will achieve this goal. In migraine prophylaxis, the numbers are higher.

In patients with ischemic heart disease, there may be increased mortality from sudden arrhythmia, and in patients with recent myocardial infarction, arrhythmia, or cardiac decompensation, tricyclics should not be used at all. Tricyclics also block histamine, cholinergic, and alpha-adrenergic receptor sites. Adverse events include fatigue, nausea, dry mouth, constipation, dizziness, sleep disturbance, blurred vision, irritability/nervousness, sedation, and hepatotoxicity.

Several antidepressants are used in the treatment of neuropathic pain. They include the classic tricyclic compounds—divided into nonselective norepinephrine/5-HT reuptake inhibitors (e.g., amitriptyline, imipramine, and clomipramine) and preferential norepinephrine reuptake inhibitors (e.g., desipramine and maprotiline), selective 5-HT reuptake (serotonergic) inhibitors (e.g., citalopram, paroxetine, and fluoxetine) and 5-HT_2 antagonists (nefazodone). The reuptake inhibition leads to a stimulation of endogenous monoaminergic pain inhibition in the spinal cord and brain. In addition, tricyclics have NMDA-receptor antagonist, sodium-channel-blocking, and potassium-channel-opening effects that can suppress peripheral and central sensitization. Block of cardiac potassium and sodium channels by tricyclics can lead to life-threatening arrhythmias. The selective 5-HT transporter inhibitors lack postsynaptic receptor blocking and membrane stabilization effects (and the resulting side effects) and therefore have only a limited role in neuropathic pain treatment.

Anxiety

Anxiety is a feeling of apprehension and fear characterized by physical symptoms such as palpitations, sweating, and feelings of stress. Anxiety disorders are serious medical illnesses that affect pain patients more frequently than the average population. These disorders fill people's lives with overwhelming anxiety and fear. Unlike the brief anxiety caused by a stressful event such as a business presentation or waiting for surgery (state anxiety), anxiety disorders are chronic, relentless, and can grow progressively worse if not treated (trait anxiety).

In the case of chronic pain, both in developing and developed countries there is an increased prevalence of anxiety disorders such as generalized anxiety disorder, panic disorder, social phobia, and post-traumatic stress disorder (PTSD) in comparison to people without pain. The prevalence increases when pain occurs at multiple sites. It is often not possible to determine the direction of causality between pain and a psychiatric disorder. In biopsychosocial models of explaining the emotions, anxiety is seen as reaction of the organism to external experience (for example, an experience of violence) and to internal stimuli (for example increased heart rate). Within the experience of anxiety there is an unspecific feeling of excitement and tension as well as unpleasantness and the experience of physical symptoms of arousal. Fears in correlation with pain are often understandable, for example, anxiety about increasing physical impairment and anxiety about losing one's employment. In consequence, disorders of anxiety can be the result of chronic pain, but they can also be the cause of physical symptoms. For example, severe chest and heart pain as well as breathlessness are some of the symptoms of a panic attack. One consequence of chronic pain can be agoraphobia, for example, if the patient is afraid to leave the house because the pain attack might occur on the street, and nobody would be there to help. In consequence, the patient tends more and more to avoid leaving the house. The most common screening instruments for anxiety disorders are the Hospital Anxiety and Depression Scale (HADS-D), State-Trait-Anxiety Inventory (STAI), and Profile of Mood States (POMS).

Anxiolytics

Anxiolytics are medications used to treat anxiety. Short-acting anxiolytics, especially from the class of benzodiazepines, maybe beneficial for panic attacks, while long-acting anxiolytics, also mostly from the class of benzodiazepines, play a role in palliative medicine when trait anxiety is uncontrolled by psychological interventions. The antiepileptic drug pregabalin also has some anxiolytic effect without the risk of addiction of benzodiazepines and may be beneficial, therefore, in pain patients with a mild anxiety disorder. Although recommended in a number of textbooks, there is no indication for anxiolytics as pain killers.

Arthritis

Arthritis is the inflammation of a joint, with typical symptoms including stiffness (especially in the morning), warmth, swelling, redness, and pain. It can be divided into osteoarthritis (with a degenerative etiology) and rheumatoid arthritis (with an inflammatory etiology). If the cause of arthritis is rheumatic, inflammation control comes before pain management to avoid ongoing tissue destruction in the joint. NSAIDs and opioids—sometimes given locally into the joint—are among the drugs of first choice for severe arthritis.

Bereavement

The act of grieving someone's death. Bereavement is integrated into palliative care by offering relatives support after the death of the patient. Therefore, palliative care does not stop with the death of the patient.

Bradykinin

Bradykinin is generated in the blood by the action of the plasma kallikrein-kinin system (involving prekallikrein activator, prekallikrein, kininogen, and kininases). It produces inflammation and activates nociceptors via bradykinin B1 and B2 receptors.

Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) is a neuropeptide expressed in sensory neurons. It works as a stimulatory (pronociceptive) neurotransmitter when it is released centrally, and as a proinflammatory mediator when it is released peripherally. The central role of CGRP in primary vascular headaches (e.g., migraine) has led to the search for suitable antagonists of CGRP receptors.

Causalgia (complex regional pain syndrome type II)

Pain, usually burning pain, that is associated with autonomic changes (changes in the color of the skin, changes in temperature, changes in sweating, and swelling). Causalgia is rare and difficult to treat and occurs after a nerve injury. The pathophysiology of causalgia includes local inflammation and reorganization processes in the central nervous system. If causalgia is suspected, diagnosis and treatment should be left to a pain specialist.

Central pain

Pain initiated or caused by a primary lesion or dysfunction in the central nervous system. It occurs in some patients after stroke and may limit the quality of life considerably. Only tricyclic antidepressants have been able to show any analgesic effectivity in these patients. All other treatment options are supported only by anecdotal evidence.

Chronic pain

Chronic pain is diagnosed if pain persists longer than 6 months. For clinical practice it is probably more helpful to define chronic pain as pain that is complicated by certain risk factors according to the biopsychosocial concept of pain chronification: central sensitization to painful stimuli, depression or anxiety, or somatoform disorders, as well as conflicts at the workplace or in the family.

Complementary medicine

Approaches to medical treatment that are outside of mainstream medical training received in medical schools. While "alternative medicine" often is in conflict with mainstream medicine and includes sometimes rather bizarre methods, complementary medicine is "extending" the conventional medical approaches to enhance its effects. Well-known complementary medicine modalities include acupuncture, low-level laser therapy, meditation, aromatherapy, dance therapy, music therapy, herbalism, osteopathy, and naturopathy.

Delirium

A disturbance of the brain function that causes confusion and changes in alertness, attention, thinking and reasoning, memory, emotions, sleeping patterns, and coordination. These symptoms may start suddenly, are due to some type of medical problem, and may get worse or better multiple times. Typical causes for delirium include acute infection or cancer progress (with liberation of TNF-alpha), sudden renal failure, certain drugs including opioids (the incidence for opioids is around 1–2%), and electrolyte imbalances. If opioids are suspected to be the cause of delirium, a switch (rotation) to another opioid usually terminates the delirium with hours.

Dependence

Physical dependence is a state in which the continuous presence of a drug is required to maintain normal functions of an organism. Discontinuation of the drug results in a withdrawal syndrome. Dependence is a "normal" phenomenon occurring with a number of different drugs. As a consequence, when opioids have been administered for a prolonged period of time (> 3 weeks) in a dose of 50–100 mg oral morphine equivalents per day or more, they should never be acutely discontinued but tapered with a daily dose reduction (e.g., a 10% daily dose reduction).

Depression

Depression is a risk factor for pain chronification. Certain screening questions aid in diagnosis. Common findings are sleeping problems, unrest, a lack of energy that is pronounced in the first half of the day, and loss of interest. Some common screening instruments for depression are the Center for Epidemiologic Studies Depression Scale (CES-D), the Beck Depression Inventory for primary care, and the Profile of Mood States (POMS). A psychopathological result should however always form the basis and include an evaluation of suicidal tendency. In accordance with the findings of

an investigation by Tang et al. in 2006, the suicide rate among chronic pain patients is increased (prevalence 5–14%) in comparison to the general public. Depression is usually the strongest predictor of desire for death. It is important to distinguish between passive thoughts of death or death wishes and active suicidal thoughts that involve an intent to take one's life. It is helpful and relieving for the patient when concrete questions are asked: For example: "Do you ever think about committing suicide?" "Do you have a plan of how you want to commit suicide?" "Are you obsessed by thoughts of suicide?" Very often, patients have set a time, and so questions regarding the point in time are important; the patient may agree to a postponement. Furthermore, previous suicide attempts should be noted because they are an increased risk factor for a renewed suicidal tendency.

Do-not-resuscitate (DNR) orders

Instructions written, usually in the patient's chart, by a doctor or other health care provider. A rather "imprecise" method to indicate that because of an advanced disease stage the treatment of a patient should be restricted and especially exclude cardiopulmonary resuscitation (CPR) or other related treatments. Usually, DNR orders are written after a discussion between a doctor and the patient and/or family members. Today another concept is slowly replacing DNR called AND ("Allow Natural Death"). In this modern concept, the limitations in therapy are precisely documented after discussion between the caregivers, the patient, and the family. Orders for AND may include specific topics such as antibiotics, ventilation, intensive care, dialysis, and catecholamines.

Durable power of attorney for health care (DPOAHC)

In some countries a legal document has been introduced in the last years to allow communication between the patient and a caregiver in case the patient is unresponsive due to his health situation. The document specifies one or more individuals (called a health care proxy) the patient wants to make medical decisions if the patient becomes unable to do so.

Dysesthesia

An unpleasant abnormal sensation, whether spontaneous or evoked. Compare with pain and with paresthesia. Special cases of dysesthesia include hyperalgesia and allodynia. A dysesthesia should always be unpleasant, and a paresthesia should not be unpleasant, although it is recognized that the borderline may present some difficulties when it comes to deciding whether a sensation is pleasant or unpleasant. It should always be specified whether the sensations are spontaneous or evoked.

Dyspnea

Dyspnea is difficulty in breathing and is often mixed up with respiratory depression. While dyspnea causes major suffering by the feeling of suffocation and may be successfully relieved by morphine or other opioids in most cases, respiratory depression is a state of unresponsiveness of the central breathing regulation, which may be caused by opioids. Since breathing depression does not cause the patient to suffer (and therefore the patient will not complain), personal or electronic monitoring, especially in the immediate postoperative period or after opioid applications, is necessary to avoid possibly fatal complications.

Epidural space

The epidural space surrounds the dura mater of the spinal cord. It is bounded by the pedicles of the vertebral arches and by the anterior and posterior ligaments connecting the bony vertebral column. The epidural space contains nerve roots, fat, and blood vessels and is routinely used for perioperative analgesia as a single analgesia technique or in combination with general anesthesia. Epidural analgesia is specially popular in the obstetrics department.

Ethics

A system of moral principles and rules that are used as standards for professional conduct. Many hospitals and other health care facilities have ethics committees that can help doctors, other health care providers, patients, and family members in making difficult decisions regarding medical care. Besides helping in difficult medical situations, ethics conferences may also help bringing together the different disciplines of health care, allowing a joint approach for optimal care. Ethics committees are usually not meant to set ethical standards—something which mostly develops in society and in religious communities—but they help to interpret and transfer society's standards into specific standards or find solutions for specific therapeutic dilemmas.

Fatigue

A feeling of becoming tired easily, being unable to complete one's usual activities, feeling weak, and having difficulty concentrating. Fatigue should not be confused

with sedation, which usually is a side effect of certain medical interventions and therefore maybe influenced by changing the therapeutic regimen. Fatigue is the symptom palliative patients complain about most, and unfortunately it is difficult to influence.

Fibromyalgia

A pain disorder—mostly affecting middle-aged females—in which a person feels widespread pain and stiffness in the muscles, fatigue, and other symptoms. Although the name "fibromyalgia" suggests a muscular disorder, recent research makes it more likely that fibromyalgia is caused by central nervous system changes with central hypersensitivity. Therefore, current treatment concepts aim at the descending inhibitory system and central sensitization. Probably fibromyalgia should be seen in the same context as other hypersensitivity syndromes, such as chronic back pain, seronegative polyarthritis, or tension headache.

Hospice

A special way of caring for people with terminal illnesses and their families by meeting the patient's physical, emotional, social, and spiritual needs, as well as the needs of the family. The goals of hospice are to keep the patient as comfortable as possible by relieving pain and other symptoms; to prepare for a death that follows the wishes and needs of the patient; and to reassure both the patient and family members by helping them to understand and manage what is happening. Hospice care especially aims to help patients who are unwilling or unable to be taken care of in their homes and have stable or manageable symptoms. Hospice care usually ends with the death of the recipient, while palliative ward care allows reambulation of the patient in many patients after stabilization. Pallium India and Hospice Africa Uganda are remarkable examples of hospice care in low-resource settings. Currently, in many countries, "home care" is promoted to avoid as long as possible and as often as possible hospice or palliative ward treatment.

Hyperalgesia

An increased response to a stimulus that is normally painful. Hyperalgesia reflects increased pain on suprathreshold stimulation. For pain evoked by stimuli that usually are not painful, the term allodynia is preferred, while hyperalgesia is more appropriately used for cases with an increased response at a normal threshold, or at an increased threshold, such as in patients with neuropathy. It should also be recognized that with allodynia the stimulus and the response are in different modes, whereas with hyperalgesia they are in the same mode. Current evidence suggests that hyperalgesia is a consequence of perturbation of the nociceptive system with peripheral or central sensitization, or both, but it is important to distinguish between the clinical phenomena, which this definition emphasizes, and the interpretation, which may well change as knowledge advances. Hyperalgesia and hyperpathia are an exaggerated response to something that causes pain, with continued pain after the cause of the pain is no longer present.

Hyperesthesia

Increased sensitivity to stimulation, excluding the special senses. The stimulus and location should be specified. Hyperesthesia may refer to various modes of cutaneous sensibility, including touch and thermal sensation without pain, as well as to pain. The word is used to indicate both diminished threshold to any stimulus and an increased response to stimuli that are normally recognized. Allodynia is suggested for pain after stimulation that is not normally painful. Hyperesthesia includes both allodynia and hyperalgesia, but the more specific terms should be used wherever they are applicable.

Hyperpathia

A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. It may occur with allodynia, hyperesthesia, hyperalgesia, or dysesthesia. Faulty identification and localization of the stimulus, delay, radiating sensation, and aftersensation may be present, and the pain is often explosive in character. The changes in this note are the specification of allodynia and the inclusion of hyperalgesia explicitly. Previously hyperalgesia was implied, since hyperesthesia was mentioned in the previous note and hyperalgesia is a special case of hyperesthesia.

Hypoalgesia

Diminished pain in response to a normally painful stimulus. Hypoalgesia was formerly defined as diminished sensitivity to noxious stimulation, making it a particular case of hypoesthesia. However, it now refers only to the occurrence of relatively less pain in response to stimulation that produces pain. Hypoesthesia covers the case of diminished sensitivity to stimulation that is normally painful. Hypoalgesia, as well as allodynia, hyperalgesia, and hyperpathia, do not have to be symmetrical and are not symmetrical at present.

Lowered threshold may occur with allodynia but is not required. Also, there is no category for lowered threshold and lowered response—if it ever occurs.

Hypoesthesia

Decreased sensitivity to stimulation, excluding the special senses.

Informed consent

The process of making decisions about medical care that are based on open, honest communication between the health care provider and the patient and/or the patient's family members. The idea behind informed consent is that the patient may act as a "symmetrical" conversation partner. In practice, this idea is often difficult to fulfill, when the specific situation of the patient and the highly specialized knowledge of the caregiver may have to result in specific recommendations to the patient without alternatives (e.g., in advanced chronification of pain).

Intrathecal

The intrathecal space is located between the arachnoid and the pia mater of the spinal cord. It contains the cerebrospinal fluid and the spinal nerves. For anesthesia the intrathecal space may be reached by needle puncture, in special situations, such as advanced cancer pain; catheters also may be placed there.

Local anesthetics

Local anesthetics interfere with the generation and propagation of action potentials within neuronal membranes by blocking sodium channels. By use of regional anesthetic techniques they are injected in close proximity to the spinal cord (the intrathecal or epidural space), to peripheral nerves or nerve plexuses, or—on rare occasions—intravenously infused.

Myofascial pain

Myofascial pain is characterized by muscle pain and tenderness. Very often chronic back pain or shoulder-arm syndromes originate in myofascial pain and not in nerve entrapment, instability of the spine or skeletal or disk degeneration. Relaxation techniques and specific physiotherapy are therefore more successful than analgesics or injection therapies in these pain syndromes.

Neuralgia

Pain in the distribution of a nerve or nerves. Neuralgia is often—incorrectly—used to describe paroxysmal pains.

Neuraxis

Nerve structures within the spinal column. Therefore epidural, caudal, and spinal anesthesia may be called neuraxial anesthesia techniques.

Neuritis

Inflammation of a nerve or nerves.

Neurogenic or neuropathic pain

Pain initiated or caused by a primary lesion, dysfunction, or transitory perturbation in the peripheral or central nervous system. Neuropathic pain occurs when a lesion or dysfunction affects the nervous system. Central pain may be retained as the term when the lesion or dysfunction affects the central nervous system. The causative agent may be nerve compression, trauma, nerve-invading cancer, herpes zoster, HIV, stroke, diabetes, alcohol, or other toxic substances.

Neuropathy

Any disease or malfunction of the nerves.

Nociception

Nociception is the sensory component of pain. It encompasses the peripheral and central neuronal events following the transduction of damaging mechanical, chemical, or thermal stimulation of sensory neurons (nociceptors).

Nociceptor

A receptor preferentially sensitive to a noxious stimulus or to a stimulus that would become noxious if prolonged. Often called a pain receptor.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs inhibit cyclooxygenases, the enzymes that catalyze the transformation of arachidonic acid (a ubiquitous cell component generated from phospholipids) to prostaglandins and thromboxanes. Two isoforms, COX-1 and COX-2, are expressed constitutively in peripheral tissues and in the central nervous system. In response to injury and inflammatory mediators (e.g., cytokines, growth factors), both isoforms can be upregulated, resulting in increased concentrations of prostaglandins. As a result, nociceptors become more responsive to noxious mechanical (e.g., pressure, hollow organ distension), chemical (e.g., acidosis, bradykinin, neurotrophins), or thermal stimuli.

Noxious stimulus

A noxious stimulus is one that is damaging to normal tissues.

Opioids

Opioids act on heptahelical G-protein-coupled receptors. Three types of opioid receptors have been cloned (mu, kappa, and delta). Additional subtypes have been proposed but are not universally accepted. Opioid receptors are localized and can be activated along all levels of the neuraxis including peripheral and central processes of primary sensory neurons (nociceptors), spinal cord (interneurons, projection neurons), brainstem, midbrain, and cortex. All opioid receptors couple to G-proteins (mainly G_i/G_o) and subsequently inhibit adenylyl-cyclase, decrease the conductance of voltage-gated Ca^{2+} channels and/or open rectifying K^+ channels. These effects ultimately result in decreased neuronal activity. Opioid peptides are expressed throughout the central and peripheral nervous system, in neuroendocrine tissues, and in immune cells.

The commonly available opioids (e.g., morphine, codeine, methadone, fentanyl, and their derivatives) are pure mu-agonists. Naloxone is a nonselective antagonist at all three receptors. Partial agonists must occupy a greater fraction of the available pool of functional receptors than full agonists to induce a response (e.g., analgesia) of equivalent magnitude. Mixed agonist/antagonists (e.g., buprenorphine, butorphanol, nalbuphine, and pentazocine) may act as agonists at low doses and as antagonists (at the same or a different receptor) at higher doses. Such compounds typically exhibit ceiling effects for analgesia, and they may elicit an acute withdrawal syndrome when administered together with a pure agonist. All opioid receptors mediate analgesia but with differing side effects. Mu-receptors mediate respiratory depression, sedation, reward/euphoria, nausea, urinary retention, biliary spasm, and constipation. Kappa-receptors mediate dysphoric, aversive, sedative, and diuretic effects, but do not mediate constipation. Tolerance and physical dependence occur with prolonged—and eventually short—administration of all pure agonists. Thus, the abrupt discontinuation or antagonist administration can result in a withdrawal syndrome.

Opioids are effective in the periphery (e.g., topical or intra-articular administration, particularly in inflamed tissue), at the spinal cord (intrathecal or epidural administration), and systemically (e.g., intravenous or oral administration). The clinical choice of a particular compound is mostly based on economical and pharmacokinetic considerations (route of administration, desired onset or duration, and lipophilicity) and on side effects associated with the respective route of drug delivery. Dosages can vary widely depending on patient characteristics, type of pain, and route of administration. Systemically as well as spinally administered opioids can produce similar side effects, depending on the dosage, with some nuances due to the varying rostral (to the brain) or systemic redistribution of different compounds. Small, systemically inactive doses are used in the periphery and are therefore devoid of side effects. Opioids remain the most effective drugs for the treatment of severe acute and cancer-related chronic pain, while they are only a second choice in neuropathic pain and have only a limited indication in chronic noncancer pain that is not neuropathic or inflammatory. Detrimental side effects are usually preventable by careful dose titration and close patient monitoring, or they are treated by comedication (e.g., laxatives) or naloxone. Current research aims at the development of opioids with restricted access to the brain.

Osteomyelitis pain

Inflammation of the bone due to infection, for example by the bacteria *Salmonella* or *Staphylococcus.* Osteomyelitis is sometimes a complication of surgery or injury, although infection can also reach bone tissue through the bloodstream. Both the bone and the bone marrow may be infected. Symptoms include deep pain and muscle spasms in the area of inflammation, and fever. Especially if the history reveals previous surgery in the painful area and pain does not decrease with rest in the night, osteomyelitis—especially spondylodiscitis—should be suspected. Treatment is by bed rest, antibiotics, and sometimes surgery to remove infected bone tissue.

Osteoporosis

Thinning of the bones with reduction in bone mass due to depletion of calcium and bone protein. Osteoporosis predisposes a person to fractures. Osteoporosis is more common in older adults, particularly postmenopausal women, and in patients on steroids. Osteoporosis can lead to changes in posture (particularly in the form of a hunched back known colloquially as "dowager's hump") and decreased mobility. Often the vertebral body is affected. Pain is usually not constant but temporary and a symptom of pathological fractures.

Pain

The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." This broad definition acknowledges that pain is more than a sensation subsequent to the electrical activation of nociceptors (nociception). It includes cognitive, emotional, and behavioral responses, which are also influenced by psychological and social factors. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life. Biologists recognize that those stimuli which cause pain are liable to damage tissue. Accordingly, pain is that experience we associate with actual or potential tissue damage. It is unquestionably a sensation in a part or parts of the body, but it is also always unpleasant and therefore also an emotional experience. Experiences that resemble pain but are not unpleasant, e.g., pricking, should not be called pain. Unpleasant abnormal experiences (dysesthesias) may also be pain but are not necessarily so because, subjectively, they may not have the usual sensory qualities of pain.

Many people report pain in the absence of tissue damage or any likely pathophysiological cause; usually this happens for psychological reasons. There is usually no way to distinguish this experience from that due to tissue damage if we accept the subjective report. If people regard their experience as pain and if they report it in the same ways as pain caused by tissue damage, it should be accepted as pain. This definition avoids tying pain to the stimulus. Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not pain, which is always a psychological state, even though we may well appreciate that pain most often has a proximate physical cause.

Pain threshold

The least experience of pain that a subject can recognize.

Pain tolerance level

The greatest level of pain that a subject is prepared to tolerate. As with pain threshold, the pain tolerance level is the subjective experience of the individual.

Paresthesia

An abnormal sensation, whether spontaneous or evoked. It has been agreed that paresthesia be used to describe an abnormal sensation that is not unpleasant while dysesthesia be used preferentially for an abnormal sensation that is considered to be unpleasant. Dysesthesia does not include all abnormal sensations, but only those which are unpleasant.

Patient-controlled analgesia (PCA)

Pain medication given through an intravenous or epidural catheter may be either applied continuously or by the nurse or doctor or self-administered by the patient. With PCA, patients control the frequency of medication dosing, depending on how much they need to control the pain. PCA is usually used for patients recovering from intra-abdominal, major orthopedic, or thoracic surgery, and for chronic pain states, such as those due to cancer requiring parenteral administration of opioids. Usually PCA uses electronic pumps that allow documentation of the patient's analgesic demand and safety by locking the pump function for some time (usually 10 minutes) after each demand dose self-administered by the patient.

Peripheral neuropathic pain

Pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system, such as diabetic polyneuropathy.

Phantom pain

Pain that develops after an amputation in the area of the missing limb. The diagnosis of phantom pain has to exclude first the presence of stump pain (e.g., due to insufficient surgical coverage of the stump tissues) and phantom sensations (nonpainful, but nevertheless frightening "feelings" in the lost limb). Since phantom pain is mostly generated in the central nervous system, mostly in the corresponding sensory-motor region of the cortex, therapy is usually not directed peripherally but centrally. Patients and their relatives sometimes feel that—since pain in a missing body part should not be possible—something is wrong with them. Therefore, simply educating the patient and family about the causes of the pain may bring considerable relief.

Physician-assisted suicide

Actions by a doctor that help a patient commit suicide. Though the doctor may provide medication, a prescription, or take other steps, the patient takes his or her own life (for instance, by swallowing the pills that are expected to bring about death). While physician-assisted suicide is legal in The Netherlands, Belgium, Luxemburg, and Switzerland, it is illegal in all other countries

worldwide. The expansion of physician-assisted suicide is expected to be harmful and to be in competition with the development of palliative care. Experiences in the countries practicing physician-assisted suicide suggest that too many patients not meeting the original requirements for this "last resort" are included. Apart from legal discussions, physician-assisted suicide has to be balanced against the Hippocratic oath of the physicians and religious teachings.

Placebo

A "sugar pill" or any dummy medication or treatment that causes the placebo response. A remarkable phenomenon in which a placebo—a fake treatment—can sometimes improve a patient's condition simply because the person has the expectation that it will be helpful. Expectation plays a potent role in the placebo effect. Also, preconditioning effects generate a placebo response. Therefore, testing the "adequate reaction" by a placebo will not be able to prove "inadequate analgesic demand." The reason is that expectations and preconditioning are potent principles that are able to mimic the analgesic response. To be able to truly test an "adequate reaction" of a patient to an analgesia procedure, short- and long-acting substances should be tested subsequently. An "inadequate response" would be if the patient responds identically to both substances (e.g., short-acting lidocaine and long-acting bupivacaine in a nerve block).

Postherpetic neuralgia (PHN)

Neuropathic pain in the affected dermatome following a varicella infection with herpes zoster ("shingles"), usually defined as pain longer than 6–12 weeks after the onset of herpes zoster. Allodynia is often present and difficult to treat.

Post-traumatic stress disorder (PTSD)

The reasons for developing PTSD can be manifold. In the field of research, a number of categories have been examined—criminal victimization, partner abuse, sexual victimization, childhood abuse, political trauma, disasters, or a threat to one's life. The prevalence of PTSD in pain patients varies from 0.5% to 9%, in comparison to persons without pain, where it ranges from nearly 0.5% to 3%. An extreme experience of pain during the trauma increases the likelihood of developing the symptoms of PTSD. The symptoms of a PTSD are intrusions (involuntary and stressing memories), nightmares, and flashbacks. On the cognitive and emotional level, avoidance of thought and feeling dominates, along with (partial) amnesia, limited emotional scope, reduction in interest levels, and alienation. Physiological reactions are difficulties in falling asleep or disturbed sleep, increased irritability, inability to concentrate, hypervigilance, and exaggerated shock reactions. Chronic pain may also occur after the trauma in connection with injuries or even later, particularly in the case of headaches.

Psychiatric comorbidity

With regard to the prevalence of psychiatric disorders such as anxiety, depression, and somatoform disorders in chronic pain patients, there are great differences in the results of clinical tests. Statements of prevalence vary from 18% to 56%; furthermore, the details are dependent on the treatment parameters. The prevalence of chronic pain and comorbidity with the depression-anxiety spectrum are nearly consistent across developed and developing countries. The age-standardized prevalence of chronic pain conditions in the previous 12 months was 37% in developed countries and 41% in developing countries, and overall the prevalence of pain is greater among females and older persons, but the large majority do not meet the criteria for depression or anxiety disorder.

Public health

The approach to medicine that is concerned with the health of the community as a whole. Public health is community health. It has been said that: "Health care is vital to all of us some of the time, but public health is vital to all of us all of the time."

Quackery

Deliberate misrepresentation of the ability of a substance or device for the prevention or treatment of disease. We may think that the day of patent medicines is gone, but look around you and you will still see them. They appeal to our desire to believe that every disease is curable or at least treatable. Quackery also applies to persons who pretend to be able to diagnose or heal people but are unqualified and incompetent.

Receptor

In cell biology, a structure on the surface of a cell (or inside a cell) that selectively receives and binds a specific substance. There are many receptors; for example, the receptor for substance P, a molecule that acts as a messenger for the sensation of pain, is a unique harbor on the cell surface where substance P docks.

Reflex sympathetic dystrophy (complex regional pain syndrome type I)

Pain, usually burning pain, that is associated with "autonomic changes"—changes in the color of the skin, changes in temperature, changes in sweating, and swelling. Reflex sympathetic dystrophy is caused by an injury to the bone, joint, or soft tissues without nerve damage. The most frequent cause is a radius fracture. Apart from nerve damage, CRPS type I is not distinctive from CRPS type II. An older term is Sudeck disease, which should not be used, because sympathetic dysfunction may be part of CRPS, but is no prerequisite for diagnosis. Diagnosis and treatment are difficult and should be left to a specialist. Advanced CRPS may leave the patient with a permanently unusable extremity.

Rheumatoid arthritis

An autoimmune disease that causes chronic inflammation of the joints and the tissue around the joints, as well as other organs in the body. Autoimmune diseases occur when the body tissues are mistakenly attacked by the body's own immune system. The immune system is a complex organization of cells and antibodies designed to "seek and destroy" invaders of the body, particularly infections. Patients with autoimmune diseases have antibodies in their blood that target their own body tissues, where they can be associated with inflammation. Because it can affect multiple other organs of the body, rheumatoid arthritis is referred to as a systemic illness and is sometimes called rheumatoid disease. While rheumatoid arthritis is a chronic illness (meaning it can last for years), patients may experience long periods without symptoms. Pain management includes NSAIDs and opioids. Pain control should not be attempted without controlling the inflammation, otherwise joint destruction will continue.

Sciatica

Pain resulting from irritation of the sciatic nerve, typically felt from the low back to behind the thigh and radiating down below the knee. While sciatica can result from a herniated disk directly pressing on the nerve, any cause of irritation or inflammation of this nerve can reproduce the painful symptoms of sciatica. Diagnosis is by observation of symptoms, physical and nerve testing, and sometimes by X-ray or MRI if a herniated disk is suspected. Very often, physical examination and careful taking of the history will reveal that the pain is not radiating along typical dermatomes. Therefore, other pain etiologies than radicular compression have to be taken into account, such as facet-joint pain, sacroiliacal joint irritation, or myofascial pain.

Somatoform disorders

The somatoform disorders are a group of psychiatric disorders that cause unexplained physical symptoms (somatoform disorder, hypochondriasis, pain disorder,and conversion disorder). The pathophysiology of these complaints still remains unclear. A common main symptom of these disorders is that physical symptoms cannot be completely explained by means of a physiological process. Somatic disorders can be accompanied by defined physical illnesses, but they may not be adequately explained by these illnesses. Patients who suffer pain without an organic cause are often unable to cope with emotional stress; this is converted into physical stress factors. These diffuse stress factors can no longer be understood as a physical expression of an intrapsychic conflict, but are nonspecific, vegetative stress factors (e.g., with agitation, shaking, and pain) as a result of emotional pressure experienced primarily physically. Various physical disorders can result. The standard medical treatment is often limited. These disorders should be considered early on in the evaluation of patients with unexplained symptoms to prevent unnecessary interventions and testing. The identification of a life event that is important enough to be taken as a cause of this disorder may prove helpful to "solve" the stress of this life event with behavioral interventions. Consequently, the somatoform pain may diminish over time.

Spinal stenosis

Narrowing of the spaces in the spine, resulting in compression of the nerve roots or spinal cord by bony spurs or soft tissues, such as disks, in the spinal canal. Stenosis occurs most often in the lumbar spine (in the low back) in patients older than 60 years, but it also occurs in the cervical spine (in the neck) and less often in the thoracic spine (in the upper back). The typical symptoms to ask when suspecting spinal stenosis are claudication (pain increases after a certain time of exercise without evidence of peripheral artery disease) and pain relief with bending forward. If surgery is not possible, a few therapeutic options are left for analgesia, including epidural steroids, physiotherapy, opioids and NSAIDs, and flexion-orthostasis.

Spondylolisthesis

Forward movement of one of the vertebrae of the spine in relation to an adjacent vertebra, most often at the level of L5/S1. Simple "functional" X-ray (lateral view in full extension and full flexion of the spine) may demonstrate spondylolisthesis. Only a major forward movement (>25–50% of the vertebral length) is an indication for surgery.

Substance P

Substance P is a member of the tachykinin family of neuropeptides that is expressed in sensory neurons. It works as a stimulatory neurotransmitter or neuromodulator when it is released centrally, and as a proinflammatory mediator when it is released peripherally. It activates the neurokinin-1 receptor, a major factor in central sensitization.

Withdrawal syndrome

The abrupt cessation of a repeatedly or continuously administered opioid agonist, or the administration of an antagonist, typically results in withdrawal syndrome. Signs and symptoms include sweating, tachycardia, hypertension, diarrhea, hyperventilation, and hyperreflexia. See also the entry on "Dependence".

Tolerance

Tolerance is the need for progressively increasing doses of an agonist to maintain the same effect (e.g., analgesia). In chronic pain, the need for increasing doses of opioids can be due to alterations in receptor functioning (e.g., coupling to G proteins, second messengers) and/or to increasing painful stimulation (e.g., by a growing tumor), among other reasons. Tolerance is fortunately not common in patients who have opioid-sensitive pain. In patients seeking opioid treatment for mood stabilization, tolerance is frequent. Therefore, in patients with nonmalignant pain and nonprogressing disease, the repeated need for dose escalation (typically every 4 to 8 weeks, when tolerance to the sedating and euphoric effects of opioids develops) should be a warning sign for "inadequate" opioid use, and the opioid medication should be gradually discontinued.

Trigeminal neuralgia

A disorder of the trigeminal nerve in its root area (e.g., secondary trigeminal neuralgia due to malignant masses in the cerebellar region) or due to pulsatile compression by the cerebellar artery that causes brief attacks of severe pain in the lips, cheeks, gums, or chin on one side of the face. Only a symptom complex including attack-like pain of less than 2 minutes, no neurological deficits, absent or minor chronic pain, and typical trigger factors should be diagnosed as trigeminal neuralgia. Carbamazepine is still considered to be the drug of first choice. If drug therapy fails, trigeminal neuralgia is one of the few pain syndromes where surgery is indicated (Janetta surgery).

World Health Organization

An agency of the United Nations established in 1948 to further international cooperation in improving health conditions. Although the World Health Organization (WHO) inherited specific tasks relating to epidemic control, quarantine measures, and drug standardization from the Health Organization of the League of Nations (which was set up in 1923) and from the International Office of Public Health at Paris (established in 1909), the WHO was given a broad mandate under its constitution to promote the attainment of "the highest possible level of health" by all people. WHO defines health positively as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity." The cancer pain management recommendations of the WHO (the analgesic ladder) have had a major effect on the rate of opioid prescriptions to patients with cancer and HIV-related pain, mainly in countries belonging to the Organization for Economic Co-operation and Development (OECD). Unfortunately, Eastern European countries and many low-resource countries continue to have only very restricted opioid delivery rates to cancer patients, which should be considered a health emergency. The Pain and Policy Study Group of the WHO is investing a lot of effort to influence this situation by advising government authorities and health care workers on legislative, educational, and treatment changes necessary to be able to provide adequate amounts of opioids to patients in need. For further information see their website for a lot of relevant facts regarding opioids in most countries of the world.