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Breakthrough Pain in Cancer Patients
Giovambattista Zeppetella

Mechanisms of Neuropathic Pain
Nanna Finnerup and Troels Jensen

Pamidronates for Non-Cancer Pain
Marco Pappagallo

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Dear Colleagues,

Welcome to the first issue of Advances in Pain Management. Advances in Pain Management, a new CME accredited journal, has been founded to identify and highlight the important developments in the assessment and treatment of pain. The journal will appear quarterly and will provide access to a critical and clinically relevant review of information regarding pain management, providing up-to-date and clinically important information as it pertains to the appropriate diagnosis, treatment, and management of chronic pain.

Each issue will include major review articles authored by leading specialists. These manuscripts are peer-reviewed for quality and CME accredited to provide an ongoing educational resource. In addition, summaries and analyses of recent papers, chosen for their impact upon the field, are provided for the reader together with highlights from recent international conferences.

Dr. Portenoy and Cruciani (Beth Israel Medical Center, New York, NY, USA) lead us into this first issue with an editorial highlighting the challenges facing pain physicians in terms of the immensity of the problem and the many difficulties in the research and treatment of this condition.

This first issue contains three articles. Dr. Zeppetella (St Clare Hospice, Hastingswood, Essex, UK) discusses breakthrough pain (BTP) in cancer patients, emphasizing the importance of distinguishing BTP from background pain, and implementing a specific strategy for its management. Involving a number of pharmacological and non-pharmacological treatment modalities, along with thorough patient assessment and reassurance of the individual and carer, can help ease this burden.

In the second article, Drs. Finnerup and Jensen (Aarhus University, Aarhus, Denmark) provide an overview of neuropathic pain, discussing its clinical characteristics and the mechanisms involved. After summarizing the different mechanisms behind neuropathic pain, they go on to discuss the extent to which available treatment can target specific mechanisms or specific signs and symptoms, thereby improving the standard of care for these patients.

Dr. Pappagallo (Mount Sinai School of Medicine, New York, NY, USA) reviews the use of bisphosphonates for non-cancer pain. Bisphosphonates have been of vital importance in the treatment of bone pain. This article provides a background to their development, method of analgesia, and their utilization in painful joint and bone syndromes as well as complex regional pain syndrome.

This issue concludes with a synopsis and critique of recently published scientific findings from several key areas of pain management.

We hope you find Advances in Pain Management an educational and valuable tool. We welcome your feedback regarding the material presented as well as your suggestions for future topics to be covered. On behalf of the Editorial Board, we would like to thank you for reading the first issue of what we believe will be an exciting and useful new journal in this developing field.

The Remedica Medical Education and Publishing Team

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There are few areas of healthcare broader in scope or more profound in importance than pain management. The array of issues in this field extends from the most sophisticated basic science to concerns that must be addressed at a public policy level. In basic science, interest has recently drilled down to the level of molecular biology, which may illuminate factors that predispose to the development of persistent pain after injury or the specific response to targeted therapies. The breadth of the issues relevant in clinical investigation and clinical practice is suggested by the apt description of pain as a “biopsychosocial” phenomenon. The clinical issues cross epidemiology, the pathophysiology and characteristics of diverse set of chronic pain disorders, assessments that range from objective changes in neurological functioning to complex processes involving somatization and coping, and a complicated and evolving science and practice of pain therapy. At yet a higher level, the public health perspectives include concerns as varied as disparities in access to care, the financing of specialist-level care, the approach to pain-related productivity loss in the workplace, the regulation of controlled prescription analgesics, mandated educational policies, and many others issues.

The scope of the problem
The number and complexity of the issues surrounding pain and its management take on critical importance in light of the epidemiology of the problem and the impact of rapid change in both pain-related research and practice. Large population-based surveys have demonstrated that chronic pain occurs in approximately 10–45% of adults in developed countries. Some of these surveys further suggest that pain-related functional impairment is clear in at least one-third of this group [1]. Chronic pain costs Americans upwards of US$100 billion/year in healthcare costs and lost productivity related to absenteeism from work. The adverse outcomes associated with poor performance among those who continue to work despite uncontrolled pain have not been measured but are likely to be huge. Further impact relates to the problem of poorly controlled acute pain, which prolongs hospitalizations and accounts for a substantial number of visits to emergency departments. Given this epidemiology, pain must be viewed as a major public health issue, as large as any other facing developed countries today.

New disciplines
Pain research and management are, relatively speaking, young disciplines, a status that augments the challenges that must be faced in addressing the scientific, clinical, and public health aspects. In the US, the concept of specialist-level, multidisciplinary pain management emerged only about 40 years ago and specialized programs to manage acute pain arrived years later. Support for a specialist physician workforce continues to be in the formative stage. An independent American Board of Pain Medicine began certifying physicians in pain management in 1992, and the American Board of Anesthesiology began offering a “Certificate of Added Qualification in Pain Management” in 1993. Although other disciplines in the US (including neurology, psychiatry, and physical medicine and rehabilitation) now recognize pain as a subspecialty, there are only 2500 board-certified physician specialists in pain management, a number that suggests a total of four board-certified specialists per 100 000 patients with chronic pain [2]. All of these specialists seek advanced training in only 105 accredited Fellowship training programs, a number that is likely to decline in the coming years. These limitations are mirrored in the status of pain research. In the US, for example, research continues to be minimally supported at a federal level. A recent analysis showed that only 1% of the 2003 National Institutes of Health budget was devoted to research primarily focused on pain [3].

Transitions
Although a daunting disparity exists between the scope of the problems related to pain and current efforts to understand and manage it, there is reason for optimism in the extraordinary progress that has occurred during the past few decades. Some of these are summarized below.
Research
Despite limited support for research, advances in basic neuroscience have burgeoned and begun to elucidate both nociception and pain pathophysiology. Findings are now being translated into new treatments. Studies that described pathways involved in pain perception and modulation, and the localization of neurotransmitters that contribute to pain signaling, have helped identify new targets for pain therapy. Early on, autoradiography allowed mapping of these neurotransmitters and their receptors, both in brain and spinal cord. Subsequent experimentation 20–30 years ago utilized voltage clamp methods and generated data that clarified the effect of opioids on electrical transmission. Later, with the advent of patch-clamp techniques, these effects were studied at the channel level, and more recently, molecular biological methods have identified numerous molecules that participate directly (N-methyl-D-aspartate [NMDA] receptors, opioid receptors) or indirectly (sodium channels) in the transmission of pain signals.

Advances in opioid research are representative of the progress that is being made. The discovery of endogenous opioid ligands and multiple opioid receptors, which began in the 1970s and extended over two decades, had profound influence in neurobiology and drug development [4]. Further progress was made with the cloning of the opioid receptors, beginning with the δ-receptor in the early 1990s [5]. This new knowledge allowed the sequencing of the proteins, the description of splice variants of opioid receptors, the elucidation of the concept of dimerization, and ultimate recognition that there are actually many genetically determined receptor variations that may underlie individual differences in opioid responsiveness. The implications of these findings are immense. It is possible, for example, that side effects and analgesia might be mediated by different receptors. The synthesis of specific agonists to selected receptors could result in analgesia with fewer side effects. Opioids less likely to produce physical dependence could be on the horizon. Tests that could be given to patients before treatment to determine the differential response to available drugs may be coming.

All of these advances have occurred in parallel with neurophysiological, biochemical, pharmacological, and most recently, neuroimaging studies to reveal the nature of the processes that underlie pain persistence after injury, including inflammation and neuroplasticity. In the realm of neuroimaging, the potential for functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) scanning to reveal cerebral processes involved in the perception of noxious events is just beginning to be recognized. Recent studies on brain plasticity in amputees with phantom limb pain, for example, suggest that the excitability and the cortical representation of the affected body part change in association with pain and that these changes are reversible [6]. This type of information is beginning to yield insights into the mechanisms of brain plasticity important in the genesis of pain.

Clinical paradigm
As basic research has explored the pathophysiology of varied pain-related disorders, a critical conceptual leap has evolved that promises a fundamental change in the way pain is addressed in the clinical setting. The concept of “pain as illness” is now accepted among specialists and suggests that pain should not be viewed as merely a symptom of disease, but rather, as a disease in its own right. The science supporting this notion is clear: In the acute pain setting, uncontrolled pain is associated with a broad array of adverse physiological and medical outcomes. In the chronic pain setting, disability and suffering appears far less determined by pain etiology than other characteristics of the pain and the person who is experiencing it. When persistent, pain itself is the main impediment to functional restoration. Equally important, there are many millions of patients with chronic pain that cannot be ameliorated by addressing an underlying disease. For these patients, primary pain management is the only avenue toward renewed health. Recognition of pain as illness appears to be growing among non-specialist physicians and others, and this change in paradigm may lead to significant improvements in programs and resources devoted to this problem.

Pain therapies
Advances in pain management have provided numerous new therapies and more refined use of older ones. Striking change has occurred, for example, in the use of opioid therapy. Although relatively well accepted in the treatment of acute severe pain for many years, the role of opioid therapy in chronic pain has defied a simple guideline. In cancer pain, the World Health Organization (WHO) provided an important foundation for care when an expert committee proposed an “analgesic ladder” approach to cancer pain management during the mid-1980s [7]. This approach has had a worldwide effect on clinical practice. Equally important, a consensus evolved among pain specialists since that time that chronic opioid therapy should also be used in a subpopulation of patients with persistent non-cancer pain. This consensus has been accompanied by ongoing controversy, however, as clinical practice attempts to apply limited science to important questions related to the long-term effectiveness of this treatment, patient selection, approach to monitoring, appraisal of risk associated with abuse and addiction, strategies for risk management, concurrent therapies, and other issues. Pain specialists no
longer argue about whether opioid therapy is appropriate for chronic pain, but instead debate the pragmatic issues related to the best approach to patient selection and care [8].

New pharmacotherapies (and new delivery) systems for analgesic drugs have also begun to change practice in a very positive way and are likely to have significant impact in the future. Very active research focused on the creation of drugs with specific mechanisms is already yielding an expanding therapeutic armamentarium for acute and chronic pain, an armamentarium that is beginning to tap modes of action that have never been applied for analgesic purposes before. During the past 10 years, evidence that pain that is clinically classified as neuropathic can be specifically attenuated by varied classes of drugs, such as those that modulate the α2δ protein of the voltage-gated neuronal calcium channel, or those that alter synaptic levels of monoamines, has radically altered the clinical approach to these problems [9]. The future is likely to bring other drugs that may be selectively analgesic in neuropathic pain, inflammatory pain, bone pain, and visceral pain – all with modes of action that involve neurotransmitters, neuromodulators, receptors, and channels that previously were not routinely targeted for therapy.

Technological advances
There also has been a revolution in drug delivery systems. Short-acting medications can now be slowly released into the bloodstream, providing sustained pain relief after a dose. Both oral and transdermal formulations have been successfully developed and have become the convention for opioid management of chronic pain. The success of patient-controlled analgesia during the past several decades has underscored the value of self-administered, rapidly acting analgesics in the setting of acute severe pain, and new studies are yielding a group of rapid-onset short-acting drugs for non-parenteral administration, such as the oral transmucosal formulations, which may provide better management of acute severe pains, including breakthrough pain [10]. Abuse-deterrent formulations of opioid drugs are in development and may help in the management of inappropriate use, or diversion, associated with long-term opioid therapy of chronic pain.

Other advances involve interventional approaches [11]. Both spinal cord stimulation and neuraxial infusion have led to the potential for improved application of these interventions. In the future, entirely new technologies, such as transcranial stimulation, may become available and offer novel strategies for selected patients with pain.

Education and policy
Although variation across states, regions, and countries is large, there is, overall, a gradual worldwide movement to mainstream pain management in healthcare, increase access to basic analgesic drugs, improve the availability and reliability of specialist-level care, and in some cases, to require that medical education include information about pain. In the US, for example, many states have substantively changed policies in an effort to eliminate barriers to the legitimate medical use of controlled prescription drugs; others have mandated pain education. It is, in many settings, an era of open discussion about the need to balance conflicting forces – access to controlled prescription drugs for pain versus reduction in drug abuse and diversion; increased availability of sophisticated pain management techniques versus fiscal constraints on healthcare; more intensive education about the molecular basis of disease versus greater emphasis on holistic care including symptom control – in a way that will ultimately yield a class of healthcare professionals and healthcare systems capable of addressing the enormous problem of acute and chronic pain.

Conclusion
The problem of pain undertreatment is widely recognized, notwithstanding the significant advances in both the science of pain and clinical practice. Access to state-of-the-art care is limited even in developed countries, and is lacking in the developing world. Remedies are possible, however, and are being driven by vibrant research and the translation of research findings into innovative therapies. Basic and clinical research, education, and societal change can provide an ever-expanding foundation for efforts to improve pain management and so address a major source of human suffering.

References
Breakthrough Pain in Cancer Patients

Giovambattista Zeppetella

Medical Director, St Clare Hospice, Essex, UK

Pain is a common feature of cancer. It is one of the most feared consequences of the disease and presents a significant clinical challenge. As pain assessment and management strategies have evolved it has become increasingly clear that patients with cancer often report variations in their pain during the course of the day. Two types of pain patterns have been identified; background pain, which is present for most of the day, and breakthrough pain (BTP), which involves a transitory exacerbation of pain. It is increasingly apparent that successful pain management strategies should distinguish BTP from background pain and implement a specific plan for its management. This is best achieved by a thorough assessment, good communication, reassurance about pain relief, and encouraging patient and care giver participation. Treatment should be appropriate for the stage of the disease and may involve a number of pharmacological and non-pharmacological modalities. Adv Pain Manage 2007;1(1):5–11.

Definition of breakthrough pain

Breakthrough pain (BTP) is a transient increase in pain intensity over background pain. It is a common and distinct component of cancer pain first highlighted in 1990 by Portenoy and Hagen [1]. The term BTP has been used to describe reports of pain that “breaks through” around-the-clock (ATC) analgesia (Fig. 1). Portenoy and Hagen described BTP in cancer patients taking opioids who reported transient increases in pain to a greater than moderate intensity [1]. However, it has since become clear that BTP is not specific either to cancer or opioid therapy. The literature contains a number of different definitions for BTP, some of which are broader than others [1–4]. This lack of consensus on a formal definition has led to difficulties when comparing studies and recommending management strategies. An international study suggested that BTP was often defined or characterized differently in different countries [5]. Additionally, variations in the terminology include episodic pain, transient pain, and pain flare [6].

The prevalence of BTP has been evaluated in a number of studies and ranges from 19–95% [7]. This wide range can be partly explained by variations in sampling procedures and inclusion/exclusion criteria across the studies. Several subtypes of BTP have been described, including incident pain, spontaneous pain, and end-of-dose pain. However, like the definition of BTP, there is no universal agreement on the subtypes, for example some describe incident pain as a subtype of BTP whilst others consider BTP as a subtype of incident pain [8].

Incident pain has been reported in 32–94% of patients [9,10]. It may be predictable when precipitated by volitional factors, such as movement, coughing, dressing changes, and increased activity, or unpredictable when precipitated by non-volitional factors, such as bladder or bowel spasm. Incident pain has been shown to be a poor predictor of successful pharmacological therapy [11,12].

Spontaneous pain has been reported in 28–45% of patients [1,10]. It develops in the absence of a specific trigger and can occur randomly and unpredictably with little or no warning. Spontaneous pain is generally less severe and of longer duration than incident pain [6] and its unpredictability makes management difficult.

End-of-dose pain has been reported in 2–29% of patients [1,10]. It consistently occurs just prior to the next scheduled dose of ATC analgesia, usually because of an inadequate analgesic dose or the interval between administrations being too long. This pain subtype typically has a gradual onset and lasts longer than incident or spontaneous pain. However, not all clinicians agree that end-of-dose pain is a true BTP subtype, as baseline pain is by definition not controlled with the optimum dose of ATC medication.

Characteristics of BTP

Investigations into the characteristics of BTP have been carried out in patients attending cancer centers, pain clinics, and hospice inpatient and outpatient units, with some studies specifically addressing BTP and others reporting BTP as an incidental finding [7]. There are currently no validated tools to assess BTP, although most studies have characterized it according to location, severity, temporal characteristics, relationship to regular analgesia, precipitating factors, predictability, pathophysiology, etiology, and palliative factors [13].

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The current evidence in cancer patients suggests that BTP can be predictable or unpredictable, typically of fast onset (reaching maximum severity within 5 min), of short duration (subsiding in most within 30 min), and feel similar to background pain although it is usually more severe. Like background pain, the pathophysiology of BTP may be visceral, somatic, neuropathic, or mixed, and the etiology may be directly due to cancer or its treatment, or may be unrelated to the cancer. Patients typically report between one to four episodes daily [6] and these can be from multiple sites or causes. Each episode of BTP should be distinguished from uncontrolled background pain.

Despite the self-limiting nature of BTP it can place significant physical, psychological, and economic burdens on both patients and their care givers. Patients with BTP are often less satisfied with their analgesic therapy [14,15], they have decreased functioning because of their pain, and may also experience social and psychosocial consequences, such as increased levels of anxiety and depression [14]. BTP can be a poor prognostic indicator [11,16] and the site of BTP may predict the response to treatment [17]. Furthermore, inadequately relieved BTP can place additional burdens on the healthcare system, with increases in emergency and medical visits, more hospital admissions, and longer stays [18]. Understanding this impact on the patient’s quality of life is important in setting realistic treatment goals.

Although most studies have focused on BTP in the cancer population, recent reports suggest that BTP is prevalent in patients with non-cancer chronic pain, sharing many of the characteristics associated with BTP in cancer pain [19,20]. Therefore, the distinction between cancer and non-cancer BTP may be arbitrary and a focus on the pain mechanisms may be more helpful in understanding this clinical problem [21].

Management of BTP
Successful management of BTP is best achieved by a thorough assessment, good communication, reassurance about pain relief, and encouraging patient and care giver participation. Key features to be identified in the assessment include the severity, pathophysiology, and etiology of the pain. Previous studies have shown that BTP is usually related to the mechanisms that cause background pain although it is often more severe. Treatment should be integrated into the overall care regime; it should be appropriate for the stage of the disease and may involve a number of treatment modalities, both pharmacological and non-pharmacological.

Non-pharmacological therapies
The non-pharmacological approaches for the management of BTP include stimulatory, rehabilitative, psychological, and complimentary techniques. Each of these options may be helpful in preventing or relieving BTP and can encourage patients to become involved in their management. Patients may volunteer that such treatments are successful although in most cases non-pharmacological therapies have not been proven through appropriately designed clinical trials. Non-pharmacological treatments can be tried either before or alongside pharmacological therapy.
Pharmacological therapies
There is currently no “gold standard” for the pharmacological treatment of BTP. It is important to individualize management and three principles have been proposed [13]:

- Implementation of primary therapies.
- Optimization of scheduled analgesia.
- Specific analgesia for BTP.

Given the heterogeneous nature of BTP a combination of the above may be required.

Implementing primary therapies
BTP may be precipitated by numerous processes, some of which may be amenable to therapy. Examples of primary interventions include management of reversible causes, such as cough, constipation, and infection, which might be related to the disease or its treatment. Other primary interventions that modify the pathological process of the disease may result in an improvement in both background pain and BTP analgesia; these include chemotherapy, hormone therapy, biological therapy, radiotherapy, and surgical procedures.

Optimizing scheduled analgesia
The World Health Organization (WHO) analgesic ladder provides a simple framework for the pharmacological management of cancer pain [22]. Presented in the form of a three-step ladder it recommends that both opioid and non-opioid analgesics should be adequately tailored for each patient according to the severity of their pain and not the disease; adjuvant analgesics may be considered at each step. In the absence of dose-limiting adverse effects, an increase in ATC opioid dose may be considered in an effort to reduce the frequency or intensity of BTP.

Adjusting the dose of ATC medication appears to be most appropriate for end-of-dose pain; the value for other types of BTP remains unclear. One study demonstrated a fall in incidence of BTP from 70% to 32% within 1 week when both ATC and adjuvant analgesics were increased; some types of BTP did not respond [17]. In another open study of patients with incident pain titration beyond analgesia and to the point of adverse effects appeared to prevent or limit BTP [23]. However, a study of 137 oncology outpatients with pain from bone metastases suggested that patients using opioids on an as-required basis reported similar degrees of pain relief to those taking opioids ATC, despite the former taking an average lower daily dose of opioid [24]. The challenge presented by short-lasting pain is that when the dose of ATC is titrated sufficiently to control it the patient may experience adverse effects during pain-free periods (Fig. 2). In these cases the ATC dose should be lowered and another management option considered.

Although the mainstay of pharmacological BTP management is opioid therapy, the possible role of non-opioids and adjuvant analgesics should not be overlooked. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in the management of mild cancer pain. There is little evidence supporting acetaminophen used alone and studies examining a possible additive analgesic effect adding concurrent opioid therapy have had conflicting
results[25,26]. In contrast, the evidence suggests NSAIDs are effective in cancer pain, both when used in a single dose and with chronic dosing, although the heterogeneity of study designs and outcome measures make analysis difficult[27–30].

Adjuvant analgesics are a heterogeneous group of drugs that include bisphosphonates, antidepressants, anticonvulsants, corticosteroids, membrane-stabilizing drugs, tranquilizers, and antispasmodics[31]. Adjuvant analgesics are usually indicated for a variety of conditions other than pain, but are capable of producing an analgesic effect. Studies have suggested a role for anticonvulsants and antidepressants in the treatment of paroxysmal neuropathic pain[32,33], and for bisphosphonates in reducing the frequency or intensity of BTP in bone metastases[34].

Nerve blocks and spinal analgesia can be used to complement oral medication in the control of cancer pain[35]. These procedures may be helpful when pain is controlled at rest, but not on movement or when localized pain breaks through otherwise well-controlled background pain. A number of procedures may be used, including local anesthetic agents, neurolytic agents, and physical agents. In the case of spinal administration, drugs may be administered through either a percutaneous catheter or a fully implanted system.

**Specific analgesia for BTP**

The management of BTP typically involves the use of supplemental analgesia or rescue medication. A number of factors should be taken into account when selecting rescue medication, including the class of drug, the route of administration, the dosage, the patient setting, and the BTP subtype[36]. The ideal rescue medication should be efficacious and patient friendly, with a rapid onset of action, a relatively short duration of action, and minimal adverse effects (Fig. 3). Rescue medication can be used either prophylactically for predictable pains or as soon as pain starts for unpredictable pains. Opioids are the most commonly used rescue medication.

**Oral opioids:** The most common method of providing rescue medication is with normal-release formulations of morphine, hydromorphone, or oxycodone. In most cases, oral opioids can take 30–40 min to produce an analgesic effect, which then lasts for 4 h[37]. Therefore, BTP with a slow onset and lasting for ≥1 h is likely to respond best to oral opioids whereas BTP of short duration may not (Fig. 4). Methadone is occasionally used for BTP rescue therapy, typically in patients receiving methadone as their ATC opioid. There is some evidence to suggest that methadone has a faster onset of action than the other oral opioids[36]; however, its use is complicated by complex pharmacokinetics and pharmacodynamics.

The most effective dose of rescue medication remains unknown. A fixed proportion of the ATC is usually advised, typically 10–15% of the daily dose, although this is based on anecdotal evidence only[38]. As BTP can vary in etiology, intensity, and duration it may be possible that the effective rescue dose will also vary. Indeed, the results of recent controlled trials with transmucosal fentanyl formulations did not confirm that the most effective dose for BTP was in fact proportional to the ATC medication dose (see below).
Although the oral route is often preferred for drug delivery, the pharmacokinetic and pharmacodynamic profile of many orally delivered opioids does not always closely mirror the characteristics of BTP. This can result in only partially effective treatment and/or troublesome adverse effects. In an effort to deliver more effective treatment, alternative routes of administration have been explored, including transmucosal opioid delivery.

**Transmucosal opioids**: Transmucosal formulations comprise a variety of delivery systems that present the drug to the oral, nasal, bronchial, or rectal mucosa. Rectal administration has been used for many years and a number of opioids are available as rectal formulations. These drugs may be useful when patients are temporarily unable to tolerate oral medication or the parenteral route becomes compromised by a bleeding disorder or generalized edema. The use of rectal drugs for BTP is compromised by dose-to-dose variability in absorption and effects, as well as limited patient acceptance for long-term use [39,40].

Inhaled opioid therapy has been described for post-operative pain [41–43], although there are few data on patients with BTP [44]. Standard nebulizer equipment can be inefficient and cumbersome and more precise devices are in development, including a formulation of free and liposome-encapsulated nebulized fentanyl in a patient-controlled analgesia system.

A number of reports have described the nasal administration of opioids [45–50]. The nasal sprays contained morphine, fentanyl, alfentanil, or sufentanil and allowed self-administration of opioid with a rapid onset of action. However, a major disadvantage with the currently available preparations is the relatively small volume of drug the nose is able to accommodate; more concentrated preparations are currently being tested by this route in clinical trials.

Sublingual and buccal transmucosal routes offer an easily accessible, convenient, non-invasive route of administration, which does not require technical equipment, expertise, preparation, and supervision. There have been reports of morphine, fentanyl, alfentanil, sufentanil, and diamorphine administered sublingually with variable results [45,51–54]. The buccal route has been a recent focus of drug development and two preparations are currently available; oral transmucosal fentanyl citrate (OTFC) and fentanyl buccal tablet (FBT), both of which have been specifically developed for the management of BTP.

OTFC is a fentanyl-impregnated lozenge applied to and absorbed across the buccal mucosa. The unit can provide pain relief within minutes and is indicated in cancer-related BTP in patients using ATC opioids for background pain. Peak effects occur within 20–30 min after the beginning of administration; approximately one-quarter of the total dose is rapidly absorbed from the buccal mucosa and becomes immediately available and approximately one-third of the remainder becomes systemically available, giving a total bioavailability of 50% [55]. A number of trials have confirmed the efficacy, safety, and tolerability of OTFC, including two randomized controlled studies and a long-term follow-up study [56–58].

FBT is a sugar-free tablet formulation that provides rapid penetration of fentanyl through the buccal mucosa by using effervescence to cause pH shifts that enhance the rate and
extent of fentanyl absorption. Compared with OTFC, FBT provides a larger proportion of the dose transmucosally (48% vs. 22%) and has an earlier T_max (47 min vs. 91 min) [59]. The efficacy of this formulation has been shown in a randomized placebo-controlled study with an open-label titration phase that demonstrated an onset of effect more rapid than would be expected from oral therapy [60].

The results of clinical trials with both OTFC and FBT suggest that the successful rescue dose cannot be predicted from the ATC opioid dose [56,57,60]. Therefore, it is recommended that each patient should be titrated to a successful dose that produces adequate analgesia and minimal adverse effects.

Parenteral opioids: Intravenous morphine has been shown to be effective, well tolerated, and safe for the inpatient management of BTP [61,62], and hydromorphone has been delivered subcutaneously using a “pain pen” [63]. In all three studies the successful dose of rescue medication was a fixed ratio of ATC opioid. However, the use of parenteral opioids is not always practical as they are invasive, inconvenient, and uncomfortable, although if pain is severe this route appears to be acceptable.

Non-opioids: Both non-opioid analgesics and adjuvant analgesics are commonly used as rescue medication. However, the slow onset, relatively long duration of action, and dose-limiting adverse effects of non-opioids often limit their utility. A number of reports have described the use of other adjuvant analgesics in the management of BTP, including nitrous oxide, ketamine, midazolam, and cannabinoids [64–68]. The evidence for these treatments is mostly in the form of case reports or small controlled studies and is often conflicting.

Summary
BTP is a heterogeneous pain state that is different for each patient, often unpredictable, typically occurs on quickly, lasts as long as 1 h, and feels much like background pain except that it may be more severe. Despite the self-limiting nature of BTP it can have a significant impact on both patients, and caregivers quality of life. The successful management of cancer pain depends on a comprehensive assessment that must take into account both background pain and BTP and may require a combination of pharmacological and non-pharmacological treatment strategies. Of the available pharmacological options, rescue dosing is commonly employed and currently the strongest evidence is for the OTFC and FBT; other options are currently being evaluated in controlled studies.

Disclosures
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References
Neuropathic pain is characterized by negative symptoms associated with the primary injury or disease affecting the nervous system as well as positive symptoms including spontaneous pain and various types of evoked pain. Several neuroanatomical, neurochemical, and inflammatory changes in the nervous system contribute to the development and maintenance of neuropathic pain. Despite common neuropathic pain symptoms in a range of neuropathic pain conditions, patients differ in their phenotypic presentation of pain, which is suggested to reflect different pain mechanisms. This review summarizes some of the mechanisms involved in neuropathic pain and discusses to what extent available treatment target specific mechanisms or specific symptoms and signs. *Adv Pain Manage* 2007;1(1):12–8.

Mechanisms of Neuropathic Pain

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Neuropathic pain can be a debilitating complication to an injury or disease of the peripheral nervous system (PNS) or central nervous system (CNS), and often has a substantial impact on the quality of life of the patient. The treatment of neuropathic pain is challenging and patients often continue to experience chronic pain despite various treatment attempts. Our understanding of the mechanisms behind neuropathic pain has grown substantially in recent decades and preclinical trials have identified new possible drug targets. However, the pain-relieving effect of any given treatment is unpredictable and patients with the same condition may respond differently to the same treatment. Therefore, a mechanism-based classification has been proposed where the symptoms and signs of pain are translated into mechanisms in an effort to improve treatment by targeting the underlying pain mechanism(s) in the individual patient [1–5].

**Mechanism-based classification**

The identification of neuropathic pain mechanisms and the translation from symptoms and signs to mechanisms is essential for a mechanism-based classification. Even though our understanding of neuropathic pain has come a long way, the translation from clinical manifestations to mechanisms is not straightforward:

- A single mechanism may be responsible for many different symptoms and signs.
- A particular symptom or sign may be caused by different mechanisms in different patients.
- Many mechanisms may operate in the same patient.
- The pain system is a dynamic and plastic system; mechanisms may change over time and may be influenced by past pain experience.
- Pain is influenced by several factors such as expectation, mood, social interactions etc. in an unpredictable way.
- Treatments that target specific symptoms and signs (or clusters of these) are needed for clinical benefit.

**Clinical characteristics of neuropathic pain**

In the clinical setting, neuropathic pain presents with a variety of symptoms. It is characterized by ongoing spontaneous pain that may be accompanied by stimulus-dependent (evoked) types of pain [6]. The spontaneous pain may be continuous and described in terms such as burning, aching, pricking, squeezing, or cold. It could be dominated by paroxysms of short-lasting shooting or electric-like pains with pain-free intervals or by a less intense background pain. Dynamic mechanical or touch-evoked allodynia (pain due to a stimulus that does not normally provoke pain) is the most common form of stimulus-dependent pain. However, allodynia to cold, warmth, pressure, and movement may also be seen. In some patients, alldynia is the dominating clinical feature. In these cases even a gentle touch, contact with clothes, or taking a shower may cause intense pain and can be disabling. Hyperalgesia (an increased response to a stimulus that is normally painful) and after-sensations (pain outlasting the time of the stimulation) may be present (Fig. 1). In some neuropathic pain conditions there are signs of sympathetic hyperactivity with excessive sweating, change in skin temperature and color, and trophic changes in the skin.

An essential part of the diagnosis of neuropathic pain is the ability to demonstrate a nervous system lesion and pain...
perceived in areas of sensory abnormality. As such, neurological examination and mapping of sensory abnormalities is essential for the diagnosis of neuropathic pain and for characterizing its numerous signs (Table 1).

**Mechanisms of neuropathic pain**

Under normal physiological conditions, pain is transmitted through small afferent C- and Aδ-nociceptors to the dorsal horn of the spinal cord. In the dorsal horn, the primary afferent releases glutamate, calcitonin gene-related peptide, substance P, and other neurotransmitters. Continuous release causes a depolarization of post-synaptic neurons displacing magnesium from the ionotropic N-methyl-D-aspartate (NMDA) glutamate receptor, which now can become activated. In basic terms, there are two ascending systems that project to the brain – a lateral system projecting via the lateral part of the thalamus to the somatosensory cortex responsible for the sensory discriminative aspects of pain, and a medial system projecting via the medial thalamus or nuclei in the brainstem and midbrain to the anterior cingulated and prefrontal cortices responsible for the motivational-affective aspects of pain [7,8].

Endogenous pain modulating systems project from the peri-aqueductal grey matter to serotonergic and noradrenergic nuclei and endogenous opiate systems. These project in turn to the spinal cord and trigeminal nuclei and modulate the transmission of pain either directly or via interneurons such as γ-aminobutyric acid (GABA) and glycine interneurons [7,9].

Neuropathic pain is a result of an abnormal response to noxious activity in the nociceptive system and a plasticity that may take place at several levels of the neural axis. Animal models of neuropathic pain have revealed a range of neuroanatomical, physiological, cellular, and chemical changes that may be involved in the development or maintenance of neuropathic pain [10–12].

**Sensitization of primary afferents**

The sensitization of nociceptors may result in spontaneous nociceptor activity and a lower threshold and higher response to suprathreshold stimuli. Microneurographic recordings from C-fibers in patients suffering from erythromelalgia and phantom limb pain suggest that spontaneous active and sensitized C-fibers play a role in both ongoing and evoked types of pain [13,14].

There are multiple mechanisms of nociceptor sensitization. After a nerve injury or inflammation of the nerve trunk, pro-inflammatory cytokines, chemokines, and neurotrophic factors released from immune cells may sensitize the nociceptor by acting on the immune receptors on its surface (Fig. 2) [15]. Wallerian degeneration may cause recruitment of macrophages and the release of chemical substances such as nerve growth factor that can sensitize spared nociceptors in their vicinity [16]. Accumulation of tetrodotoxin-resistant sodium channels may

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**Table 1. Assessment of positive symptoms and signs during bedside testing or when using quantitative sensory testing [3].**

<table>
<thead>
<tr>
<th>Clinical sign</th>
<th>Testing procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dynamic mechanical allodynia</td>
<td>Stroke the skin with a light tactile stimulus (e.g. a brush or cotton wool)</td>
</tr>
<tr>
<td>Pinprick hyperalgesia</td>
<td>Prick the skin with a pin (e.g. graded monofilaments)</td>
</tr>
<tr>
<td>Static hyperalgesia</td>
<td>Gentle pressure (e.g. a pressure algometer)</td>
</tr>
<tr>
<td>Temporal summation to punctuate</td>
<td>Repetitive pinprick stimuli (e.g. 2/s for 30 s)</td>
</tr>
<tr>
<td>stimuli (wind up)</td>
<td></td>
</tr>
<tr>
<td>Cold hyperalgesia or allodynia</td>
<td>Stimulate skin with cold metal roller or acetone or measure cold pain threshold and pain evoked by graded thermal stimuli</td>
</tr>
<tr>
<td>Heat hyperalgesia or allodynia</td>
<td>Stimulate skin with warm metal roller or measure heat pain threshold and pain evoked by graded thermal stimuli</td>
</tr>
</tbody>
</table>

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**Figure 1.** Mapping of spontaneous pain, touch-evoked allodynia, and pinprick hyperalgesia in a patient with a distal thumb amputation.
accompany increased excitability as well as spontaneous neuronal ectopic discharges in sprouts, peripheral nerves, and dorsal root ganglia [17,18]. Neurotransmitter release may also be increased by upregulation of the \( \alpha_\delta \) subunit of voltage-gated calcium channels [19]. In addition, changes in gene expression of both injured and uninjured primary afferents with increased expression of brain-derived neurotrophic factor and transient receptor potential channels have been shown to alter pain behavior in neuropathic pain models [20].

**Figure 2.** A. Upregulation of sodium channels in sprouts with spontaneous activity and reduced thresholds of peripheral nociceptors; B. nerve lesions causing deafferentation; C. sprouting of sympathetic nerve fibers around the dorsal root ganglion, upregulation of \( \alpha \)-adrenoreceptors; D. neuroimmune inflammation sensitizing peripheral nociceptors are examples of changes in the peripheral afferent that may cause changes in the central nervous system with central sensitization, disinhibition, synaptic reorganization, and descending facilitation, thereby causing higher gains in the pain system.

Spouting of primary afferents
Following peripheral nerve injury, A\( \beta \)-fibers have been shown to sprout into lamina II of the dorsal horn [21], which may be an underlying mechanism of mechanical allodynia mediated by large diameter A-fibers (as a consequence of A\( \beta \)-fibers gaining access to second-order nociceptive projection neurons). However, it has been suggested that phenotypic changes of small neurons bias the interpretation of these studies and that such sprouting of afferent fibers may be less pronounced than originally assumed [22,23]. In addition,
intraspinal sprouting of calcitonin gene-related peptides and substance P-containing fine primary afferents has been demonstrated in CNS lesions, and presumably, enhanced input to secondary order nociceptive pathways by intraspinal sprouting may contribute to abnormal somatosensory processing and development of hypersensitivity [24].

Deafferentation
Loss of C-fibers may be associated with neuropathic pain and touch-evoked allodynia (Fig. 2) [25]. The mechanism(s) by which this loss of neurons and the resulting imbalance of sensory input may cause pain are not yet clear; however, changes in the CNS due to deafferentation, such as reduced inhibition and bursting activity, may play a role. As discussed above, regenerative sprouting of A\(\beta\)-fibers due to vacant synaptic sites may be another mechanism. Alternatively, ectopic activity in the central branches of injured nociceptors or in intact deep nociceptors may be important. In central pain states, complete lesion of ascending pathways may be associated with ongoing neuropathic pain in deafferented areas [26], and lesion of the spinothalamocortical tracts has been suggested as a necessary condition for central pain in patients with stroke and multiple sclerosis [27]. Increased bursting activity in thalamic neurons may signal the pain following deafferentation [28].

Adrenergic sensitivity
In a subset of patients, the sympathetic nervous system may play a role in the maintenance of pain. In animal models of nerve injury, upregulation of \(\alpha\)-adrenergic receptors in primary afferents and sprouting of sympathetic fibers forming basket-like structures around cell bodies in dorsal root ganglia have been demonstrated [29,30]. The resulting adrenergic sensitivity may explain why, for example, the injection of norepinephrine in a stump neuroma may induce intense pain [31]. Moreover, it could be a possible mechanism for sympathetically maintained pain.

Disinhibition
Spinal inhibition plays a significant role in controlling nociceptive transmission. The ongoing activity from primary afferents has been shown to cause degeneration of inhibitory dorsal horn interneurons containing GABA, which may have an additional effect on disinhibition and thereby increase sensitivity [32,33]. Moreover, downregulation of GABA and opioid receptor levels may contribute to a reduction in tonic inhibition [34,35]. Evidence from randomized trials shows that opioids are effective in treating neuropathic pain, but the apparent lower response of neuropathic pain to opioids has been suggested to be caused by this downregulation of opioid receptors [35].

After nerve injury, reduced expression of the potassium–chloride transporter KCC2 results in a shift in the transmembrane anion gradient, causing a loss of GABA and glycinergic inhibitory tone and even inverting its action into excitation [36]. Downregulation of potassium channels and reduction in the generation of the M current, a subthreshold potassium current that stabilizes the membrane potential and controls neuronal excitability, has been implicated in enhanced excitability and ectopic activity [37].

Central sensitization
Central sensitization (enhanced responses of central pain-signaling neurons) is manifested by an increased response to synaptic inputs, decreased threshold, and expansion of receptive fields [38]. Whether or not central sensitization can become independent of peripheral input in neuropathic pain conditions is important from a treatment perspective. If it can become independent, treating the initiating mechanisms at the peripheral level will no longer be effective. Activation of NMDA receptors plays a central role in central sensitization by increasing influx of calcium ions and initiating a cascade of intracellular events [39]. Changes in the expression of sodium channels may also play a role in central sensitization, since sodium channel expression is altered in second-order dorsal horn and thalamic neurons after either PNS or CNS lesions [40].

Central sensitization is thought to explain how low-threshold A\(\beta\) mechanoreceptors gain access to pain-transmitting systems, causing normally pain-free stimuli to be perceived as painful [41]. However, other pathways may be responsible for touch-evoked allodynia. Recent studies have found that dorsal column lesions abolish touch-evoked allodynia, suggesting that higher centers are important for the access of touch stimuli to pain pathways [42,43]. This is in accordance with the notion that, in spinal cord injury patients, touch-evoked allodynia may be present in areas of complete abolition of spinothalamic function [44].

Glia cell activation
Peripheral and central nerve injuries have been shown to activate spinal cord glia cells. Microglia activation following peripheral nerve injury leads to the release of pro-inflammatory cytokines that act upon neurons, and is likely to be an important mechanism of exaggerated pain and spread of pain to neighboring healthy tissue outside of the nerve injury [15,45]. The role of glia cells in neuropathic pain is supported by studies on the transplantation of stem cells in spinal cord injury patients to improve motor impairment. If stem cells differentiate into astrocytes, allodynia-like behavior may be seen. This behavior is associated with the sprouting of nociceptive afferents, an effect that can be
blocked by directing differentiation of stem cells away from astrocytes and into oligodendrocytes [46,47].

**Descending inhibition and facilitation**

Lesions of descending inhibitory norepinephrine, serotonin (5-HT), dopamine, and opioid pathways in the dorsolateral funiculus may contribute to enhanced pain sensitivity. Descending pathways can also exert excitatory influences that facilitate noception, and studies have suggested an important role for facilitatory 5-HT pathways working via 5-HT<sub>1</sub> receptors in maintaining neuropathic pain [48].

**Are mechanism-specific treatments available?**

As discussed above, various peripheral and central mechanisms may cause an increased gain in the central pain pathways, and any drug that increases inhibition or decreases excitation (thereby exerting a net neuronal depressant effect) may relieve pain despite various initiating pain mechanisms (Fig. 2). This may be the case for opioids, for antidepressants that block the reuptake of norepinephrine or serotonin (thereby augmenting endogenous pain-suppressing pathways descending from the brainstem [49]), or for gabapentinoids that bind to presynaptic α<sub>2</sub>δ subunits of voltage-dependent calcium channels and cause a reduction in calcium influx and a reduced release of substances including excitatory amino acids [50]. Even systemic sodium channel blockers may inhibit sustained high-frequency repetitive firing in central neurons and thus be effective in pain conditions, in spite of the fact that the initiating mechanism does not involve upregulation of sodium channels in the peripheral nerve [40]. For similar reasons, it has been argued that, for the currently available drugs, efficacy in one diagnostic entity may support the use of such drug for other neuropathic pain conditions despite multiple etiologies [51].

Topical lidocaine has been assumed to act on accumulated sodium channels on sensitized nociceptors, and has thus been suggested to be effective in post-herpetic neuralgia patients with “irritable” nociceptors as opposed to patients with nociceptor deafferentation [25]. Recent studies have questioned this putative mechanism of action of topical lidocaine. In a randomized trial, patients with complete or considerable nociceptor impairment (examined using quantitative sensory testing and the histamine axon reflex test) responded well to topical lidocaine, and the authors proposed that lidocaine may target αβ-fibers, decreasing ectopic αβ-fiber discharges, thereby relieving both evoked and ongoing pain [52]. In an uncontrolled study in patients with post-herpetic neuralgia, skin biopsy, nerve conduction velocity, and quantitative sensory testing were unable to predict the patients who might respond to lidocaine [53]; even patients with complete loss of epidermal nerve fiber densities showed a response to the lidocaine patch [53]. In this study, the authors found no clear association between large-fiber sensory function and treatment response to support the hypothesis that topical lidocaine acts by stabilizing αβ-fibers. Instead, they suggested an action of lidocaine on intact nociceptors in deeper tissue. These trials emphasize the challenges researchers are facing along the way to a mechanism-based treatment approach, and that a further understanding of the mechanism of action of drugs used in neuropathic pain and development of new, more specific drugs are prerequisites for the success of such an approach.

**Are symptom-specific treatments available?**

There is little evidence from human clinical trials that specific symptoms or signs respond to specific drugs, or that the presence of specific symptoms and signs predicts a positive outcome to any given treatment. For example, randomized controlled trials have shown an effect on touch-evoked allodynia by a variety of drugs, including sodium channel blockers, NMDA antagonists, opioids, GABA-A agonists, and serotonin norepinephrine reuptake inhibitors [5].

Few studies exist that were specifically designed to evaluate the efficacy of these drugs on different neuropathic pain symptoms and signs. In patients with peripheral neuropathic pain, the effect on various types of evoked pain of intravenous alfentanil (α-opioid agonist), ketamine (an NMDA antagonist), and lidocaine (a sodium channel blocker) have been studied [54–57]. Alfentanil reduced ongoing pain, cold- and touch-evoked allodynia, and pinprick hyperalgesia [54,55], while ketamine reduced touch-evoked allodynia but had an inconsistent effect on ongoing pain, pinprick hyperalgesia, and cold allodynia [54,55,57]. In one study, lidocaine only reduced pain evoked by repetitive pinprick [57], while in another, lidocaine reduced ongoing pain and mechanical allodynia and hyperalgesia but not thermal hyperalgesia [56].

Pharmacological studies such as these are important tools in identifying pain mechanisms, but the varying results among them underscores the complex interactions between responsiveness of pain symptoms and pain mechanisms – statistical power, drug dose, placebo response, psychological factors, genetic polymorphisms etc.

Open-label studies have provided evidence that patients with post-herpetic neuralgia respond to topical lidocaine only if they have touch-evoked allodynia [58]. However, more recently, an open-label study found a significant effect of topical lidocaine patch 5% in patients with painful diabetic polyneuropathy, with comparable efficacy in patients with or without mechanical allodynia [59]. Whether or not the presence of mechanical allodynia predicts the...
response to treatment in post-herpetic neuralgia or other peripheral neuropathic pain conditions needs to be evaluated in randomized controlled trials.

Post hoc analyses of randomized trials have suggested that the presence of mechanical allodynia is predictive of the response to sodium channel blockers in both peripheral and central neuropathic pain [56,60]. In one such analysis, the severity of punctuate allodynia at baseline was found to correlate with the effects of lidocaine on spontaneous pain [56]. However, in a study designed to test this hypothesis, the presence of mechanical and/or thermal allodynia did not predict response to lidocaine in spinal cord injury pain [61]. Further studies are needed to assess whether specific types of evoked pain may be a differentiating factor.

Further studies are also needed to evaluate which symptoms and signs may be predictive of a response to treatment. Various neuropathic pain scales have been developed to assess treatment outcomes for different pain qualities:

- Neuropathic Pain Scale [62].
- Pain Quality Assessment Scale [63].
- Neuropathic Pain Symptom Inventory [64].
- Neuropathic Pain Questionnaire [65].

Each of these questionnaires assesses burning and evoked pain and, depending on the scale, descriptors such as shooting, freezing, squeezing, dull, and itchy pain are also evaluated. Quantitative sensory testing (QST) may aid in assessing and quantifying sensory loss, as well as sensory hypersensitivity to mechanical and thermal stimuli. Other procedures such as the histamine test, capsaicin application, and skin biopsies have been used to explore the function of the sensory nervous system. The German Research Network on Neuropathic Pain is an initiative that uses a standardized QST protocol to phenotypically characterize patients with various neuropathic pain conditions [66]. It is assumed that a specific pattern of symptoms and signs predicts an underlying mechanism. It remains to be seen whether the phenotypic classification of patients will result in treatment benefits, and whether this and other such initiatives will lead to better prediction of underlying mechanisms and improved treatment of the individual pain patient.

Conclusion
Despite the increasing knowledge on pain mechanisms, treatment of neuropathic pain is still unsatisfactory. Development of pharmacological agents with specific targets and of diagnostic methods to identify mechanisms are important steps for further progress in developing a mechanism based treatment approach. Further studies will show whether we will be able to identify underlying mechanisms in the single pain patient and treat these accordingly.

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Bisphosphonate Therapy for Non-Cancer Pain

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Over the years, intravenous bisphosphonate therapy has been proven highly valuable in the management of pathological conditions associated with abnormal bone metabolism: hypercalcemia of malignancy, cancer bone pain, and osteoporosis. A growing clinical experience and a number of studies have recently helped identify a role for bisphosphonates in the management of chronic non-cancer pain states. Bisphosphonate-responsive pain mechanisms might not be unique to cancer, and may play a role in maintaining pain in subgroups of non-oncological patients suffering from complex regional pain syndrome, chronic back pain, Paget’s disease, ankylosing spondylitis, and other inflammatory arthropathies. Moreover, multiple lines of evidence gleaned from preclinical studies have corroborated the analgesic action of bisphosphonates and have revealed a dose-dependent effect in numerous animal models of inflammatory and neuropathic pain. Recently, immunohistochemical studies have revealed an extensive network of nerve fibers in the vicinity and within the skeleton, not only in the periosteum but also in cortical and trabecular bone as well as in the bone marrow. The activation of bone nociceptors is the pathophysiological basis of bone pain. Putative bisphosphonate-responsive pain mechanisms and how they interfere with the network of bone nociceptors are hereafter discussed. Bone pain mechanisms might be more prevalent and clinically more relevant than previously thought. This review will focus on the bisphosphonates putative mechanisms of analgesia and on the off-label use of bisphosphonates as analgesics or analgesic adjuvants in the management of several non-cancer painful conditions. Adv Pain Manage 2007;1(1):19–23.
quickly as a sponge, absorbing almost the entire IV infusion dose. The rest of the dose remains unmetabolized and undergoes urine excretion. The pharmacokinetics of bisphosphonates is complex. These drugs remain attached to bone for weeks to months. The amount of drug released in the plasma and then in the urine is related to the rate of bone metabolism and turnover, which can result in a protracted terminal elimination half-life of bisphosphonates.

Bisphosphonates are generally well tolerated and when appropriately administrated, are associated with very transient and manageable side effects; however, in the oncology field, there is an emergent concern about a complication known as osteonecrosis of the jaw [1]. The disorder may affect a subgroup of patients with cancer on chronic bisphosphonate treatment for multiple myeloma or breast, prostate, or lung cancer bone metastases. Tissue biopsies of the affected jaw lesions have revealed findings consistent with osteomyelitis. Major risk factors include prolonged treatment with potent bisphosphonates (i.e. monthly IV administration for more than 1–2 years), poor oral hygiene, and a history of a recent dental extraction or dental implant.

This review will focus on the bisphosphonates putative mechanisms of analgesia and on the off-label use of bisphosphonates as analgesics or analgesic adjuvants in the management of several non-cancer painful conditions, including bone and joint pain states and complex regional pain syndrome.

Mechanisms of analgesia

The idea that IV bisphosphonates might decrease pain arose from observations of patients who were receiving intravenous clodronate for hypercalcemia due to bone metastases. Bisphosphonate treatment was associated not only with a significant reduction in pathological fractures and hypercalcemia, but also with a quick relief of severe bone pain [2,3], e.g. “immediately after the first infusion” [4] “within 10–14 days” [5], “within a matter of days” [6], and “within 1 month of infusion” [7].

Approximately 50% or more of the patients treated with intravenous pamidronate at regular intervals, ranging from weekly to every 3 months, had relief of cancer-related bone pain [5,8].

Bone is a common site of metastatic spread for renal cell carcinoma, non-Hodgkin’s lymphoma, as well as for cancer of the thyroid, breast, and colon. We are just beginning to understand the pathophysiological mechanism of pain in cancer patients with bone metastases. The presence of pain is not associated with the type of tumor or its location, the number or size of metastases, gender, or age of patients. Moreover, although approximately 80% of patients with breast cancer will develop osteolytic or osteoblastic metastases, about two-thirds of demonstrated sites of bone metastases are painless [9].

Therefore, while metastasis may be strongly associated with cancer-related bone pain, its presence is not a sufficient requirement for the development of pain.

Immunohistochemical studies have revealed an extensive network of nerve fibers in the vicinity and within the skeleton, not only in the periosteum but also in cortical and trabecular bone as well as in the bone marrow [10]. Thinly myelinated and unmyelinated peptidergic sensory fibers, as well as sympathetic fibers, occur throughout the bone marrow, mineralized bone, and the periosteum. Although the periosteum receives the densest innervation, when the total bone volume is taken into consideration, it is the bone marrow that receives the highest number of nerve fibers.

When malignant cells infiltrate bone spaces, osteoclastic activity is enhanced. Multiple algogenic factors such as increased concentration of extracellular protons, local synthesis of nerve growth factor (NGF), and release of proteases and inflammatory substances, such as cytokines and prostaglandins (PGs), might act synergistically to achieve enough critical mass and activate the extensive network of nociceptors and sensory fibers innervating the cortical and trabecular bone as well as the bone marrow. The activation of bone nociceptors is the pathophysiological basis of bone pain.

The majority of sensory afferents in the bone are calcitonin gene-related peptide (CGRP)-, capsaicin receptor transient receptor potential vanilloid subtype 1 (TRPV1)-, and the high affinity tyrosine kinase receptor for NGF (TrkA)-expressing fibers [11,12].

A potential mechanism of bone pain may be the acidic microenvironment (pH 4.0) produced by the local release of...
protons from activated osteoclasts. A low pH activates the capsaicin receptor TRPV1 involved in primary sensory afferents heat- and proton-transduction mechanisms [13,14]. Therefore, by inhibiting activity of osteoclasts or even causing their apoptosis [15], bisphosphonates can decrease local tissue acidosis and act as analgesics for all those pain conditions where noceception is driven by osteoclasts.

Another potentially relevant pain mechanism for bone cancer pain is the activity of NGF on bone nociceptors. NGF was lately found to have a relevant role in bone pain; it induces hyperalgesia via upregulation of transcription for genes encoding receptors, ion channels (e.g. capsaicin receptor TRPV1), and neuropeptides (e.g. CGRP, substance P). Pre-clinical evidence indicates that bone pain can successfully be relieved by anti-NGF immunoglobulin G (IgG) therapy [16]. NGF expression is enhanced in bone inflammation, bone cancer, trauma, and fractures. NGF is produced by many cellular elements, including resident mast cells, activated macrophages, endothelial cells, and bone marrow stromal cells [17,18].

Bisphosphonates may act as analgesics by inhibiting NGF expressing cells and interfering with their NGF synthesis. There is evidence that tumor cells, endothelial cells, and activated macrophages when directly exposed to bisphosphonates in vitro or in vivo can suffer from bisphosphonate-induced toxic effects and even undergo apoptosis [19–21].

Of further interest is the role of neuropeptides such as CGRP and substance P in generating the so-called neurogenic inflammation of bone and periosteum. Within the bone, unmyelinated peptidergic nerve fibers run intertwined with the blood vessels. Once activated, afferent nerve fibers release CGRP and substance P. Neuropeptides can activate mast cells (a potent source of NGF) and endothelial cells to cause vasodilatation and plasma extravasation. Moreover, the presence of receptors for CGRP and substance P has recently been described on osteoclasts and osteoblasts. CGRP and substance P appear to regulate osteoclast formation, bone formation, and resorption [10].

Other relevant effects of the bisphosphonates include inhibition on the synthesis of matrix metalloproteinases (MMP-1, MMP-3, MMP-8), as well pro-inflammatory cytokines, and PGE2 [19,22].

Multiple lines of evidence gleaned from pre-clinical studies corroborate the analgesic action of these drugs. These studies have revealed a dose-dependent analgesic effect in animal models of inflammatory, neuropathic, and cancer pain [15,23–25].

In the tail-flick and writhing tests in rodents, the analgesic effect of several bisphosphonates administered IV and/or intracerebroventricularly (ICV) was identified. Pre-clinical studies revealed prolonged central and peripheral analgesic properties of the bisphosphonates for non-bone-related pain states [26,27].

Alendronate suppressed the acetic acid-induced writhing response, but had no effect on the formalin-evoked nociceptive response in the hindpaws of mice [28]. In the sciatic nerve ligation animal model of neuropathic pain, bisphosphonates not only reduced the number of activated macrophages infiltrating the injured nerve and Wallerian nerve fiber degeneration, but also decreased experimental hyperalgesia [29]. Lastly, in animal models of arthritis, some evidence suggests that bisphosphonates not only possess an anti-inflammatory effect via apoptosis of active macrophages, but also can prevent arthritis-induced joint degeneration [30,31].

Bisphosphonates for painful joint and bone syndromes
The vast majority of patients with chronic axial back pain are diagnosed as having chronic back pain of non-specific origin (i.e. without evidence of specific structural diseases or etiologies known to cause back pain). This pain is conventionally regarded as pain secondary to spondylitic disease or degenerative disc disease (i.e. discogenic pain). Nevertheless, the exact mechanisms underlying chronic back pain of non-specific origin have remained elusive. The poor correlation between back pain and routine imaging studies (X-ray, magnetic resonance imaging) findings is not surprising since most mechanical pain is unrelated to gross anatomical conditions that alter skeletal anatomy, such as degenerative disc disease or spondylitic disease. Approximately 95% of adult patients with back pain have mechanical pain of non-specific origin, and a precise pathoanatomical diagnosis cannot be identified in the vast majority of patients with axial back pain. An open-label trial of intravenous pamidronate therapy was recently conducted in patients (n=25) with chronic axial back pain of non-cancer origin unresponsive to nonsteroidal anti-inflammatory drugs (NSAIDs). None of the patients had a history of osteoporotic vertebral fractures or metastatic disease. Improvement in pain was observed in the majority of these patients. Their average pain intensity following treatment decreased by 3.6 points (on the 0–10 numeric rating scale) from baseline. The investigation revealed no increase in opioid or non-opioid analgesics associated with the bisphosphonate-related pain relief [32]. This experience, although very preliminary, suggests that a subgroup of patients with chronic back pain might suffer from bisphosphonate responsive bone pain. Within the spine, bone pain mechanisms might be active at the vertebral endplates, at the facet joint subchondral surface, and at the periosteum. Moreover, bone pain
Complex regional pain syndrome

Complex regional pain syndrome (CRPS), formerly known as reflex sympathetic dystrophy (RSD), is a debilitating pain syndrome that has been recognized for more than a century. In 1993, a Special Consensus Workshop of the International Association for the Study of Pain (IASP) convened to examine and revise the IASP taxonomy and to redefine RSD by international agreement. It was determined that RSD should be reclassified in the pain taxonomy as CRPS. Despite the long history of this disorder, the pathophysiology of CRPS has remained elusive.

Of interest are the regional skeletal changes observed in several cases of CRPS. Although it has lost diagnostic purposes, a three-phase bone scintigraphy is still used in the evaluation of this disorder. Bone scintigraphy utilizes a technetium-99 radio-labeled bisphosphonate as an intravenous marker. The review of pre-IASP diagnostic criteria literature reveals that this test was reported to have a 50% diagnostic sensitivity and 90% diagnostic specificity, especially in cases of RSD with a duration <6 months and in patients >50 years [43,44]. The typical RSD bone scan findings consisted of a homogeneous unilateral marker uptake or hyperperfusion within the bone of the affected limb during phase 1 (“perfusion phase” 30 s after the marker injection) and phase 2 (“blood pool phase” 2 min after injection). During phase 3 (“mineralization phase”, 3 h after injection), the hyperperfusion is followed by a characteristic uptake of the radio-labeled bisphosphonate in the joints of the affected limb.

A review of the literature reveals multiple studies of bisphosphonates for CRPS. To date, four trials of intravenous pamidronate for CRPS have been published. Maillefert et al. in 1995 reported on seven of 11 patients with CRPS, who experienced clinically significant improvement from pamidronate therapy [45]. Cortet et al., in 1997, reported on 10 women and 13 men with CRPS, who showed highly significant pain reduction and physical functional improvement [46]. Kubalek et al., in 2001, treated 29 patients with CRPS [47]. Twenty-five of the patients experienced excellent pain relief from IV pamidronate at a dose of 60 mg/day for 3 consecutive days. Lastly, in a double-blind, randomized placebo-controlled trial of IV pamidronate (n=27), the active treatment group (n=14) reported significant improvement in pain and physical function at 3 months post-infusion [48]. In a controlled trial of clodronate, 32 CRPS patients were randomized to receive either IV clodronate (300 mg daily) for 10 consecutive days or placebo [49]. This trial demonstrated significant efficacy of the clodronate treatment over placebo. Adami et al. reported that among 20 patients with CRPS, IV alendronate relieved pain by at least 50% in 13 patients, and those who received two infusions performed better than those who received one [50]. Finally, Manicourt et al. conducted a randomized controlled trial of oral alendronate (40 mg daily) for 8 weeks versus placebo in patients (n=40) with post-traumatic CRPS of the lower extremities [51]. The alendronate-treated patients exhibited a significant and sustained improvement in levels of spontaneous pain, mechanical pressure, and joint mobility.

Several lines of evidence suggest that a subgroup of patients with CRPS might have bisphosphonate-responsive bone pain. Therefore, it is conceivable that bisphosphonate-responsive pain mechanisms might be involved in maintaining some of the symptoms of CRPS.

Conclusion

Over the years, IV bisphosphonate therapy has proved highly valuable in the management of numerous bone-related conditions, including hypercalcemia of malignancy, cancer bone pain, and osteoporosis.

A growing experience and a number of studies have recently help to identify a role for bisphosphonates in the management of pain states. It appears that bisphosphonate responsive bone pain mechanisms might not be unique to cancer and might play a role in a subgroup of non-oncological patients suffering from chronic back pain, AS, other inflammatory rheumatoid diseases, Paget’s disease of bone, and CRPS.
Bone pain mechanisms might be more prevalent and clinically more relevant than previously thought. These considerations will hopefully help us to better understand complex pain mechanisms and pursue new research avenues for the treatment of some of the most challenging and distressing pain conditions.

Disclosure

Dr Pappagallo is a member of the scientific advisory boards for Anesiva and GSK.

References

Clinical reviews were prepared by Lara Dhingra and Helena Knotkova

NOVEL THERAPIES

Efficacy and safety of a single botulinum type A toxin complex treatment (Dysport®) for the relief of upper back myofascial pain syndrome: results from a randomized double-blind placebo-controlled multicentre study
Göbel H, Heinze A, Reichel G et al., on behalf of Dysport myofascial pain study group.

This randomized, placebo-controlled, double-blind trial evaluated the efficacy and safety of botulinum type A toxin (BoNT-A) for the treatment of myofascial pain syndrome. Participants (n=145) received 10 trigger point injections weekly for 12 weeks. At week 5, significantly more patients who received BoNT-A reported “mild or no pain” (51%) compared with patients who received placebo (26%). Baseline changes in pain intensity were significantly better in the BoNT-A group compared with the placebo group at weeks 5–8. Significantly more adverse events (AEs) were reported in the intervention arm (46) versus the control arm (19), with 75% of AEs reported as mild-to-moderate in severity. In this sample, BoNT-A significantly alleviated myofascial pain compared with placebo, and was well-tolerated.

Botulinum type A toxin (BoNT-A; Dysport®, Ipsen Ltd., Slough, UK) is a useful treatment for a variety of pain disorders. Prior studies show that BoNT-A may be an efficacious therapy for myofascial pain syndrome. These small studies (6–40 patients) demonstrated that BoNT-A injections are associated with significantly reduced pain compared with placebo and methylprednisolone therapy. This study addressed previous research gaps by utilizing a larger sample size, using larger doses of BoNT-A, and tailoring the site of trigger point injections based on patient preference.

The narrow inclusion criteria for the study precluded mild pain intensity, prior treatment with BoNT-A, recent participation in other trials, and use of specific medications up to 4 weeks pre-treatment.

Following a 1-week baseline period, physicians injected placebo or 40 Ipsen units of Dysport into 10 trigger points for a 12-week period, and patients completed daily pain diaries.

The primary outcome was the percentage of patients with mild or no pain at week 5 (e.g. mean scores from diary data). Secondary outcomes included changes in pain severity (intensity and duration), number of pain-free days/weeks, sleep duration, trigger point data (number and pain intensity), and length of time to reduced pain. Patient and physician preference for repeated treatments were recorded. Safety indices included number of adverse events (AEs), vital signs, and tolerability.

Results indicated that 145 patients were randomized to the study (placebo group=70, Dysport group=75), with 120 completers in the analyses. At week 5, significantly more patients in the Dysport group reported mild or no pain (51%) compared with patients in the placebo group (26%). Overall, the number of responders in the Dysport group was higher than in the placebo group, with significant differences at 5, 6, and 11 weeks. The change from baseline in pain intensity over time was statistically significant during weeks 5–8. The Dysport group had significantly more pain-free days and more “mild or no pain” days during weeks 5–12. Mean pain intensity for trigger points was significantly lower in the Dysport group compared with the placebo group at weeks 4–12. Physicians’ and patients’ preferences for repeated treatments were higher in the Dysport group. A trend for AEs resolution was observed by weeks 8 and 12. Dysport showed beneficial effects at weeks 4–6 following treatment initiation.

A major strength of the study is the sample selection, which included a clearly defined patient population. Sound methodological design and a large sample size are additional strengths. The current study might have benefited from more details about how the intention-to-treat analyses were conducted, and a rationale for the selection of dosages and for expected improvement of pain at 5 weeks. Future trials are needed to replicate and extend these promising results.

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Fentanyl buccal tablet (FBT) for relief of breakthrough pain in opioid-treated patients with chronic low back pain: a randomized, placebo-controlled study

This randomized, double-blind placebo-controlled trial evaluated fentanyl buccal tablet (FBT) for breakthrough pain (BTP) in opioid-treated patients with chronic low back pain. The results showed that FBT was efficacious and well tolerated in the treatment of BTP. This was the first study of FBT in a population with chronic non-cancer pain.

There is an emerging consensus that long-term opioid therapy may be effective in carefully selected patients with chronic non-cancer pain. The standard of care for the treatment of cancer-related breakthrough pain (BTP) relies on the oral administration of an immediate-release, short-acting opioid formulation, taken as required to supplement a fixed-schedule opioid regimen. This approach has been empirically extrapolated to the treatment of BTP in selected patients with chronic non-cancer-related pain. The present randomized, double-blind placebo-controlled study was undertaken to evaluate the efficacy and tolerability of fentanyl buccal tablet (FBT; Fentora, Cephalon, Inc., Frazer, PA, USA), in a population of opioid-treated patients with chronic low back pain. Participants were patients receiving long-term opioid therapy for chronic low back pain at 16 pain treatment centers in the US. Of the 105 patients enrolled, 77 entered the double-blind phase. Following open-label titration to identify an effective FBT dose, patients were randomly assigned to one of three double-blind dose sequences (six doses of FBT, three placebo) to treat nine BTP episodes. Pain intensity, measured on an 11-point scale (0=no pain, 10=worst pain), and other outcomes were assessed for 2 h after dosing. Results showed that 81% of patients with BTP associated with chronic non-cancer pain identified an effective dose during the open-label dose-titration phase. In the double-blind phase, FBT was found to be efficacious compared with placebo, producing effects as early as 10 min after administration that were sustained throughout the 2-h period of observation. Evidence of early treatment effect was observed in all secondary efficacy measures. No correlations were found between the effective doses of FBT and either the baseline fixed-schedule opioid regimen or quantity of supplemental opioids used prior to the study. This observation indicates that selection of a supplemental dose based on the dose of the fixed-schedule regimen, which is conventional practice, is not appropriate for FBT.

FBT should be initiated at a low starting dose (100 μg) and then titrated to an effective dose. The exploratory covariate analyses suggested that age, gender, and functional status were associated with the response of patients to FBT. The reasons that women, patients in some age groups, and patients with relatively high (but not the highest) disability may be more likely to respond to FBT than to placebo are not apparent from the data. The results of this controlled study show that FBT was efficacious and well tolerated in the management of opioid-treated patients with BTP associated with chronic low back pain. It is the first such study in non-cancer-related BTP and provides evidence that a rapid-onset opioid can provide meaningful pain relief in patients with chronic pain not associated with cancer.

Randomised controlled trial of a short course of traditional acupuncture compared with usual care for persistent non-specific low back pain

The aim of this study was to determine whether a short course of traditional acupuncture improves lower back pain at 12 and 24 months after treatment to a greater extent than usual care. The results showed no functional improvement at any time point after the acupuncture. In terms of pain, there was weak evidence of a beneficial effect of acupuncture at 12 months, and stronger evidence of a small benefit at 24 months.

Non-specific lower back pain is typically intermittent and recurrent, and is associated with high health, social, and economic costs. The aim of this open-label randomized study was to determine whether a short course (10 sessions) of traditional acupuncture improves long-term outcomes in patients with persistent non-specific lower back pain in primary care.

The 241 participants were adult patients (aged 18–65 years) who were assessed by their general practitioner after presenting with lower back pain. Participants were randomized to receive either 10 sessions of acupuncture or usual care only. The usual care involved a variety of approaches, including physiotherapy, massage, and exercise. The primary outcome measure was the bodily pain dimension of the 36-item short form health survey (SF-36), scored on a scale of 0–100, at 12 months. Secondary outcomes were measured at 3, 12, and 24 months using the disability index, the McGill present pain index, and

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remaining dimensions of the SF-36. At 12 months there were no significant differences between the two groups in any outcome measure. At 24 months, patients receiving acupuncture reported significantly less pain than the group receiving usual care only, with an estimated intervention effect of 8.0 points (95% confidence interval 2.8–13.2) after adjustment for baseline score and for any clustering of intervention patients by acupuncturist. No significant differences were found for other outcomes (e.g. the disability index). Thus, from a long-term perspective, a short course of acupuncture may result in better pain relief than conventional treatment, but not functional improvement.

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OPIOIDS

Opioid escalation in patients with cancer pain: the effect of age
Mercadante S, Ferrera P, Villari P et al.

This study evaluated differences between younger and older cancer patients in terms of opioid effects during dose refinement. Data were gathered from 100 patients requiring opioid dose escalation. The authors evaluated pain intensity, opioid dose, number of opioids used, routes of administration, and opioid-related symptoms from admission until dose stabilization. The results indicated that, although the elderly required lower doses of opioids, opioid effects did not vary with age.

Patients with cancer pain often require opioid escalation to maintain opioid efficacy, and this may cause considerable concern in the elderly, who are potentially more susceptible to the development of adverse effects as a result of age-related changes in pharmacokinetics. Based on this, the authors of this prospective cohort study aimed to determine whether there are any differences between younger and older cancer patients with respect to opioid effects during dose refinement.

Consecutive patients (n=100) who were already receiving opioids and were admitted to a palliative care unit for inadequate pain control participated in the study. For the purpose of the analysis, patients were divided into three age groups:

- <65 years (n=58).
- 65–74 years (n=27).
- ≥75 years (n=10).

Five patients had incomplete data and were not included in the analysis. The authors recorded patients' pain intensity, opioid dose, number of opioids used, routes of administration, and opioid-related symptoms from admission until dose stabilization, and opioid escalation indexes (OEIs) were calculated. The results showed that older patients were on lower doses of opioids at admission. However, there were no differences between younger and older patients in terms of routes of administration, need to switch, OEIs, or other parameters. Moreover, adverse effects did not significantly differ between the three age groups. An overall distress score worsened in older patients during acute titration but improved when the dose stabilized.

The results of this study contradict the assumption that older patients who are already receiving opioids are more susceptible than younger patients to opioid effects during opioid titration. The data indicate that, although the elderly require lower doses of opioids, opioid effects do not vary with age. However, these findings should be interpreted with caution because the sample size in this study was relatively small.

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Factors associated with early opioid prescription among workers with low back injuries
Stover BD, Turner JA, Franklin G et al.

In this prospective cohort study, the authors examined factors associated with, and the prescription of opioids for, work-related lower back injuries. The results indicated that, compared with non-Hispanic, white individuals, Hispanic individuals were less likely to receive opioid prescriptions. Other characteristics associated with opioid prescription included daily tobacco use, greater pain and physical disability, greater injury severity, pain radiating below the knee, very high body mass index, and worse mental health.

The prescription of opioids for non-malignant musculoskeletal pain has substantially increased in recent years. However, there is little empirical evidence to guide decisions on opioid prescriptions for musculoskeletal pain. The present study therefore aimed to investigate potential relationships between early opioid prescription and worker characteristics in 1067 individuals with work-related back injuries.

The authors examined whether any administrative, pharmacy, or worker-reported data were associated with the
The mechanisms of opioid-induced hyperalgesia need illumination. This study examined the function of neurokinin-1 (NK-1) receptor expressing cells in the spinal dorsal horn on morphine-induced hyperalgesia and spinal antinociceptive tolerance in rats. Ablation of NK-1 receptor expressing cells via intrathecal substance P-saporin prevented thermal and tactile hypersensitivity, and antinociceptive tolerance. Ablation appears to trigger descending pathway activity and relates to spinal neuroplasticity, even when tissue damage is absent.

Opioid-induced hyperalgesia (OIH) may be an important effect of opioid therapy. Thus, evaluating potential mechanisms of OIH could optimize new therapeutic strategies. Neurokinin-1 (NK-1) receptor expressing cells have been implicated in OIH. Prior studies show that ablation blocks opioid-induced thermal and tactile hypersensitivity, neuropathic pain, and sensitization of spinal dorsal horn cells when tissue injury is present.

To examine the functional role of NK-1 receptor expressing cells in conditions without tissue injury, the authors of this study ablated these cells using intrathecal substance P-saporin (SP-SAP). Groups of 6–8 rats received intrathecal SP-SAP or placebo with uninterrupted delivery for 1 week by osmotic minipumps. To establish thermal hyperalgesia, latency responses to noxious thermal stimuli were recorded. Antinociceptive tolerance was indicated by rightward shifts in morphine dose–response curves. Post mortem immunoassays revealed spinal dynorphin content and evaluation of mild tactile stimulation determined FOS protein expression. Morphine-induced thermal and mechanical hypersensitivity, and antinociceptive tolerance was assessed using injections of saline or ondansetron (e.g. 5-hydroxytryptamine 3 receptor antagonist).

The ablation of NK-1 receptor expressing cells resulted in the prevention of the following effects:

- Morphine-induced thermal and tactile hypersensitivity.
- Amplified touch-evoked spinal FOS expression.
- Upregulation of spinal dynorphin.
- Rightward displacement of the morphine dose–response curves (e.g. antinociceptive tolerance).

These findings showed that spinal NK-1 receptor expressing cells:

- Are essential to opiate-induced spinal plasticity, a potential underpinning of behavioral hypersensitivity and central sensitization.
- Are vital for opiate-induced antinociceptive tolerance.
- May be a vehicle for activating the descending facilitatory pathways.

Furthermore, by blocking OIH, spinal ondansetron demonstrated that serotonin may play a role in descending facilitation from the rostral ventromedial medulla.

These effects are consistent with other studies in injury-induced pain that support the role of NK-1 receptor expressing cells in mechanisms of hyperalgesia and antinociceptive tolerance. Ablation of the lamina I projection neurons that express NK-1 receptors appeared to eradicate the ascending limb of this “spinal-bulbospinal loop”, the resultant features of central sensitization, and antinociceptive tolerance. These results may lead to the development of an
explanatory model of OIH and innovative therapeutic approaches that do not heighten pain sensitivity. However, the relevance of the results and the translation of these data from animal models to clinical studies in humans is unknown. This study might have benefited from additional details differentiating mechanisms of OIH from opioid tolerance.

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### Parental history of chronic pain may be associated with impairments in endogenous opioid analgesic systems

**Bruehl S, Chung OY.**


This double-blind, placebo-controlled crossover study investigated whether a positive parental chronic pain history was associated with impaired endogenous opioid analgesic responses to acute pain. Subjects with a positive parental chronic pain history failed to exhibit any endogenous opioid analgesia to acute ischemic pain, while subjects without a positive parental chronic pain history elicited effective opioid analgesia. However, there were no significant differences between these two groups of subjects in terms of finger pressure pain responses.

Previous studies have suggested an association between a family history of chronic pain and an increased risk of both spontaneous acute pain and chronic pain conditions [1–6]. The authors of this study tested whether a parental history of chronic pain (PH+) is associated with the degree of endogenous opioid analgesia elicited in response to two laboratory acute pain stimuli.

The study sample consisted of 73 patients with chronic lower back pain (including 43 PH+ subjects) and 46 healthy, pain-free controls (including 13 PH+ subjects) received opioid blockade and placebo blockade in separate sessions. During each session, participants underwent a finger pressure pain task and an ischemic forearm pain task. The effects of blockade were determined by subtracting placebo from blockade condition pain responses. The results of placebo blockade revealed that both that both PH+ subjects and subjects with lower back pain reported greater acute pain sensitivity than their respective comparison groups (both p<0.05). PH+ subjects had an impaired endogenous opioid analgesic response to acute ischemic pain, whereas PH− subjects elicited effective opioid analgesia (p<0.05); the observed opioid analgesic impairments were particularly prominent in PH+ subjects with lower back pain, and there were no significant differences in pain duration or intensity between PH− and PH+ subjects with lower back pain. The impairment of the endogenous opioid analgesic response was not detected in the finger pressure pain task. Because of the inconsistency of the response across the two tasks, the results should be interpreted with caution.


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### Do opiates affect the clinical evaluation of patients with acute abdominal pain?

**Ranji SR, Goldman LE, Simel DL et al.**

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This study investigated the effect of opiate analgesics on the rational clinical examination and the decision of whether to perform surgery in patients with acute abdominal pain. Using a literature survey, the authors analyzed data from placebo-controlled trials on opiate analgesia. The results indicated that, although opiate administration may alter the physical examination findings, these changes do not result in a significant increase in management errors.

In the US, abdominal pain is the most common reason for presentation at the emergency department. Historically, the provision of opiate analgesia to patients with acute abdominal pain has been discouraged. Thus, patients with acute abdominal pain may have to wait several hours before receiving analgesia, particularly when surgical evaluation is required. Qualitative reviews of the literature have reached inconsistent conclusions about the evidence supporting the traditional practice of withholding analgesics [1,2]. Thus, the aim of the present study was to perform a quantitative assessment of the effects of opiate administration to patients with acute abdominal pain.

The authors performed a focused search in medical databases (MEDLINE, EMBASE) and hand searches of article bibliographies to identify placebo-controlled, randomized trials on opiate analgesia reporting changes in the history, physical examination findings, or diagnostic errors. Nine trials in adults and three trials in children were identified and analyzed. The results showed trends toward increased risks...
of altered findings on the abdominal examination due to opiate administration. Analyzed trials exhibited significant heterogeneity, and only two trials distinguished between clinically significant changes (such as loss of peritoneal signs) and other, potentially beneficial, changes. However, across adult and pediatric trials with adequate analgesia, opiate administration was associated with non-significant changes in the risk of management errors.

The study indicated that opiate analgesics do alter the physical examination in patients with acute abdominal pain but seem to have little impact on the risk of clinical management errors. However, these results should be interpreted with caution because of the methodological limitations of the study (e.g. heterogeneity of trials or inconsistent data, low number of analyzed trials).


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POST-OPERATIVE PAIN

Fentanyl iontophoretic transdermal system for acute-pain management after orthopedic surgery: a comparative study with morphine intravenous patient-controlled analgesia


The results of this multicenter, randomized, open-label active-controlled study indicate that the fentanyl HCl iontophoretic transdermal system and morphine intravenous patient-controlled analgesia are comparable methods of pain control for management of acute post-operative pain following unilateral hip replacement.

Post-operative pain after total hip replacement is commonly managed with intravenous patient-controlled analgesia (IV PCA). Limitations of IV PCA pumps include the need for IV access, restricted patient mobility, and the possibility of interrupted pain control as a result of device-related events. A novel patient-controlled system that administers on-demand doses of fentanyl via the transdermal route (ITS) has recently been approved by the US Food and Drug Administration for the management of acute post-operative pain in adults. A previous study demonstrated similar rates of success between ITS and IV PCA, as measured by Patient Global Assessment (PGA) [1]. However, it is possible that adequate pain control was not achieved when these systems were initiated because the entry criteria of this study did not include a minimum pain intensity score. The current study investigated whether the predefined level of comfort required before randomization led to higher rates of success according to PGA rating. The authors’ primary aim was to demonstrate that fentanyl ITS is comparable to morphine IV PCA in terms of convenience, safety and efficacy as a method of maintaining established pain control after total hip replacement.

Subjects were randomized to receive ITS (n=395, 40 μg fentanyl, 10-min infusion/lockout, up to 6 doses/h) or IV PCA (n=404, 1-mg morphine bolus, 5-min lockout, up to 10 mg/h) after unilateral total-hip replacement. A pain intensity score of ≤4 on a verbal numerical rating scale (where 0=no pain and 10=worst possible pain) during post-operative screening was required for inclusion into the study. The PGA success ratings (“good” or “excellent”) and the mean last pain intensity scores were similar for the ITS and IV PCA groups in the first 24 h after the operation. The two groups had a comparable incidence of adverse events; however, a higher proportion of patients in the ITS group withdrew from the study because of inadequate analgesia. This difference in the dropout rate warrants further investigation to determine whether it remains in a more naturalistic setting.


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Postoperative analgesia after radical retropubic prostatectomy: a double-blind comparison between low thoracic epidural and patient controlled intravenous analgesia


This double-blind randomized study compared low thoracic epidural analgesia and patient-controlled intravenous analgesia for treatment of post-operative pain after radical retropubic prostatectomy. Sixty patients participated in the study. The study results indicated better pain relief and improved expiratory muscle function in the group of patients receiving low thoracic epidural analgesia.
functions, the time to mobilization, home readiness, and actual duration of hospital stay. Sixty patients undergoing radical retropubic prostatectomy for prostatic cancer were randomized to receive post-operatively either an infusion of:

- 1 mg/mL ropivacaine, 2 g/mL fentanyl, and 2 g/mL adrenaline, 10 mL/h during 48 h epidurally, and a placebo intravenous PCA pump.
- An intravenous PCA pump with morphine and 10 mL/h placebo epidurally.

Pain, the primary outcome variable, was measured using the numeric rating scale at rest and on coughing. The results showed significantly lower pain scores in the epidural group compared with the intravenous PCA group. This resulted in improved expiratory muscle function as measured by the maximum expiratory pressure. However, the authors found that the improvement in pain relief with epidural analgesia did not translate into a reduction in minor or major post-operative complications or duration of hospital stay. Quality of life was poorer in both groups at 1 month compared with preoperative values, but no interaction was seen between group and time during the study period. The benefits of low thoracic epidural anesthesia should be weighed against the rare complications seen, the possible higher costs, and the increased time taken in patient preparation.

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PALLIATIVE CARE

Multidisciplinary management of cancer pain: a longitudinal retrospective study on a cohort of end-stage cancer patients
Peng WL, Wu GJ, Sun WZ et al.

This retrospective survey of 772 patients with advanced cancer investigated the epidemiology of cancer pain and the outcomes associated with pain treatments. The cumulative prevalence of pain in the study sample was 87%. Strong opioids had been used in 85% patients, and 79% of patients with pain received non-surgical antineoplastic treatment for pain control. No more than 11% had substantial pain in the last 6 months of life.

Pain is a very common and potentially debilitating symptom in cancer patients. Besides the guidelines set out by the World Health Organization for improving the treatment of cancer pain, multidisciplinary pain management has also been widely accepted as a standard of care. Although previously published surveys presented data from large samples of patients [1–3], they were not representative of a general cancer population at various stages of disease. Thus, the present survey intended to investigate the pain management of a wide range of cancer patients generally cared for by oncologists and surgeons, rather than only those referred to a pain clinic, to reduce possible selection, referral, and observer bias.

The authors examined the medical records of 772 patients with advanced cancer. The results revealed that 87% of patients suffered from pain at various time periods, while 13% of patients were pain-free throughout their survival; the mean duration of pain was approximately 7 months. During the last 6 months of life, the prevalence of pain increased as the survival time shortened. The survey also identified a list of analgesics used to manage pain:

- Tramadol was predominantly used in the “weak” opioid category.
- Meperidine was briefly used for post-operative pain or after invasive interventions
- Patient-controlled analgesia and intraspinal analgesia were used in patients with intractable pain.
- Strontium-89 was indicated in patients with multifocal bone pain.

Strong opioids had been used in 85% patients, and 79% of patients with pain received non-surgical antineoplastic treatment for pain control. No more than 11% experienced substantial pain in the last 6 months of life.

The authors concluded that a multidisciplinary approach to pain management offers effective pain control for most patients with advanced cancer. Although this study was a retrospective review, which has disadvantages such as incomplete data collection and a lack of control subjects, the survey overcomes the limitations of previous studies, and contributes to a better understanding of the current status of management of cancer pain.

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A population-based study of the impact of specific symptoms on quality of life in women with breast cancer 1 year after diagnosis

Arndt V, Stegmaier C, Ziegler H et al.

This study aimed to identify specific symptoms predicting long-term impairment and overall quality of life (QOL) in 314 women with breast cancer who had completed primary therapy. Fatigue was the strongest predictor of QOL, accounting for approximately 30–50% of the variability within function scores and overall QOL, while other symptoms, including pain, nausea and/or vomiting, breast symptoms, systemic therapy side effects, and arm symptoms, generally accounted for <5% of the variability of various QOL scales.

Specific symptoms such as pain, fatigue, and sleeping disorders are a particular concern in women with breast cancer, and these symptoms may have a negative effect on their quality of life (QOL) even after the period of acute treatment. However, little is known about the importance of various breast cancer symptoms to impairment of function, and few studies have specifically addressed the impact of specific symptoms such as fatigue and arm or breast symptoms on performance of life functions in cancer survivors. Therefore, in the present study, the authors aimed to quantitatively assess the role specific symptoms or health complaints play in specific impairments to function and in overall QOL.

The study included a population-based, state-wide cohort of 387 German breast cancer patients. After a comprehensive baseline interview, patients were followed with respect to QOL using mailed questionnaires, namely, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 Items (QLQ-C30) and the EORTC breast cancer-specific module QLQ-BR23 1 year after diagnosis, and the vital status of non-respondents was obtained from the municipal registration offices. Multiple linear regression analysis revealed that fatigue was the strongest predictor, accounting for approximately 30–50% of the variability within function scores and overall QOL. In contrast, sociodemographic and clinical factors did not affect QOL to a significant extent. As fatigue is relatively common in women with breast cancer, efforts to reduce fatigue may have a large potential to improve overall QOL in women with breast cancer. The authors suggest that patients may benefit from physician-initiated discussion of causes of and treatments for fatigue, and that physicians may benefit from education regarding available treatment modalities. It is interesting to note that this is the first study to provide a comprehensive quantitative analysis of the contribution of various symptoms to overall QOL and its specific dimensions.

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NEUROPATHIC PAIN

Analgesic action of nicotine on tibial nerve transection (TNT)-induced mechanical allodynia through enhancement of the glycinergic inhibitory system in spinal cord

Abdin J, Morioka N, Morita K et al.

It is unclear which subtypes of nicotinic acetylcholine receptors (nAChRs) are involved in the antinociceptive effect of nicotine on allodynia induced by nerve injury. This study investigated the effects of nicotine at the spinal level against mechanical allodynia in an animal model of neuropathic pain. The results indicate that the α4β2 and α7 nAChRs exert the suppressive effect on the nociceptive transduction in neuropathic pain by enhancing activity of glycinergic neurons at the spinal level.

Damage to peripheral nerves triggered by surgery, an infection, or diabetes has been suggested to induce a tactile allodynia, which is a state of pain produced by innocuous stimuli. Although several studies have suggested antinociceptive actions of nicotine or nicotinic acetylcholine receptor (nAChR) agonists [1–4], it is not unclear whether stimulation of nAChRs at the spinal level has an antinociceptive effect on nerve injury-induced allodynia, and it remains to be established which subtypes of the receptor might be involved in the analgesic action of nicotine. Therefore, in the present study, the authors aimed to characterize the effects of nicotine or nicotinic agonists, at the spinal level, on mechanical allodynia in an animal model, inducing neuropathic pain by the tibial nerve transection (TNT).

In a set of experiments in male Wistar rats, the intrathecal injection of nicotine, RJR-2403 (a selective α4β2 nAChR agonist), and choline (a selective α7 nAChR agonist) stimulated an antinociceptive effect on the TNT-induced allodynia. Pretreatment with mecamylamine (a nonselective nicotinic antagonist), or dihydro-β-erythroidine (a selective α4β2 nAChR antagonist) almost completely blocked the effects of nicotine, and pretreatment with methyllycaconitine (a selective α7 nAChR antagonist) partially reversed the...
effects. Pretreatment with strychnine (a glycine receptor antagonist) blocked the antinoceptive effect of nicotine, RJR-2403, and choline, whereas the γ-aminobutyrate (GABA) antagonist bicuculline did not.

These results indicate that the intrathecal administration of nicotine has an antinoceptive effect on TNT-induced allodynia, which might involve stimulation of the α4β2 and α7 subtypes of nAChR at the spinal level. The authors concluded that the glycnergic inhibitory system, but not the GABAergic inhibitory system, might contribute to the antinoceptive effect of nicotine on nerve injury-induced allodynia.


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Effect of spinal cord stimulation in an animal model of neuropathic pain relates to degree of tactile “allodynia”


This study evaluated the impact of spinal cord stimulation (SCS) on analgesia according to the severity of mechanical allodynia in a rat model of neuropathic pain. Based on measurement of the withdrawal response to tactile stimuli, rats with severe allodynia did not respond to SCS, whereas rats with mild allodynia had more optimal pain relief. These findings may have potential clinical implications on predicting patient response to SCS as related to allodynia severity.

Spinal cord stimulation (SCS) is widely-used for the treatment of chronic neuropathic pain. For patients treated with SCS in complex regional pain syndrome (CRPS), mixed results have been found on the relationship between pain relief and allodynia severity. It is possible that the degree of allodynia severity (mild, moderate, or severe) predicts the magnitude of pain relief from SCS.

Following sciatic nerve ligation in 45 rats, the role of allodynia severity on pain was examined in 27 rats with tactile sensitivity due to neuropathic pain. Tactile sensitivity in rats was comparable to tactile allodynia in humans with nerve damage. Allodynia was classified as “mild” (n=6), “moderate” (n=14), or “severe” (n=7) based on the withdrawal response in the lesioned foot following tactile stimulation with von Frey filaments.

SCS systems were implanted in the epidural space of rats following protocols in previous studies. Following the administration of SCS for 30 minutes, the withdrawal thresholds were measured at 15 minute intervals.

A series of t-tests for dependent samples were conducted, comparing withdrawal threshold during and after SCS, with the withdrawal thresholds prior to the stimulus.

Results showed that the severity of allodynia was positively correlated with response to SCS. Rats with mild allodynia had the most superior response, with a full return to baseline, pre-nerve lesion withdrawal threshold levels. In contrast, rats with moderate allodynia responded to SCS; however, the withdrawal thresholds improved to approximately 33% of the baseline function. Finally, rats in the severely allodynic group had no response to SCS.

In this study, rats with mild allodynia had a more rapid and optimal response to SCS compared with rats with severe allodynia. The potential clinical significance of allodynia severity on differences in SCS pain relief outcomes in humans requires additional investigation.

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Prevalence of contraindicated medical conditions and use of precluded medications in patients with painful neuropathic disorders prescribed amitriptyline


Amitriptyline is often prescribed in the management of painful neuropathic disorders (PNDs). However, the amitriptyline label contains many preclusions (contraindications, warnings/precautions, drug interactions). This study investigated the frequency of amitriptyline prescriptions in PND patients and assessed whether prescriptions were given to patients with any of the preclusions listed in the product label. Based on data from 13 546 patients, the results indicated that, in a significant number of cases, the existence of preclusions did not prevent the prescribing of amitriptyline.

Amitriptyline is recommended as first-line therapy for the management of neuropathic pain, although it is not approved for this indication in the UK. The decision to prescribe this medication to patients with painful neuropathic disorders (PNDs) must be made following a careful evaluation of the preclusions (contraindications, warnings/precautions, drug...
interactions) listed in the label. In cases where the use of amitriptyline is not completely contraindicated, but there is a comorbid presence of a warning or potential for a drug interaction, an intensified level of medical vigilance may be required. The present study aimed to determine the frequency of amitriptyline prescriptions in PND patients and to evaluate whether prescriptions are given to patients with any of the preclusions. Using the UK General Practice Research Database, the authors identified a total of 13,546 patients diagnosed with PND who had received at least one prescription for amitriptyline between July 1998 and June 2001. Overall, 46.7% of PND patients prescribed amitriptyline had one or more preclusions for its use, 3.5% had at least one contraindication, 22% had one or more warning or precaution, and 33% were taking one or more medication with a potential for drug interactions with amitriptyline. These results indicate that the prescribing of amitriptyline among PND patients with any preclusions is relatively common in UK. According to the authors, a possible explanation for this practice is that the number and efficacy of medications available for management of neuropathic pain are limited. Furthermore, amitriptyline is relatively inexpensive and is indicated for the treatment of depression, a known comorbidity among PND patients. Thus, it is possible that the proven efficacy of amitriptyline in depression as well as in neuropathic pain was the primary impetus for its prescribing in PND patients. The findings of this study raise concerns about the way in which amitriptyline is being used.

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Molecular mechanism for analgesia involving specific antagonism of α9α10 nicotinic acetylcholine receptors
Vincler M, Wittenauer S, Parker R et al.
PNAS 2006;103:17880–4.

Using a rat model, this study proposes a molecular mechanism for the pathogenesis of neuropathic pain involving RgIA, a potent antagonist of the α9α10 nicotinic acetylcholine receptor (nAChR). Findings show that blockade of the α9α10 nAChRs produces antinociceptive effects in peripheral nerve damaged rats, and decreases the movement of choline acetyltransferase-positive cells, macrophages, and lymphocytes into the nerve injured site.

Neuropathic pain is prevalent worldwide; however, the complex determinants require much investigation. Previous studies have shown that nicotinic acetylcholine receptors (nAChR) are implicated in peripheral nerve damage. This study examined an animal model to expand on prior studies in order to specify a mediator of nAChR site activity.

Following chronic constriction injury (CCI) of the sciatic nerve in rats, behavioral testing and immunohistochemistry revealed the following:

- RgIA, a potent α9α10 antagonist, at the highest dose produced analgesia and negated CCI-induced mechanical hypersensitivity.
- Vc1.1 in CCI rats significantly lengthened paw withdrawal thresholds due to analgesic effects, and subsequently reduced CCI-induced mechanical hypersensitivity similar to RgIA.
- Following CCI's effects on amplifying the number of choline acetyltransferase (ChAT)-immunoreactive cells in the ligated sciatic nerve, RgIA modified the peripheral immune response by decreasing the number of ChAT immunoreactive cells.

In this study, the administration of RgIA produced analgesia on nerve injured rats. Furthermore, selective blockade with RgIA decreased the number of ChAT-positive cells, macrophages, and lymphocytes. Whereas previous findings have shown that nicotinic agonists result in analgesia, this study demonstrated that nAChR antagonism of the α9α10 receptor subtype produced analgesia. Future studies focusing on α9α10 nAChRs may lead to the development of novel pharmacological therapies for neuropathic pain.

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Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial
Siddall PJ, Cousins MJ, Otte A et al.
Neurology 2006;70:1792–800.

This randomized controlled trial examined the efficacy and safety of pregabalin (150–600 mg) on central neuropathic pain in adults with spinal cord injury. At day 7 of this 12-week trial, the lowest dose of 150 mg was associated with significant reductions in pain intensity. Efficacy findings were consistent for 12 weeks, suggesting that pregabalin taken as a monotherapy or supplemental therapy may be effective for moderate-to-severe neuropathic pain.

Central neuropathic pain is a consequence of multiple medical conditions, including 40% of spinal cord injured patients. Pregabalin is presently effective in treating seizure disorders,
anxiety, peripheral neuropathic pain, and pain-related sleep disturbance. To evaluate the efficacy of pregabalin on central neuropathic pain in spinal cord injured patients, a multicenter, randomized, placebo-controlled trial was conducted.

Using flexible dose escalation, patients were randomized to pregabalin 150–600 mg twice daily (n=70) or placebo (n=67) over 12 weeks. Pregabalin was given as a monotherapy or supplemental therapy, with continuation of pre-study medications permitted. Patients were treated with 150 mg of pregabalin for 1 week, followed by 300 mg at week 2, and escalated to 600 mg at week 3, if needed.

The primary endpoints included mean pain intensity (based on the following 7 days of patients’ pain diary data) and safety. Secondary endpoints included responder rates, the Short-Form McGill Pain Questionnaire, sleep interference (diary data; Medical Outcomes Study Sleep Scale), and psychological distress (Hospital Anxiety and Depression Scale).

Pregabalin was associated with significant reductions in mean pain intensity from baseline to endpoint (6.5 vs. 4.6) while placebo was not (6.7 vs. 6.3). At day 7, pain was significantly reduced with pregabalin 150 mg/day, the lowest dose, and continued to be lower than placebo for 12 weeks. The average dose of pregabalin was 460 mg between weeks 4–12. The magnitude of improvement did not differ significantly whether pregabalin was supplemental (70% of patients) or administered as a monotherapy. In the pregabalin group, 42% reported ≥30% pain reduction and 22% reported ≥50% reduction. Over 33% of patients reported no to mild pain at endpoint (compared with 11% in placebo).

Overall, pregabalin was well-tolerated, with somnolence the most common adverse event (41.4%) followed by dizziness (24.3%). Attributed due to adverse events was 21%. Pregabalin was related to significantly better sleep quality, lower sleep disturbance, and lower levels of anxiety, but was unrelated to depression.

In this study, pregabalin was associated with clinically significant reductions in central neuropathic pain. Future trials are needed to validate these results in patients with spinal cord injury and other patient subgroups.

**CLINICAL REVIEWS**

Based on the finding that fibromyalgia syndrome (FMS) is more prevalent among women than men, this study investigated whether and how sex hormones may be involved in the pathophysiology of the disorder. The authors evaluated levels of sex hormones and pain sensitivity during different phases of the menstrual cycle in women with FMS and in age-matched healthy controls. The results suggest that the disproportionate prevalence of FMS in women is not likely due to hormonal factors.

Fibromyalgia syndrome (FMS) is a musculoskeletal pain disorder estimated to affect 3–5% of population. One of the intriguing characteristics of this disorder is its higher prevalence in women (4.9%) than in men (1.3%). The authors of this study investigated whether FMS is associated with any abnormalities in sex hormone levels during different phases of the menstrual cycle, and whether pain sensitivity is affected by sex hormone levels in female FMS patients or healthy controls. The study included 74 women with FMS and 74 age-matched healthy controls who were regularly menstruating and not taking hormone-based contraception. All participants underwent a 9-day urine test to identify the date of ovulation, and then three study visits were scheduled to determine levels of sex hormones at the late-follicular phase, mid-luteal phase, and peri-menstrual phase of the menstrual cycle. At each visit, pain threshold and tolerance were determined using the ischemic pain test. The results showed that, compared with healthy controls, women with FMS had lower pain thresholds and tolerance throughout the menstrual cycle. Levels of luteal hormone, follicular-stimulating hormone, estrogen, and testosterone were similar in the two groups throughout the menstrual cycle. FMS patients had slightly elevated progesterone levels during the mid-luteal phase, but these were within the normal range. The phasing of the menstrual cycles in this study appeared to show normal cycling patterns for both groups, with high levels of estradiol and progesterone in the mid-luteal phase, low levels of these hormones in the peri-menstrual phase, and elevated levels of estradiol and low levels of progesterone in the late follicular phase. The results suggest that the disproportionate representation of women among FMS patients is not likely due to abnormal levels of sex hormones. The results are consistent with previous studies performing single-phase assessment of sex steroids [1–3].

**MISCELLANEOUS**

**Sex hormones and pain in regularly menstruating women with fibromyalgia syndrome**

Okifuji A, Turk DC.


Pain perception and expression: the influence of gender, personal self-efficacy, and lifespan socialization

Miller C, Newton SE.


Behavioral and psychosocial factors may affect pain experience more than biomedical factors. This review of the empirical literature describes the roles of gender, self-efficacy, and lifespan socialization on pain experience.

Pain is not only a function of physical pathology, but psychosocial and behavioral factors that contribute to the pain experience. This literature review describes three relevant variables that may play important roles on pain experience: gender, self-efficacy (SE), and lifespan socialization.

Gender predicts pain perceptions and pain experience. A review of the findings shows that women have lower pain thresholds, greater ability to differentiate pain, and report higher pain ratings for noxious stimuli compared with men. Women report more sites of pain in endogenous pain compared with men. A large survey showed that women were more likely to report severe pain and have more frequent episodes of severe pain than men.

One potential explanation is that SE mediates the relationship between gender and pain perception. Perceived SE is the belief in one’s ability to perform specific behaviors in order to produce a desired outcome due to personal experience, modeling of social behavior, and arousal [1]. Jackson et al. showed that physical SE fully mediated the relationship between gender and pain [2]. In this study, beliefs about physical capabilities accounted for gender differences in pain. Men reported lower pain sensitivity and higher pain tolerance compared with women. Therefore, sociocultural influences may shape personal beliefs about one’s capacity to manage pain and express pain-related distress. More men report discouragement in childhood from expressing pain-specific distress and encouragement to display more stoic responses to pain.

In addition, coping style may moderate the relationship between gender and pain experience. Women may report more psychological distress to elicit interpersonal support, as women tend to prefer communal approaches; therefore, SE for intrapersonal coping with pain may be less salient to their preferred style of coping.

Developmental data show that infants with acute pain express no differences in pain behaviors or facial muscle action by gender. Thus, the theory that sociocultural influences shape pain perception and experience appears relevant. Cross-cultural findings show that women and men believe it is more appropriate for women to report pain than men. Overall, Indian men and women believed it was less appropriate to express pain compared with participants in the US.

Implications for nursing include pain assessment techniques that appreciate the potential influence of these person-level variables. Healthcare providers may need to increase awareness of possible differences in communication, expression, and preferred coping approaches. Tailoring the delivery of pain education and pain management strategies according to gender may be useful.


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Multiple dose gabapentin attenuates cutaneous pain and central sensitisation but not muscle pain in healthy volunteers

Segerdahl M.

Pain 2006;125:158–64.

This double-blind, placebo-controlled, crossover study compared the effect of gabapentin (GBP; 0, 1200, 1800, and 2600 mg) on muscle and cutaneous pain in healthy participants. Single or multiple dosing of GBP relieved pain sensitivity to intracutaneous electrical stimulation, but did not attenuate pain induced by intramuscular infusion of hypertonic saline.

Gabapentin (GBP) is well-known to be efficacious in the treatment of chronic neuropathic pain. The efficacy of GBP as an adjunct to acute post-operative pain therapy has been recently demonstrated. No known studies have evaluated the effect of GBP on muscle and cutaneous pain. Muscle pain is a major clinical concern, and efficacious treatments for chronic muscle pain are presently limited.

The author of the current study examined the effect of single-dose GBP (1200 and 2600 mg) and placebo on continuous intracutaneous electrical stimulation (CESS), and intramuscular (IM) infusion of hypertonic saline in eight men and eight women volunteers. Participants received the following treatments in a randomized, crossover design: a single-dose of GBP 1200 mg over 24 h; GBP 600 mg three times daily plus 800 mg (2600 mg in total); and placebo. CESS was administered in the forearm and intensified until the current produced pain intensity of 5/10 or reached 70mA. CESS has been proposed to induce pain by activating mechano-insensitive C-fibers.

The study of variance analyses for multiple dependent samples compared placebo and active treatment, and chi
Clinical Reviews

Sacral insufficiency fractures: current concepts of management

Sacral insufficiency fractures (SIFs) are a type of stress fracture causing significant pain and disability in elderly adults. The incidence of SIFs is expected to rise worldwide as the population ages. However, SIFs are commonly underdiagnosed in elderly patients due to nonspecific symptoms and radiographic findings. Postmenopausal osteoporosis is the main risk factor for SIFs, followed by corticosteroid-induced osteopenia and pelvic irradiation. Treatments include bed rest, analgesia, rehabilitation, and physical therapy, with some patients requiring hospitalization. This article describes the epidemiology, pathophysiology, and differential diagnosis of SIFs, and reviews best practices for prevention and treatment.

Rates of sacral insufficiency fractures (SIFs) will increase significantly by 2030 due to the growing elderly population and improved imaging. Research is needed to examine the prevalence and financial costs of SIFs. Multiple case studies (e.g. 3–20 patients) have documented the biomedical and clinical characteristics of SIFs.

SIFs are frequently underdiagnosed as a cause of pain and disability in elderly and high-risk populations. At present, there is no standardized classification criteria. Denis et al. have proposed classifying SIFs by site (zone) and sequelae [1]:

- Zone 1 (most cases): Fractures of the sacral ala that are unrelated to neurological impairments, but may cause injury to the lumbar-sacral nerve roots.
- Zone 2: Fractures of the sacral foramina that are linked to unilateral lumbosacral radiculopathies.
- Zone 3: Fractures throughout the sacrum that are associated with neurological deficits and sphincter dysfunction.

The pathophysiology of SIFs is bilateral on onset, occurring in the sacral ala, with concurrent fractures of the pelvic ring causing breakdown of the osteoporotic sacrum. Approximately 66% of patients with SIFs lack a history of trauma, therefore fracture is rarely suspected.

Post-menopausal osteoporosis is a leading risk factor for SIFs, with corticosteroid-induced osteopenia, pelvic irradiation, and secondary osteoporosis also potential factors. In addition, vitamin D insufficiency and pregnancy-related osteoporosis are associated with SIFs.

Clinical symptoms are gradual in onset and are characterized by potentially severe pain in the low back and pelvis, causing functional impairment. Physical examination is remarkable for Sacral tenderness on lateral compression (sacroiliac joint tests such as flexion-abduction-external rotation, Gaenslen’s test, and squish test are diagnostically useful) and a slowed gait.

The use of radiographic imaging is compromised by a lack of trauma or visible fractures, curvature of the sacrum, and demineralization. Differential diagnosis is complex given that findings often resemble metastatic disease, sacroiliac joint infection, and spinal stenosis. Many SIFs are confused with malignancies and osteomyelitis; thus, computed tomography is useful for differential diagnosis. Magnetic resonance imaging is the most valid diagnostic method.

Given the link with osteopenia, SIFs may be prevented by vitamin D, calcium, and bisphosphonates. Teriparatide and selective oestrogen receptor modulators are effective for treating osteoporosis. Opioids may be indicated, but the efficacy of nonsteroidal anti-inflammatory drugs on fractures is unknown. Recent data show that rehabilitation may be more effective in reducing SIF-associated morbidity than bed rest. Ongoing research is evaluating the efficacy of sacroplasty for stabilization of the fracture.

This quality review provides a comprehensive analysis of SIFs and establishes a clear rationale for their significance to clinicians. However, it could benefit from greater discussion of areas for additional research, a critique of the empirical findings, and clearer differentiation of SIFs from other insufficiency fractures of the pelvic ring.

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