Advances in PAIN MANAGEMENT

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Dear Colleagues,

Welcome to the second issue of Advances in Pain Management.

In our first leading article, Drs Hsu and Clauw (University of Michigan Medical School, Ann Arbor, MI, USA) discuss fibromyalgia and chronic widespread pain, focusing on the translation of the most recent concepts in pathophysiology into clinical practice. In addition, this article provides a comprehensive update on the clinical presentation and natural history of the condition as well as a discussion on the state-of-the-art pharmacological and non-pharmacological treatment strategies.

In the second article, Dr Fillingim (University of Florida, Gainesville, FL, USA) explores sex differences in the experience of pain, with a discussion that includes epidemiological considerations, differences in the response to the analgesic effect of opioids, and the clinical implications of these differences. This topic, which is frequently overlooked by the general reader, provides important insight into clinical practice.

In the third article, Drs Manchikanti, Boswell, and Giordano (University of Louisville, KY, USA and Georgetown University Medical Center, Washington, DC, USA) present an evidence-based review on the interventional approaches to the diagnosis and treatment of chronic lower back pain. The review includes clinical pearls and guides the reader through the complex diagnostic algorithm. Due to the high prevalence of this condition and the financial implications associated with this disability, this has become an extremely important topic to those who practice in the front line of the healthcare system.

This issue also includes highlights from the American Academy of Pain Medicine 23rd annual meeting and a synopsis and critique of recently published scientific findings from several key areas of pain management.

In this era where communication reigns and the volume of information escapes scrutiny by the time it reaches the most dedicated reader, this publication can be a very 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 and the publisher of Advances in Pain Management, we would like to thank everyone for all the positive feedback received after the first issue of what we believe will be an exciting and useful new journal in this developing field.

Faculty Disclosures

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Aims and Scope

Advances in Pain Management is designed to bring a critical analysis of the world pain medicine literature, to an international, multidisciplinary audience. Our mission is to promote a better understanding of pain medicine by providing an active forum for the discussion of clinical and healthcare issues. Leading Articles—These major review articles are chosen to reflect topical clinical and healthcare issues in pain medicine. All contributions undergo a strict editorial review process. Clinical Reviews—The most important articles from the best of the international literature on pain medicine are systematically selected by the Editor-in-Chief and Associate Editor. The Editors then prepare concise and critical analyses of each article and, most importantly, place the findings into clinical context. Meeting Reports—Advances in Pain Management also provides incisive reportage from the most important international congresses.

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Update on Fibromyalgia and Chronic Widespread Pain: Translating Recent Findings into Clinical Practice

Michael C Hsu, MD1 and Daniel J Clauw, MD2

1Department of Physical Medicine & Rehabilitation, and 2Division of Rheumatology, Department of Medicine, University of Michigan Medical School, Ann Arbor, MI, USA.

New findings in patients with fibromyalgia (FM) and chronic widespread pain (CWP) have fundamentally changed the way we view these syndromes. Once thought to be largely inflammatory in nature, FM and CWP have since been shown to be primarily disorders of central pain processing. This review summarizes the recent epidemiological and mechanistic research in these syndromes and proposes a three-stage model for the pathogenesis and maintenance of FM and CWP. Furthermore, this article will review the clinical presentation and natural history of these disorders, and provide evidence-based guidelines for various pharmacological and non-pharmacological treatments. In addition, future research may show these interventions to be successful in other chronic multisymptom illnesses. Adv Pain Manage 2007;1(2):38–45.

The past decade has seen an increasing acceptance among clinicians regarding the validity of fibromyalgia (FM) as a disease entity. In addition, there has been a surge of high-quality research in FM and related syndromes. FM is now recognized to be one of many central pain syndromes that include irritable bowel syndrome (IBS), temporomandibular joint disorders (TMJD), and a variety of other conditions in which the fundamental problem seems to be a disturbance in pain processing, rather than tissue damage or inflammation at the site where the pain is experienced. This review will focus on new insights into the epidemiology and pathogenesis of FM and its related condition, chronic widespread pain (CWP), and will provide recommendations regarding evidence-based treatment.

Epidemiology

CWP is defined as pain lasting for at least 3 months involving both left and right sides of the body and regions above and below the waist, including the axial skeleton. The 1990 American College of Rheumatology (ACR) defines FM as CWP plus the presence of 11 out of 18 possible tender points [1]. In Western countries, CWP afflicts approximately 4–11% of the population [2], whereas the more narrowly defined syndrome of FM affects 0.5–4% [3].

The tender points that distinguish FM from CWP have no inherent biological properties and research has revealed that patients with FM have tenderness not only at these points, but throughout their entire body [4]. Furthermore, the tender point count has been shown to reflect levels of psychological distress, and is weakly associated with more sophisticated tests of pain sensitivity to mechanical pressure [5]. It remains unclear whether FM is pathologically distinct from other syndromes that might present with CWP, such as myofascial pain syndrome [6]. Given that there has been no new consensus regarding a clinical definition of FM since 1990, this article is limited to discussing FM and CWP as separate diagnostic entities, despite the lack of biological distinction between FM and other forms of CWP.

Risk factors

Prospective population-based studies have identified several risk factors for the development of CWP and FM (Table 1). These include previous pain in multiple distinct locations (such as the shoulder, back, and neck), increased age, high levels of somatic symptoms and health-seeking behavior, sleep difficulties, and workplace stress [7–10].

Comorbid overlapping conditions

Individuals with CWP and FM are more likely to meet criteria for the diagnosis of chronic fatigue syndrome (CFS), IBS, TMJD, vulvodynia, and migraine compared with the general population [11]. In addition, the symptom spectrum of CWP and FM overlaps considerably with multiple chemical sensitivity...
and Gulf War Illness [12,13]. Due to the co-aggregation of these diagnostic entities, some authors use the term “chronic multisymptom illness” (CMI) to refer to this spectrum of disorders [14].

Familial and genetic inheritance
One of the most dramatic findings in recent years has been the considerable degree of familial inheritance found in FM and other CMI diagnoses. In a study involving 533 relatives of 78 probands with FM, Arnold et al. found a markedly increased prevalence of FM in the relatives of the patients suffering from FM compared with the relatives of probands with rheumatoid arthritis (odds ratio of 8.5) [15]. Buskila and colleagues found that a dopamine D4 receptor exon III repeat polymorphism occurred less frequently in FM patients than in controls [16]. Moreover, Offenbaecher et al. reported a two-fold increase in the S/S genotype of the serotonin transporter gene in FM patients compared with healthy controls [17]. A key observation regarding these genetic studies is that the genes of interest are relevant to central and sympathetic nervous system pathways, rather than musculoskeletal tissues. Furthermore, physiological studies suggest dysfunction of descending antinociceptive pathways, which generally involve catecholamine and serotonin neurotransmission, in the pathophysiology of FM [18].

Pathogenesis and maintenance of CWP and FM
Although controversy continues among researchers regarding the pathogenesis of CWP and FM, it has been established that they are multifactorial in nature, with both genetic and environmental factors being involved. The following three-stage model (Fig. 1) reflects the authors’ interpretation of various mechanistic and epidemiological findings in this spectrum of illness. This model should be treated as speculative and is not meant to act as an authoritative consensus regarding the pathogenesis of CWP and FM.

Stage 1: Baseline neurobiological factors
A healthy individual may be at risk of developing FM or CWP if he or she displays certain baseline neurobiological factors due to genetic predisposition or early life stress [19], such as:

- General sensory augmentation (including non-nociceptive signals).
- Dominance of facilitative over inhibitory pain processing centers within the central nervous system (CNS).
- Dysregulation of descending monoaminergic (e.g. dopamine, norepinephrine, serotonin) pathways.
- Hypothalamic–pituitary–adrenal (HPA) axis dysfunction.

General sensory augmentation is thought to occur within the CNS of such individuals, and refers to increased sensitivity to pressure, heat, cold, loud noises, and other sensory stimuli [20]. Dysregulation of descending monoaminergic pathways refers to reduced activity of descending “gate-control” mechanisms involving serotonin, norepinephrine, and dopamine, which has been suggested by several studies in FM [21–23]. Conversely, the endogenous opioid system seems to be functioning properly in these patients [24].

HPA axis dysfunction refers to a decrease in counter-inflammatory cortisol response and diurnal cortisol fluctuation, which has been found in healthy subjects who subsequently develop widespread pain [25,26]. This profile of HPA dysfunction is typically found in settings of chronic psychosocial stress [27], which is commonly reported in patients preceding the onset of their FM [28].

Stage 2: Excessive nociceptive firing and central sensitization
The neurobiological factors in stage 1 may set the individual up for acute widespread pain when combined with an inflammatory trigger such as acute trauma, infection, or even a brief period (e.g. 10 days) of sleep and exercise deprivation (which would typically follow an acute injury). In stage 2, this “trigger” would lead to an unchecked increase in inflammatory cytokines due to the impaired cortisol response, which would then stimulate and sensitize peripheral nociceptors [29,30], causing acute local or widespread pain and tenderness. After a sufficient period of time, particularly in the absence of adequate gate-control mechanisms, “central sensitization” (via N-methyl-D-aspartic acid receptor-mediated mechanisms) may develop in the dorsal horn of the spinal cord [31], leading to hyperesthesia and allodynia. Although none of these processes has been documented in the development of FM as yet, the authors believe that this
stage may provide a link between baseline neurobiological factors, triggers of acute pain, and the eventual development of centrally mediated pain in FM.

Some autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis, may serve as triggers in stage 2 [32]. Similarly, hepatitis C, Epstein–Barr virus, Lyme disease, and other infections may also play a role in triggering the onset of symptoms for a subset of patients [33]. However, by the time individuals are diagnosed with CWP or FM, the overwhelming majority of patients do not have any evidence of ongoing infection or frank inflammation [34].

**Stage 3: Perpetuation of the diathesis**

Stage 3 involves the maintenance of widespread pain via neurobiological and cognitive–behavioral traits that perpetuate the various conditions found in stages 1 and 2. For example, fear-avoidance behavior often leads to exercise cessation and subsequent sleep disruption, both of which can elevate circulating levels of interleukin-6 (IL-6) and other pro-inflammatory cytokines [35,36], thus perpetuating a certain degree of nociceptor sensitization. Catastrophic thinking has been shown to increase pain sensitivity and pain processing in the CNS [37]. Thus, the authors believe that these maladaptive coping strategies, along with genetic and hard-wired neurobiological factors, are at least partly responsible for the continuation of CWP and FM as represented by stage 3 of the model.

While the three-stage model presented above is inevitably incomplete, it may serve as a useful framework to promote better understanding of the etiology behind these syndromes.
Clinical presentation and natural history
The typical presentation of CWP and FM can vary widely, depending on the clinical practice setting. Patients seen in tertiary care settings may have a disproportionately high degree of psychological comorbidity compared with those seen in primary care settings. Several recent community-based, cross-sectional studies have helped to better characterize the FM population at large [28,38].

The typical age of presentation is between 35–65 years, and the majority of patients are female [38]. Chief complaints usually include pain, fatigue, non-restorative sleep, morning stiffness, forgetfulness, difficulty with concentration, and difficulty falling asleep. These symptoms are typically exacerbated by emotional distress, weather changes, insomnia, and strenuous activity [28]. While most patients report no difficulty performing routine activities of daily living, only 18% are able to walk 1 mile without difficulty and just 7% are able to perform heavy household duties without any problems. Moreover, only 50% of patients with FM are able to maintain gainful employment [28].

The most common diagnoses in the past medical history of FM patients include (in descending order of frequency): low back pain (63%), headaches, arthritis, irritable bowel syndrome, CFS, depression, anxiety, sinus problems, restless legs syndrome, and tinnitus (30%). In the review of systems, tingling, numbness, and balance problems are also commonly reported (32–46%) [28].

Reports on the natural history of CWP and FM are conflicting, perhaps reflecting the differences between tertiary care populations and the general patient population at large. Clinic-based studies report little, if any, improvement in symptoms, even at 6-year follow-up [39]. In contrast, community-based studies show a much better prognosis, with approximately 11% of patients with CWP achieving resolution of their symptoms within 1 year, and a further third of patients having only regional pain by that time [8,40].

Treatment considerations
Diagnosis and education
Once the diagnosis of CWP or FM is made, providing the patient with a diagnostic “label” may improve coping and relieve some tension in their interpersonal relationships [41]. On the other hand, being diagnosed with FM may put the patient at risk of encountering a growing body of misleading and unscientific claims regarding their disease, particularly on the internet.

Initial counseling should emphasize the non-destructive nature of the condition in addition to the fact that a substantial portion of patients with these conditions experience some improvement within a year. Patients should also understand that, even though they feel pain in their muscles, the main dysfunction lies in the nervous system and that the pain does not reflect actual damage to the tissues.

While patients may be seeking a single “magic bullet”, multidisciplinary and multimodal approaches generally yield more favorable outcomes compared with single-modality treatments [42]. The treatment plan should include an individualized combination of medications, low- or moderate-intensity exercise, improvement of sleep, and cognitive-behavioral or cognitive-affective interventions (Tables 2 and 3). Recent evidence regarding each of these approaches will be reviewed below.

Pharmacological neuromodulation
Certain medications aimed at altering the neurochemistry of the CNS have been reasonably successful, based on...
randomized, placebo-controlled trials, in treating pain in patients with FM (see Table 2). Such medications include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), and dopaminergic and antiepileptic drugs. Among these drugs, only pregabalin has been approved by the US Food and Drug Administration for specific use in FM.

**TCAs**
TCAs are recommended as first-line agents, and amitriptyline and cyclobenzaprine have shown comparable efficacy in improving sleep and reducing pain, with moderate effect sizes (approximately 0.5 standard deviations [SD]) for pain [43,44]. These drugs most likely work by increasing concentrations of serotonin and/or norepinephrine via inhibition of their reuptake from the synaptic cleft, and are thus similar in action to SNRIs. As with most TCAs, drowsiness and anticholinergic side effects may affect tolerability. Compliance can be improved by titrating from very low doses (5–10 mg per dose) and administering the dose a few hours before bedtime. This dosing schedule will also enhance the beneficial effects these medications have on sleep.

**SNRIs**
If the side effect of drowsiness cannot be tolerated by the patient, the clinician may wish to try one of the newer SNRIs such as duloxetine and milnacipran (not yet available in the US), both of which have shown beneficial effects on pain and global well-being [45,46]. Tramadol, whose mechanism of action is similar to SNRIs, has shown comparable beneficial effects on pain in FM [47]. Venlafaxine has also shown encouraging results in uncontrolled studies [48].

**Dopamine agonists**
Pramipexole, a dopamine agonist, was recently found to significantly reduce pain and fatigue and improve function and overall well-being in patients with FM [49]. Despite initial concerns regarding hallucinations and other potential side effects, pramipexole was well tolerated by all subjects in the treatment group.

**SSRIs**
SSRIs, to a somewhat lesser extent than SNRIs, have shown efficacy in reducing pain and depression in FM [50,51]. The older, less-selective SSRIs (such as fluoxetine) seem to show a greater beneficial effect on pain than the newer, highly selective agents (such as citalopram), perhaps due to a mixed serotonergic–noradrenergic activity with the older compounds at high doses. Thus, when prescribing an SSRI for pain, higher doses than those typically used for depression may be needed.

**Antiepileptic drugs**
Both gabapentin and pregabalin have shown efficacy in reducing pain and improving overall well-being in FM, at doses typically used for treating neuropathic pain [52,53]. Due to the high frequency of somnolence, these drugs should be started at subtherapeutic doses, beginning with only a nighttime dose, and slowly titrated as tolerated. Weight gain may be a potentially troublesome adverse effect in this class of drugs, so careful consideration of patient factors is advised.

**Nonsteroidal anti-inflammatory drugs and opiates**
Despite their widespread use, ibuprofen or other nonsteroidal anti-inflammatory drugs have failed to show any added benefit in the pharmacological management of FM [54]. Similarly, no randomized controlled trials have shown efficacy for the use of opiates in treating FM or CWP. If the patient presents having already developed a physical dependence to
opiates, weaning the patient off opiate medications can present a formidable challenge to the clinician. The authors believe that the success of an opiate-weaning protocol can be enhanced by the use of a concomitant, multimodal treatment regimen.

**Low-impact exercise**
According to a recent review of different exercise regimens in FM [55], low- or moderate-intensity exercise of any type may yield improvements in pain, fatigue, sleep, and mood. Patients should start with a target heart rate (HR) of ≤50% of their maximum HR and initially avoid impact movements such as running or jumping. Faster improvements may be gained with deep-water running compared with land-based exercise [56]. This may be due to the withdrawal of excessive muscle sympathetic nerve activity in warm aquatic environments, counterbalancing the tendency towards exercise-induced peripheral vasoconstriction and ischemic pain in some patients.

The clinician should educate the patient (and personal trainer) about pacing themselves with respect to activity, and to avoid the extremes of hyperactivity or inactivity. As early failures may reinforce fear-avoidance behavior, the wisdom of “start low and go slow” should be followed.

**Improvement of sleep quality**
Given the high prevalence of sleep-disordered breathing (SDB) and sleep disturbances in CWP and FM [57], interventions aimed at improving sleep quality may be greatly appreciated by the patient. Better sleep is associated with reductions in pain and improvements in mental well-being in these patients [58].

For those patients with excessive snoring or daytime somnolence (according to their partners), the clinician should consider ordering ambulatory plethysmography or an overnight polysomnogram to evaluate for SDB. If present, continuous positive airway pressure may improve the quality of sleep and prevent circulatory complications [59]. In addition, improvements in sleep can be achieved with cognitive–behavioral interventions and sleep hygiene education [58]. Pharmacological treatment for insomnia can often be delivered with medications used for modifying neurotransmission, as reviewed above.

**Cognitive–behavioral interventions**
Several randomized controlled trials have shown cognitive–behavioral therapy (CBT) to yield long-term improvements in physical function and mood, but not necessarily pain itself [60,61]. While CBT traditionally refers to one-on-one therapy with a clinical psychologist, group education and discussion sessions led by a psychologist or a qualified clinician can be equally as effective [62]. Moreover, a self-directed workbook and video programme is a potentially cost-effective means of teaching similar cognitive–behavioral concepts. The authors’ group has published an online cognitive–behavioral workbook available to patients free of charge (www.med.umich.edu/painresearch/patients/self.htm).

Regardless of the format, cognitive–behavioral interventions should be aimed at decreasing fear-avoidance behaviors, reducing pain-related catastrophic thinking, and internalizing the locus of control over one’s symptoms [63]. Since patient expectations affect the outcome of cognitive–behavioral interventions [64], the clinician should explain to patients how pain-related beliefs can alter the processing of pain signals in the brain.

**Cognitive–affective interventions**
Based on the premise that unconscious emotional unrest can perpetuate pain, two recent randomized controlled trials looked at whether FM patients would benefit from written emotional expression. In this exercise, patients used pen and paper to privately recollect and ponder the significance of various stressful or traumatic events in their lives. After only three or four 20-min writing sessions, improvements were seen in pain, fatigue, sleep, global well-being, and even healthcare utilization, and these benefits continued for at least several months [65,66]. The effect sizes on pain and fatigue were comparable to TCAs (0.47 and 0.62 SD, respectively) [66].

These studies suggest that, at least for some patients with FM, the central pain state is somehow maintained by a dysfunctional interaction between cognitive and affective regions of the brain. Further research may help clarify which patients are likely to respond to this cost-effective intervention.

**Other modalities**
In recent years, increasing attention has been paid to two distinct modalities capable of modulating neurotransmission: acupuncture and magnetic or electrical brain stimulation. A recent systematic review of acupuncture in FM found inconsistent results across five randomized controlled studies [67]. However, a more recent study from the Mayo Clinic (MN, USA), showed a moderate decrease in pain at one month, and a slight decrease in fatigue and anxiety extending to 7 months post-treatment [68]. The results of these trials seem to depend on the type of placebo used. Generally, greater degrees of needle stimulation (including electro-acupuncture) seem to be more beneficial, but the effect is highly dependent on the individual clinician and patient.

Another class of treatment modality that has recently been studied in FM is transcranial stimulation of various cortical regions of the brain, either with magnetic pulses or a
direct current. It is thought that alterations in regional cortical brain activity can influence remote subcortical structures involved in pain and sensory processing. One study using repetitive transcranial magnetic stimulation (rTMS) found an unexpected dramatic reduction in pain in four patients with FM, from an average pre-treatment score of 8.2 to a post-treatment score of 1.5 [69]. A recent randomized controlled trial using transcranial direct current stimulation (tDCS) showed a significant reduction in pain that lasted throughout the 3-week follow-up [70]. Both rTMS and tDCS are typically administered in daily sessions of <30 min each, for 4–6 weeks. So far, side effects for each of these have been reported to be minimal. Further research on these neuro-modulatory treatments is needed to investigate their efficacy and safety in the treatment of intractable FM and CWP.

Conclusion

FM and CWP affect a large portion of the population, and share commonalities with other functional pain syndromes. Recent research has repeatedly shown that the ongoing dysfunction in FM and CWP is one of central pain augmentation, with only minor contributions from the immunological and peripheral nervous systems. Treatments that presumably address these dysfunctions – through monoaminergic medications, low-intensity exercise, improvement of sleep quality, and cognitive-behavioral interventions – have shown efficacy in numerous randomized clinical trials. The usefulness of acupuncture, brain stimulation, and written emotional expression is still being explored.

Disclosure

Dr s Hsu and Clauw have no financial interests to disclose.

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Sex, Gender, and Pain

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Abundant evidence indicates sex differences (SDs) in the experience of pain. Epidemiological studies demonstrate both a higher frequency of pain and a greater risk of numerous clinical pain disorders among women. Moreover, substantial experimental research reveals enhanced sensitivity to evoked pain among women compared with men. SDs in opioid analgesic responses have also been reported; however, the direction and magnitude of these differences varies considerably across studies. These findings address quantitative SDs, that is, male–female differences in the magnitude of pain and analgesia. However, it is important to recognize the significance of qualitative SDs, which refer to whether the factors underlying pain and analgesic responses differ between females and males. For example, sex-related genetic associations with both pain perception and analgesia have been reported. Furthermore, some psychological factors are more strongly associated with pain in males versus females, or vice versa. The mechanisms underlying SDs in pain and analgesia inevitably involve complex interactions among multiple biopsychosocial variables, including gonadal hormones, genetic factors, and psychosocial processes. While the direct clinical relevance of SDs in pain and analgesia sensitivity remains unknown, it seems plausible that a better understanding of them may improve pain management by allowing clinicians to individualize treatments, perhaps in a sex-dependent manner. Adv Pain Manage 2007;1(2):46–53.
of analgesics [13]. Research indicates SDs in the prevalence of several specific pain syndromes. In particular, women are more likely than men to report most forms of recurrent headache disorder, with the exception of cluster headache, which is reported significantly more frequent among men [14,15]. Moreover, women are more likely than men to report joint and abdominal pain, including irritable bowel syndrome, fibromyalgia, and temporomandibular disorders (TMD). SDs in the prevalence of back pain have been inconsistent, with some studies reporting higher frequencies in women, while other data suggest minimal SDs [16]. An important consideration is that SDs in the prevalence of pain conditions may depend on age. For example, during the reproductive years, women are at a greater risk of headaches and TMD; however, the prevalence of these conditions diminishes after middle-age, becoming more similar in females and males ≥60 years of age [16]. Table 1 shows the population prevalence and female to male ratio for several common chronic pain disorders [17,18].

In addition to epidemiological data, numerous clinical studies have examined SDs in the severity of pain. For example, women have reported greater post-operative pain compared with men following multiple types of surgical and other invasive procedures [19,20]. Furthermore, there is some evidence that women are at an increased risk of transition from acute to chronic pain. For instance, women appear to be at an increased risk of developing post-whiplash-related chronic pain conditions following acute injury, which may be related to their more severe pain in the acute stage [21]. In addition, some studies indicate an increased likelihood of chronic pain following surgery among women compared with men [22,23]. SDs in the severity of pain among individuals seeking treatment for chronic pain have been less consistent. For example, in a heterogeneous chronic pain population recruited from a multidisciplinary pain clinic, women had higher pain severity than men [24]. However, other researchers have reported little to no SDs in severity of pain in similar populations [25–27], and one study even reported higher levels of pain and greater pain-related disability among men than women with chronic pain [28]. Thus, robust SDs in pain prevalence and the severity of acute pain have been reported, whereas SDs in pain intensity have been smaller and less consistent among treatment-seeking patients with chronic pain.

SDs in experimental pain sensitivity

Findings such as those mentioned above, which indicate substantial SDs in the experience of clinical pain, have prompted some investigators to suggest that enhanced pain sensitivity among women may contribute to their greater risk of many forms of clinical pain [29]. A major advantage of experimental pain assessment over clinical pain comparison is that the former offers a far greater degree of control over stimulation parameters such as intensity, duration, and location of the pain stimulus. Moreover, multiple pain modalities can be investigated in subjects using laboratory pain, while this is generally not possible with clinical pain. The obvious disadvantage is that experimental pain fails to fully mimic the clinical pain experience; therefore, the clinical relevance of experimental findings can be questioned. In this regard, there is increasing evidence to support the clinical relevance of experimental pain assessment. For example, the author’s research group has reported associations between thermal pain sensitivity and self-reported recent pain complaints in healthy young adults [30,31], and found that ischemic pain tolerance predicted treatment outcome among women with chronic pain [32]. Lower pressure pain thresholds were associated with higher back pain intensity and a greater deterioration of physical functioning among patients with chronic low back pain [33]. Similarly, lower heat pain thresholds predicted more frequent angina episodes during exercise in individuals with coronary artery disease [34]. Furthermore pre-operative measures of thermal pain sensitivity have been found to predict post-operative pain severity [35,36], and pre-treatment measures of pain sensitivity have predicted outcomes among patients with chronic pain [32,37]. Therefore, it seems plausible that exploring SDs in experimental pain responses may provide information that is relevant to clinical pain.

The numerous studies investigating SDs in response to experimentally induced pain have been thoroughly reviewed by several authors [29,38,39]. To briefly summarize, women exhibit lower pain threshold and tolerance, and generally provide higher pain ratings in response to standardized experimental pain stimuli compared with men. A meta-analysis revealed that the effect sizes for SDs in pain threshold

| Table 1. Pain disorders that are more common among women than men (prevalence data derived from [17,18]). |
|---------------------------------------------------------|-----------------|-----------------|
| Pain disorder                                           | Population prevalence (%) | Female:male ratio |
| Migraine                                                | 15–20            | 2–3:1           |
| Tension-type headache                                   | 4–5              | 2:1             |
| Temporomandibular disorders                             | 4–12             | 1.5:1           |
| Irritable bowel syndrome                                | 15–20            | 2:1             |
| Rheumatoid arthritis                                   | 1                | 2.5:1           |
| Osteoarthritis                                          | >80 (age 65 years) | 1.5:1–4:1       |
| Interstitial cystitis                                   | 0.5              | 9:1             |
| Fibromyalgia                                            | 2–3              | 6:1             |
and tolerance were moderate, and that the magnitude of the SD varies across pain stimuli [39]. The least consistent results emerged from thermal pain measures. More recent data provide further evidence of heightened pain sensitivity among females. Figure 1 depicts standardized pain thresholds and tolerances across multiple pain modalities from a sample of healthy women (n=138) and men (n=120) studied in the author’s laboratory.

These results are consistent with the published literature, in that the direction of SDs is consistent, while the magnitude is variable across pain modalities. This average effect size (Cohen’s D) across all pain measures was 0.65, which reflects a moderate-to-large effect. In addition, published findings demonstrate that compared with men, women display greater temporal summation of thermal and mechanical pain [40,41]. Furthermore, injection of glutamate into the masseter muscle produced higher peak pain, longer lasting pain, and a greater area of pain among women compared with men [42].

It is important to recognize that these findings are primarily derived from studies of younger adults, and relatively little is known regarding SDs in pain sensitivity for older adults. Studies that have included older patients often do not report on interactions between age and sex. Those that have examined the interaction have reported conflicting results, probably due to methodological differences [43–46]. Thus, the available evidence indicates consistent SDs in sensitivity to experimentally induced pain; however, the mechanisms underlying the differences and their relevance to clinical pain are not fully understood.

SDs in response to opioid analgesics

In recent years, the question of whether women and men respond differently to analgesic medications, especially opioids, has received considerable attention. In studies of patient-controlled analgesia following surgery, women generally require significantly less opioid medication than men [47]. While these data suggest more robust opioid analgesia among women, pain was not typically assessed in such studies; thus, lower opioid consumption among women may be due to non-analgesic effects of the medication, such as side effects. This issue is of particular importance given previous findings that women report significantly more adverse effects from opioids compared with men [48–50].

As the author [51,52] and others [1,47,53–55] have recently reviewed, additional clinical and laboratory research has more directly examined SDs in analgesia, with inconsistent findings. In a study comprising >2000 patients using patient-controlled analgesia, women consumed substantially
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less opioid medication post-operatively and reported less post-surgical pain compared with men [56]. Other studies have reported no SDs in morphine analgesia after oral surgery or for treatment of chronic cancer pain [51,57]. In contrast, Cepeda and Carr [58] found that women required significantly more morphine than men in order to obtain adequate post-operative analgesia. Similarly, Aubrun et al. observed that women reported greater post-operative pain and required higher doses of morphine compared with men in order to achieve pain relief (i.e. visual analogue scale <30) [59]. Interestingly, these two post-operative studies, demonstrating greater opioid demands in women, involved drug administration by the nursing staff, whereas studies using self-administration of opioids via patient-controlled analgesia have generally shown lower opioid consumption in women. This raises the question of whether SDs in post-operative opioid requirements depend on the manner of drug administration (i.e. self-administered versus provider-administered).

In addition to these clinical studies examining μ-opioid agonists, several studies have investigated SDs in response to mixed action opioid agonist–antagonists, which appear to act as agonists at κ-opioid receptors and as high-affinity competitive antagonists or low-potency agonists at μ-opioid receptors. In a series of studies of pain after third molar extraction, the author and colleagues have shown that women experience greater analgesic responses to all three of these mixed-action agonist–antagonists (i.e. butorphanol, nalbuphine, and pentazocine) [51]. A similar study by another group found that 2 mg intranasal butorphanol produced greater analgesia compared with 1 mg among women, but there was no dose-dependent response among men [60]. While the authors did not further analyze this SD, inspection of the means suggests that 2 mg intranasal butorphanol was more effective in women than men, while the 1 mg dose showed greater efficacy in men than women. Among patients with trauma-related pain in an emergency department, butorphanol produced greater pain relief than morphine for women, while morphine analgesia was marginally higher among men compared with women [61]. On balance, the clinical studies examining mixed-action opioid agonist–antagonists suggest greater analgesic responses among women; however, the vast majority of the data are based on an oral surgery pain model, and the magnitude of the SD may be dose-dependent, with differences appearing to be greatest at lower doses of nalbuphine and butorphanol [60,62].

SDs in opioid analgesia have been investigated using experimental pain models. Sarton et al. [63] reported greater and more prolonged analgesic responses to intravenous morphine in women versus men using an electrical pain stimulus. These investigators subsequently reported no SDs in analgesic responses to the μ-opioid agonists morphine-6-glucuronide and alfentanil [64,65]. Pud et al. reported that women showed greater reductions in cold pressor pain following oral morphine than men [66]; however, women also showed greater analgesic responses to the placebo, such that the gender by drug (placebo vs. morphine) interaction was not significant. The author’s group reported no SDs in morphine analgesia using several experimental pain models [48]. Regarding experimental studies of mixed-action opioid agonist–antagonists, they reported no SDs in pentazocine analgesia [67], and Zacny et al. reported no significant trend toward greater butorphanol analgesia in males versus females [68].

Overall, the findings from studies using experimental pain models reveal little evidence for SDs in analgesic responses to either μ-opioid agonists or mixed-action agonist–antagonists. It seems likely that inconsistencies across studies are driven by methodological differences, such as the specific medications administered, the doses of medications, the pain models examined, and also possibly by differences in the populations studied, such as ethnicity and age distribution.

Explaining SDs in pain
SDs in pain are, by definition, correlational findings (as individuals have not been assigned to groups), and sex (i.e. female versus male) cannot be considered the cause of any observed group difference. Instead, sex represents a naturally occurring categorical variable that reflects the influence of numerous underlying biological and psychosocial factors. SDs in pain are inevitably mediated by multiple mechanisms, including basic “biological” variables, such as genetic and hormonal influences, as well as “psychosocial” factors, including cognitive/affective processes (e.g. pain coping, mood, expectancies), gender role influences, and family history. Of course, this distinction between psychosocial and biological factors is artificial and refers more to the level of analysis than the underlying mechanism of action. For example, gender roles represent a psychosocial variable that may contribute to SDs in pain. However, there are neurobiological correlates of these gender roles, which may directly or indirectly alter nociceptive processing.

Moreover, as mentioned above, the interactive influences of sex and age on pain responses have not been well characterized. A variety of sex-related biological and psychosocial factors change across the lifespan, and could substantially impact the pattern of SDs as a function of age (for example, hormonal status changes with age and could affect pain responses). Therefore, given the multiple interactive variables contributing to pain, the biopsychosocial model
Figure 2. Biopsychosocial model of sex differences in pain. The biopsychosocial model postulates that the experience of pain is determined by complex interactions among biological, psychological, and sociocultural factors. This figure depicts the bidirectional interactions among these factors that contribute to sex differences in pain. Examples of specific factors within each domain are listed.

"Biological" factors
- Sex hormones
- Genetics
- Endogenous opioids

"Psychological" factors
- Mood/affect
- Pain coping

"Sociocultural" factors
- Gender roles
- Ethnicity

Evidence indicates that gonadal hormones are important. The symptomatology associated with various chronic pain disorders, including TMD, headaches, fibromyalgia, and irritable bowel syndrome, can fluctuate across the menstrual cycle [70–73]. Furthermore, women using exogenous hormones in the form of hormone replacement or oral contraceptives appear to be at an increased risk of clinical pain compared with women not using such hormones [74–76]. Studies of laboratory pain responses demonstrate that pain perception varies across the menstrual cycle in healthy women [77,78]. One study found that post-menopausal women taking hormone replacement therapy show greater thermal pain sensitivity compared with women of a similar age not on this therapy [79]. Another biological contribution to SDs in pain involves endogenous pain inhibitory systems. In particular, tonic experimental muscle pain produced a greater occupancy of μ-opioid receptors in several brain regions among men than women, suggesting a more robust, endogenous opioid control of pain among men [80].

Genetic factors represent another biological contribution to SDs in pain, and may be the prototypical example of a qualitative SD. Evidence from rodents indicates that both the magnitude and direction of SDs in basal nociceptive sensitivity and opioid analgesia vary across strains of rodents [81,82]. Sex-dependent genetic associations have also emerged in humans; for example, a single-nucleotide polymorphism (SNP) of the δ-opioid receptor gene (OPRD1) was associated with thermal pain responses among men but not women [83], and an SNP of the μ-opioid receptor gene (OPRM1) was associated with pressure pain thresholds among men but not women [84]. Furthermore, in a study that directly translated a novel genetic association from mice to humans, the melanocortin-1 receptor gene (the "redhead" gene) was associated with analgesic responses to pentazocine among women but not men [85]. Thus, some genetic factors have been associated with pain and analgesic responses in a sex-dependent fashion. These sex-specific genetic associations represent qualitative SDs, as the relationship between the genetic marker and pain phenotype is dependent on the sex of the individual. This implies that there may be fundamental differences between men and women in the neurobiology of their pain systems.

Several psychosocial variables also contribute to SDs in pain responses. For instance, negative affect is more strongly associated with pain among men than women [25,86], which represents another example of a qualitative SD as relationships between psychological variables and pain responses are sex-dependent. Moreover, multiple studies demonstrate SDs in pain coping strategies, such that women report more frequent use of many cognitive and behavioral coping strategies [10,87]. SDs have also emerged for
self-efficacy, which predicts adjustment to chronic pain [88,89], decreased procedural pain [90], and lower sensitivity to experimental pain [91]. Specifically, both women and men describe males as better able to tolerate pain [92]. Stereotypical gender roles represent another psychosocial variable associated with SDs in pain, in that measures of masculinity and femininity have been associated with reduced and enhanced pain sensitivity, respectively [93,94].

Conclusions and clinical implications
Abundant evidence documents the existence of quantitative and qualitative SDs in pain. Women report more frequent and more severe clinical pain, and enhanced sensitivity to experimentally induced pain. Furthermore, there is evidence of SDs in response to analgesic medications, although the direction and magnitude of these differences are inconsistent across studies. SDs in pain responses are sculpted by multiple biopsychosocial factors (e.g. genetics, hormones, age, cognitive/affective variables, and gender roles) whose reciprocal interactions remain poorly understood. There are noticeable gaps in our knowledge regarding sex, gender, and pain. For example, the vast majority of studies have been conducted in highly industrialized countries, especially in North America and Europe. Therefore, our understanding of sex-related influences on pain in the developing world is extremely limited. In addition, epidemiological studies indicate that SDs in the prevalence of some types of pain can vary across the lifespan; however, relatively little mechanistic research has addressed whether SDs in pain sensitivity or analgesic response are age-dependent. Moreover, interactions between sex, race, or ethnicity remain largely unexplored.

Perhaps the most daunting challenge for the future will be to understand the implications of SDs in pain for clinical pain management. For example, will we ever see sex-related treatment tailoring? That is, will SDs in analgesic responses ultimately lead to the development of sex-specific medications and dosing regimens? Alternatively, will gonadal hormones and/or their receptors become sex-specific targets for pain treatment? The literature on SDs in analgesic responses is based almost exclusively on acute clinical pain and experimental pain models, and the absence of information regarding SDs in analgesic responses among chronic pain populations represents an important knowledge gap. It seems eminently feasible to analyze for SDs in these studies, as the data are already available. As long-term opioid therapy produces hypogonadism [95,96], the sex-related differences in long-term opioid therapy may differ from those observed in the acute setting. Moreover, examination of large clinical trial databases could provide the opportunity to identify sex-dependent genetic predictors of opioid efficacy in chronic pain.

Another relatively understudied issue is that of SDs in response to non-drug treatments for pain, including rehabilitation and cognitive–behavioral therapy. Some studies have demonstrated better outcomes from interdisciplinary treatments among women than men [97,98], others have shown no SDs in response to treatment [99,100], and one study reported better long-term outcomes in men [101]. Further research is needed in order to identify the treatment components responsible for producing SDs in outcome. Moreover, given that the predictors of interdisciplinary pain treatment outcomes differ for women and men in some studies [25,102,103], is it possible to customize interdisciplinary pain treatment by sex in order to enhance treatment outcomes?

Although more questions than answers remain regarding the relevance of sex and gender to clinical pain management, increasing awareness of SDs in pain should reduce sex-related biases, which serve as barriers to effective pain management. In addition, the social context of healthcare may be appraised differently across sexes, and the goals of pain-related healthcare could differ for women versus men. Indeed, in response to pain, women were more likely than men to seek social support and use coping strategies designed to reduce distress [87]. Thus, the patient–provider encounter may need to be constructed differently for women versus men in the healthcare setting. Ultimately, greater awareness of the potential role of sex and gender in the response to pain, and its treatment among clinicians and scientists, will help expedite the translation of research findings into enhanced pain management for both women and men.

Disclosure
Dr R Fillingim owns stocks in Algynomics Inc.

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Interventional Approaches to the Diagnosis and Treatment of Low Back Pain: Current Evidence

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The prevalence of chronic low back pain (CLBP) is significant; however, reliable and valid diagnosis and effective management of intractable CLBP are difficult. Modern technology, including magnetic resonance imaging, computerized tomography, neurophysiological testing and, comprehensive physical examination with psychological evaluation, can successfully identify the pathophysiology of LBP in only a small proportion of patients. Supplementation with diagnostic interventions can improve the precision of evaluations and, consequently, the effectiveness of treatments for CLBP. Pain originating from intervertebral discs and facet and sacroiliac joints constitutes the majority of CLBP. These sources have been effectively determined using diagnostic interventional techniques. CLBP that is unresponsive to conservative modalities, and persistent pain in post-surgical patients, can often be successfully managed by neural blockade and/or minimally invasive surgical procedures, including epidural injections, facet joint injections, neuroablation techniques, intradiscal therapies, percutaneous disc decompression, and implantables. While systematic reviews and guidelines have been developed to strengthen the diagnostic and therapeutic use of interventional techniques, the subjective and often ambiguous nature of pain limits a physician’s ability to weigh different types and levels of evidence and focus on the patient’s best interests.


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Interventional techniques

Based on Bogduk’s theories that only innervated spinal structures can be a cause of back pain [12], the diagnostic blockade of putatively involved structures can be performed to test the hypothesis that the target structure is in fact a pain generator. Evidence has shown that interventional diagnostic techniques, including facet joint blocks, discography, and sacroiliac joint injections, are effective toward this end.

Similarly, interventional techniques have been effectively used in pain management; these include various types of neural blockade and minimally invasive surgical procedures such as epidural and facet joint injections, neural ablation techniques, intradiscal therapies, percutaneous disc decompression, and implantable drug-delivery and stimulatory devices or systems [1,23].

Diagnostic interventional techniques

Precise anatomical diagnosis in LBP can be elusive, and thus, the persistent uncertainty of the diagnostic evaluation is often frustrating for both physicians and patients [1,14,15]. History, physical examination, and imaging provide limited information. Hence, diagnostic neural blockade has become increasingly popular in light of the somewhat ambiguous nature of LBP and its variable pathophysiology. Precise diagnostic blocks are used to determine the pathophysiology of clinical pain, the site of nociception, and the pathway of afferent neural signals. Furthermore, they afford an increased level of certainty in determining the types and course of therapeutic intervention.

The validity and reliability of precision diagnostic techniques in the lumbar spine have been widely studied. Clinical studies of precision diagnostic techniques are variable in sensitivity, specificity, accuracy, and quality. In evaluating the role of diagnostic interventional techniques, assessment of placebo responses, and false-positive and false-negative rates are crucial. As with the use of any other test in medical practice, there will always be a degree of uncertainty regarding the accuracy of diagnostic interventions. Unfortunately, an appropriate reference standard – such as biopsy, surgery, or autopsy – is not available to confirm the accuracy of diagnostic interventional techniques. Consequently, most pain provocative or relieving tests used in the diagnosis of spinal disorders are constructed more similarly to a physical examination than a laboratory test with regard to confirmatory accuracy and predictive values in long-term prognoses [22]. To avoid false-positive results, either placebo-controlled or controlled-comparative local anesthetic blocks may be performed. Pain provocation may be used in discographic assessment. In the US, pain provocation in discography, using a controlled disc with injection of two local anesthetics with different durations of action on two separate occasions, has been proposed and validated in the diagnosis of facet joint pain. While some controversy remains, the use of controlled comparative local anesthetic blocks for facet joint and sacroiliac joint pain, and controlled provocation discography, are still the most commonly employed interventional diagnostic techniques at present.

Facet (zygapophysial) joint blocks

Diagnostic blocks of a facet joint can be performed by injection of a local anesthetic intra-articularly or on the medial branches of the dorsal rami that innervate the target joint. However, valid assessment requires the use of controlled blocks.

The rationale for using facet joint blocks for diagnosis is based on the fact that these joints are innervated and, therefore, are capable of causing pain. However, while motion palpation and provocative movement (e.g. hyperextension) may be useful, there are no specific motion-based markers of facet joint pain, and conventional radiological techniques are equally unreliable.

Controlled diagnostic blocks with two local anesthetics or placebo-controlled blocks have been shown to be the only means of authentically and reliably confirming the diagnosis of facet joint pain. The value, validity, and clinical effectiveness of diagnostic facet joint nerve blocks were also illustrated by the application of therapeutic modalities based on the diagnosis with controlled, comparative local anesthetic blocks [17,23–25].

Using the criteria established by the International Association for the Study of Pain [26], facet joints have been implicated as the source of CLBP in heterogeneous groups of 15–45% of patients, with a false-positive rate of 17–50% [27–34]. The influence of psychological status and sedation was shown to be not significant [35,36]. Systematic reviews determined that the accuracy of facet joint nerve blocks in diagnosis of facet joint-related pain was considered to be strong [1,18].

Provocation discography

Discography is employed to characterize the architecture and pathological derangement of the intervertebral disc, and to determine if the intervertebral disc is a source of chronic spinal pain. Discs are innervated and can be a source of pain [37,38]. Although the exact actions by which discography causes pain have not been fully elucidated, anatomical, histopathological, radiological, and biomechanical evidence suggests that lumbar discography is useful in identifying symptomatic pathology at intervertebral discs [19,39–41]. Discography performed in asymptomatic volunteers without LBP showed that (discographically) normal discs were never painful [40].
Discography can be particularly helpful in obtaining information about the structure and sensitivity of lumbar intervertebral discs in patients with lower back or extremity pain, in order to both raise accuracy of the diagnosis, and plan and guide possible treatment options.

The validity of discograms was confirmed in studies of cadaveric discs with annular tears and disc degeneration [42,43]. In addition, the accuracy of discographic and CT/discographic findings has been confirmed at surgery, although conflicting findings still persist.

Thus, while the accuracy of discography as an imaging test is high, with good specificity and sensitivity for the diagnosis of disc degeneration, a key question is whether this test is truly accurate for the diagnosis of discogenic pain. Part of the problem is the lack of an adequate reference standard (vide supra). Surgical exposure can confirm the presence of disc degeneration or disruption, but it cannot definitely confirm the presence or absence of discogenic pain.

The face validity of discography has been established by injecting small volumes of contrast medium into the disc and determining concordant pain. On the other hand, construct validity can only be established using strict guidelines. For a response to be considered positive, concordant pain must be produced, and for the test to be valid there must be at least one (preferably two) disc(s) in which pain is not provoked following injection, thus serving as a control. Finally, although the validity of lumbar discography has been widely studied, controversy remains [19,39,41,44–49]. Despite these equivocal positions, it is generally believed that when performed appropriately, discography can be a useful test.

Selective nerve root blocks

Transformal epidural injection, or selective nerve root block, involves an injection of contrast, local anesthetic, or other substances around the spinal nerves under fluoroscopy [20]. A diagnostic, selective nerve block is typically performed in a patient with persistent pain when history, examination, imaging, and other precision diagnostic and electrophysiological tests are unable to identify the pain generator [20]. In addition, selective nerve root blocks are useful when the location of symptoms seems to be inconsistent with abnormalities identified by imaging, or when no other cause was revealed by evaluation and application of precision diagnostic techniques [20]. The strength of evidence was reported to be moderate for selective nerve root blocks in the preoperative evaluation of patients with negative or inconclusive imaging studies, and clinical findings of nerve root irritation [20].

Sacroiliac joint blocks

The prevalence of sacroiliac joint pain has been shown to be 10–26.6% in patients with CLBP, with a false-positive rate of 20–22% [21]. The rationale for diagnostic sacroiliac joint blocks is based on the fact that sacroiliac joints are innervated and have been shown to be capable of being a source of both LBP and referred pain to the lower extremity [21,37]. There are no definite historical, physical, or radiological characteristics to provide accurate diagnosis of sacroiliac joint pain.

Therapeutic interventional techniques

The rationale for interventional techniques in the treatment of spinal pain is based on considerations that [1,20,23–25,50–58]:

- Cardinal sources of CLBP, particularly discs and joints, are accessible to and effectively respond to neural blockade.
- Removal or surgical correction of structural abnormalities may fail to cure and may worsen the painful conditions.
- Degenerative processes of the spine and the origin of spinal pain are complex, and often involve pathological processes in spinal nerves without correlation between radiographic changes to the clinical picture and prognosis.
- The effectiveness of several (systemically administered) pharmacological agents (e.g. anti-inflammatories, membrane stabilizers, opioids) used to manage chronic spinal pain has not been conclusively or uniformly demonstrated.
- There is increasing evidence to directly illustrate the success and support the use of interventional techniques in managing LBP.

Facet joint interventions

Facet joint pain may be managed by intra-articular injections, medial branch blocks, or neurolysis (radiofrequency neurotomy) of medial branches [1,24,25]. Systematic reviews and evidence-based guidelines have evaluated the effectiveness of all three modalities in the management of CLBP [1,24,25]. It was concluded that the evidence for lumbar intra-articular injections and medial branch blocks in managing CLBP was moderate (>6 weeks). In contrast, the evidence for radiofrequency neurotomy in managing lumbar facet joint pain was shown to be strong for short-term relief (<3 months) and moderate for long-term relief (>3 months).

Epidural injections

The lumbar epidural space may be accessed through a caudal, interlaminar, or transforaminal approach. The latter approach is considered to be the most target-specific, requiring the smallest volume to fulfill the aim of reaching the primary site of pathology – the ventrolateral epidural space. The interlaminar entry approach is more closely
directed at the assumed site of pathology, thereby requiring less volume than the caudal approach. The caudal entry approach, although relatively easily achieved and having minimal risk of inadvertent dural puncture, requires larger volumes of injectate and thus has a greater potential to lose target specificity. The effectiveness of epidural steroid injections has been assessed in systematic reviews and guidelines that have used strict and valid criteria, and have divided epidural steroid injections into separate categories for evaluation (i.e. caudal, lumbar interlaminar, and lumbar transforaminal approaches) [1,50].

These reviews and guidelines demonstrate that there is strong evidence that caudal epidural steroid is effective for short-term relief (<6 weeks), and moderate evidence for its effectiveness in long-term relief (>6 weeks) of CLBP. However, the evidence to support caudal epidural steroid injection for the treatment of post-lumbar laminectomy syndrome and spinal stenosis was limited. These reviews also conclude that there is strong evidence that interlaminar epidural steroid injections provided short-term relief of lumbar radiculopathic pain, and that there is only limited evidence to support this technique’s ability to afford long-term relief.

In managing lumbar radicular pain, the evidence for transforaminal epidural steroid injections is strong for short-term (<6 weeks) and moderate for long-term (>6 weeks) improvement. However, there is limited evidence to support transforaminal injections to manage LBP secondary to post-laminectomy syndrome and/or spinal stenosis.

Epidural adhesiolysis
The purpose of percutaneous epidural lysis of adhesions of the peri-intervertebral foraminal space is to minimize the adverse effects of epidural scarring, which can produce nerve entrapment, pain, and physically prevent direct application of analgesic or anti-inflammatory agents to the involved neural structures [51].

Evidence syntheses were performed separately for percutaneous and endoscopic adhesiolysis [1,51]. It was concluded that there is strong evidence to support percutaneous adhesiolysis in managing CLBP and lower extremity pain in post-surgery syndrome. However, there is only moderate evidence to support the use of this technique in managing low back and lower extremity pain secondary to disc herniation producing radiculopathy. There was limited evidence to show that percutaneous adhesiolysis is effective in managing back and/or lower extremity pain secondary to spinal stenosis.

Furthermore, there was strong evidence that spinal endoscopic adhesiolysis was effective for short-term relief (<3 months), and moderate evidence that this approach provided long-term relief (>3 months) of refractory pain, CLBP, and lower extremity pain secondary to post-lumbar surgery syndrome.

Intradiscal therapies
Two minimally invasive modalities of treatments have been promoted as alternatives to major surgical interventions:

- Intradiscal electrothermal therapy (IDET).
- Radiofrequency posterior annuloplasty (RFA).

Systematic reviews have concluded that there is moderate evidence to support the use of IDET to manage chronic discogenic LBP [52,53]. However, there was only limited evidence to support the use of RFA [1].

Percutaneous disc decompression
Multiple, minimally invasive techniques have been described as alternatives to surgical discectomy or removal of the disc. Four commonly used techniques are automated percutaneous lumbar discectomy, percutaneous laser discectomy, nucleoplasty with coblation technology, and decompression using a mechanical device that has a high number of revolutions per minute (i.e. Dekompressor technology).

So far, there is moderate evidence to support the use of automated percutaneous lumbar discectomy and percutaneous laser discectomy for the short-term (<3 months) relief of discogenic back pain, and limited evidence in support of these techniques in providing long-term (>3 months) relief. Furthermore, there are only limited data to support the use of coblation or Dekompressor technology [1].

Implantable therapies
Spinal cord stimulation systems, and implantable intrathecal drug-delivery devices are frequently used to manage CLBP [55,56]. Spinal cord stimulation consists of transcutaneously implating epidural electrodes that are connected to an external power generator. Implantable drug-delivery systems involve the placement of an indwelling cannula to the intrathecal space, which is connected to a drug-delivery device (i.e. a drug pump) that can be either internally implanted or externally affixed. These systems allow time- and dose-specific administration of opioids (or other drugs) into the intrathecal space.

In an evaluation of systematic reviews [55], and randomized and non-randomized trials, Boswell et al. reported that there were strong data to indicate the success of spinal cord stimulation against failed back surgery syndrome for short-term relief (<1 year), and moderate evidence that this approach provided long-term relief (>1 year) [1].

Based on available data, the short-term (<1 year) effectiveness of intrathecal infusion in treating post-lumbar
laminec tomy syndrome is supported by strong evidence, whereas there is moderate evidence to support the effectiveness of this approach in providing long-term (>1 year) improvement [1,56].

Discussion

Interventional pain management remains a progressively developing specialty. Data have shown that the use of interventional techniques in the Medicare population from 1998–2005 has increased by 182% (i.e. 1429,277 procedures in 1998 versus 4,041,464 procedures in 2005) [23]. Despite this increase, there remains a wide variation in application methods and documented diagnostic and therapeutic effectiveness of interventional techniques against different pain pathologies [57].

This variability reflects the fact that no single technique is uniformly effective as a diagnostic tool or procedure. Diagnosis must aim to simplify, allow progressive reinterpretation, synthesize theoretical and contextual knowledge applicable to the individual patient, and resolve equipoise, so as to indicate the most technically effective and ethically sound possible treatment [58]. Therapeutics must address the nature of pathology, its expression, and the multi-dimensional (i.e. biopsychosocial) needs that such pathology incurs in each patient. A review of the available evidence and resulting evidence-based guidelines can most assuredly enhance the selection and use of particular diagnostic and therapeutic evidence-based guidelines can most assuredly enhance the selection and use of particular diagnostic and therapeutic tools and/or approaches. Yet guidelines, however stringent, only serve as an assistive process in clinical decision-making and implementation of care [59]. Despite its increasingly evidence-based orientation, medicine remains the most humanistic of the sciences: each diagnostic and treatment decision and act is both therapeutically pragmatic and moral [60]. Given the often subjective and ambiguous nature of pain, it is the physician’s ability to evaluate and weigh different types and levels of evidence, and focus on their patients’ best interests, that preserves medicine in general, and interventional pain management somewhat more specifically, as both art and skill, and impart true effectiveness and ethical soundness to the practice.

Disclosures

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References


INTERVENTIONAL APPROACHES TO THE DIAGNOSIS AND TREATMENT OF LOW BACK PAIN


Pain is one of the most common physical complaints following an individual’s admission into the healthcare system [1–6]. Moderate to severe pain is frequently reported to be experienced throughout hospitalization, during treatment, and following discharge. Unrelieved pain has been found to occur in numerous healthcare settings and to affect a variety of patient populations [7–16]. Individuals with chronic cancer or non-cancer conditions often experience pain that is debilitating and negatively impacts their quality of life [14,17–20].

There are many useful pharmacological and non-pharmacological treatments for pain, and opioid analgesics such as morphine can play an important role in relieving severe pain, especially when the pain results from cancer [20,21]. Using opioids to treat non-cancer pain remains somewhat controversial [22]; however, practitioners should evaluate patients’ pain during the initial evaluation and monitor their pain and functioning during treatment to determine whether opioids are, and remain, an effective therapeutic option [23]. Given these considerations, opioid therapy to improve pain relief and patient function remains a legitimate medical practice and has become a greater healthcare priority. As a result, there has been increased focus on the diverse factors that can interfere with the medical use of opioids for pain management and can negatively impact patients’ access to effective pain relief. Most studies have focused on issues in the clinical domain, such as the knowledge and attitudes of healthcare professionals about the legitimate use of opioids [7,18,24–27], and patient and family perceptions about the use of opioids for pain relief [28–33]. However, restrictive federal and state policy can also inhibit the appropriate use of opioid medications, which can limit medical decision-making, create undue prescribing burdens, and impede patient care.

As opioids have a potential for abuse, healthcare professionals and their patients are governed by both federal and state policies that regulate the prescribing and dispensing of “controlled substances” (see Table 1 for definitions of these types of policies). In addition to controlled substances policy, state regulatory policies (e.g. policies created by medical, pharmacy, or nursing boards) authorize professional practice, including the medical use of opioid analgesics. Regulatory policies also define unprofessional conduct, prohibit unauthorized distribution of controlled substances, and establish parameters for patient care decisions affecting pain management, palliative care, and end-of-life care.
Table 1. Types of state policies affecting pain management.

- “Laws” that have binding legal force and include:
  - Statutes adopted by a state legislative body.
  - Regulations adopted by an agency of the executive branch of state government (e.g. medical, osteopathic, pharmacy, and nursing board) pursuant to statutory authority.

The most common laws affecting pain management are statutes and regulations governing the prescribing of controlled substances; statutes such as an Intractable Pain Treatment Act and Pain Relief Acts; statutes creating and regulations implementing prescription monitoring programs or pain advisory councils; regulations issued by healthcare licensing boards governing professional and unprofessional conduct for practitioners regulated by the agency; and regulations that license healthcare facilities.

- “Guidelines” do not have binding legal force, but are officially adopted policies issued by a government agency to express the agency’s position about a particular issue. Many state medical, osteopathic, pharmacy, or nursing boards have issued guidelines regarding the medical use of opioid analgesics for the treatment of pain. Such guidelines can help healthcare practitioners to better understand their licensing board’s standards of practice regarding the treatment of pain.

Consequently, healthcare professionals’ choice to treat pain with opioids can be influenced by what their state policies say about this practice. Unfortunately, some of these policies contain restrictions that have the potential to interfere with the medical use of controlled substances for the treatment of pain, referred to as “regulatory barriers”, or fail to recognize pain relief as part of quality healthcare practice [34]. Furthermore, there can be a perception among healthcare practitioners that drug control or regulatory policies restrict professional practice, even when they do not, and this perception can make practitioners reluctant to prescribe these medications [35].

Recently, both international and national legal and healthcare organizations have expressed concern about the possible detrimental effects of regulatory barriers. International organizations such as the International Narcotics Control Board [36] and the World Health Organization [21,37] have called on all countries to identify and address regulatory barriers to cancer pain relief. In the last few years in the US, the American Cancer Society (ACS) [17], the Institute of Medicine [38], and the National Institutes of Health (NIH) [39] have called for studies to improve pain management, and to identify the legal and regulatory impediments to using opioids for pain relief. As recently as 2004, the NIH’s National Consensus Project on Quality Palliative Care identified that palliative care programs need to be knowledgeable about the legal and regulatory issues surrounding the appropriate prescribing of opioids and other controlled substances [40].

To address this long-standing imperative, the authors created a research program to longitudinally evaluate and quantify the quality of state drug control and regulatory policy, identifying language that if implemented into healthcare practice would either improve or obstruct the availability of controlled substances for patient pain relief. This article describes the current status of state policy governing the use of controlled substances for pain relief, as well as how the content of such policy has changed over time and the implications for policy change in today’s healthcare environment.

Evaluation of state policy

The University of Wisconsin Pain & Policy Studies Group (PPSG) developed a research program to improve US drug control and healthcare regulatory policies related to pain management, palliative care, and end-of-life care. To realize this objective, the PPSG created a criteria-based methodology to evaluate federal and state policies, resulting in a series of policy reports entitled “Achieving Balance in Federal and State Pain Policy: A Guide to Evaluation” (Evaluation Guide) [41–43] and “Achieving Balance in State Pain Policy: A Progress Report Card” (Progress Report Card) [44,45]. Grants from the ACS and the Susan G Komen for the Cure, as well as a partnership with the Lance Armstrong Foundation, supported the most recent policy evaluation reports (Evaluation Guide 2006 [43] and Progress Report Card 2006 [45]). The Evaluation Guide and Progress Report Card were conceived as tools that advocates from government and non-government organizations, as well as healthcare practitioners, can use to inform the identification and removal of regulatory barriers. Policy change activities guided by these tools will achieve more positive and consistent state policies regulating the use of controlled substances for pain relief.

The most recent Evaluation Guide was issued in July 2006 and evaluates all statutes and regulations governing the prescribing, dispensing, and administering of Schedule II controlled substances and medical, osteopathy, and pharmacy practice. Other healthcare regulatory policies (e.g. guidelines and policy statements) were obtained from each state’s medical and pharmacy boards. Table 2 contains examples of state policies evaluated. Evaluation results are expressed as a policy profile for the federal government and for each state and the District of Columbia. Both the
A central principle of Balance

Valid and credible principles must underlie a policy evaluation methodology [46]. A central principle of drug regulation and medical ethics, called Balance, was used as the basis for this evaluation of policies. The principle stems from a long-standing national and international recognition that efforts to control abuse and diversion must not impede the legitimate use of medications (i.e. for pain management) and, by extension, that drug regulatory policy should conform to current medical and scientific understanding. Ultimately, balanced state policies will avoid creating barriers to appropriate healthcare practice and patient care, and will encourage effective pain management, including acknowledging the use of controlled substances as an essential component of quality medical practice. It is important to note that Balance supports both public health and safety – the principle prohibits medication use outside the established system of control, and authorizes licensed healthcare practitioners’ use of opioid analgesics only for legitimate medical purposes in the course of professional practice. However, the reports described in this article evaluate only aspects of policies affecting medication availability and not their drug control and abuse prevention properties.

A number of governmental, regulatory, and healthcare organizations have recommended that controlled substances policy and medical practice policy should be balanced (see Table 3 for a list of international and national organizations). To this end, the Federation of State Medical Boards of the US (the Federation) has worked with the PPSG to develop model policies for state medical boards to adopt; the model policies encourage effective pain management and address physicians’ concerns about regulatory scrutiny [47–49], which reports have shown are prevalent and can hinder medication availability for patient pain relief [50–53]. In order to promote consistency in medical regulatory policy, in 1998 the Federation adopted a policy template for boards to use when creating policies in their states, entitled “Model Guidelines for the Use of Controlled Substances for the Treatment of Pain” [54]. In May 2004, the Federation’s House of Delegates unanimously adopted a revision of the Model Guidelines, called the “Model Policy for the Use of Controlled Substances for the Treatment of Pain” [55]. The revision is very similar to the 1998 guidelines, but also encourages state boards to address failure to treat pain as subject to professional discipline, which has been identified as an important need for state policy [56]. Twenty-eight states have now adopted or adapted the Federation’s model policies.

### Table 2. Examples of evaluated state policies.

<table>
<thead>
<tr>
<th>State</th>
<th>Policy type</th>
<th>Policy reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arizona</td>
<td>Osteopathic Board Guidelines</td>
<td>Guidelines: The Prescribing of Controlled Substances for the Treatment of Pain Management</td>
</tr>
<tr>
<td>California</td>
<td>Pharmacy Board Policy Statement</td>
<td>Dispensing Controlled Substances for Pain</td>
</tr>
<tr>
<td>Colorado</td>
<td>Law</td>
<td>Controlled Substances Act – 18-18-308: Prescriptions</td>
</tr>
<tr>
<td>Florida</td>
<td>Osteopathic Board Regulation</td>
<td>64815-14.005 Standards for the Use of Controlled Substances for Treatment of Pain</td>
</tr>
<tr>
<td>Florida</td>
<td>Pharmacy Board Regulation</td>
<td>64816-27.831 Standards of Practice for the Dispensing of Controlled Substances for Treatment of Pain</td>
</tr>
<tr>
<td>Kansas</td>
<td>Medical Board Guideline</td>
<td>Guidelines for the Use of Controlled Substances for the Treatment of Pain</td>
</tr>
<tr>
<td>Iowa</td>
<td>Medical Board Regulation</td>
<td>653 IAC 13.2: Standards of Practice – Prescribing or Administering Controlled Substances for the Treatment of Patients with Chronic, Nonmalignant or Intractable Pain</td>
</tr>
<tr>
<td>Minnesota</td>
<td>Joint Board Guideline (Medical, Pharmacy, and Nursing Boards)</td>
<td>Joint Statement on Pain Management</td>
</tr>
<tr>
<td>New Mexico</td>
<td>Law</td>
<td>N.M. Stat Ann. 24-2D-1 to 24-2D-6: Pain Relief Act</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>Law</td>
<td>961.001: Uniform Controlled Substance Act Declaration of Intent, 961.36 Prescriptions</td>
</tr>
</tbody>
</table>
Evaluation criteria
Sixteen evaluation criteria were derived from the principle of Balance, with each criterion falling into one of two categories:

- Positive provisions – policy language that can enhance pain relief.
- Negative provisions – restrictive or ambiguous language that can impede pain relief.

A complete list and description of each criterion, as well as the clinical and policy justifications for their relevance, can be found in Section VI of the Evaluation Guide 2006 [43].

Results from the Evaluation Guide 2006
The 2006 state policy evaluation identified numerous occurrences of restrictive or ambiguous language related to the use of Schedule II controlled substances, which have the potential to interfere in the management of moderate to severe pain. Older state laws and regulations typically contain these types of provisions, which do not conform to current standards of professional practice. Examples of such provisions include:

- Equating addiction with physical dependence or tolerance (found in 16 states).
- Requiring or suggesting that opioids be used only after other treatments have failed (found in 16 states).
- Requiring that physicians always consult with specialists when prescribing controlled substances, regardless of clinical skill (found in 10 states).
- Restricting prescribing of pain medication to patients with pain who also have an addictive disease or a history of substance abuse (found in nine states).
- Restricting the amount of pain medication that can be prescribed or dispensed at one time (found in nine states).
- Restricting the amount of time that a prescription is valid to <2 weeks (found in five states).

The evaluation also identified policies that promote effective pain management and could increase access to patient care; these policies are generally found in more recent regulatory policies of state agencies, rather than in legislative statutes. For example, state policies:

- Recognize the medical use of opioids as part of legitimate professional practice (found in all 50 states and the District of Columbia).
- Recognize pain management as part of legitimate professional practice (found in 45 states).
- Address physicians’ concerns about regulatory scrutiny (found in 39 states).
- Do not equate addiction with physical dependence or tolerance (found in 36 states).
- Recognize that the amount of medication alone is insufficient to determine prescription legitimacy (found in 31 states).

Without such language, a state’s drug control and regulatory policy is unbalanced, as it focuses disproportionately on the abuse potential of opioids. A summary of the policy evaluation findings for each state appears in Section VIII of the Evaluation Guide 2006 [43].

The policy evaluations led to state advocates becoming interested in improving pain policy, and identified the need for a method to compare states on the quality of their policy and to measure policy change across time. The criteria-based, policy evaluation results for each state were converted to grades for the years 2000, 2003, and 2006. The states’ policy grades, and the method to calculate the grades, are described in the Progress Report Card 2006 and are available on the PPSG website [45]. Grades range from A to F, with higher grades representing more balanced policy and lower grades associated with potential barriers to healthcare practice and patient pain relief. A letter grade serves to simplify a state’s complex policy and regulatory environment.

Results from the Progress Report Card 2006
Table 4 contains the number of states at each grade level for each study year. In 2006, 16% of states scored the average grade of C, whereas 82% scored above C. Only one state (Georgia) was below the average with a D+, and represented the least balanced policies. Michigan and Virginia achieved the highest grade (A), and therefore, have the most balanced...
policies in the country; given a sufficient number of positive provisions, to achieve an A grade a state must have no restrictive or ambiguous policy language. No state received a grade of D or F. California, New York, and Texas, three states representing approximately a quarter of the US population, each earned an average grade of C. These grades result from the state policies containing numerous instances of both positive and negative provisions.

In addition, results showed that while the quality of policies varies greatly among states, it has improved over time. Although 35 states changed their policies between years 2000–6, the changes were sufficient in 19 states to improve their grade. Rhode Island demonstrated the most improvement, increasing from a D+ to a B, primarily by repealing numerous unduly restrictive requirements or ambiguities from state legislation. No states’ grade decreased between years 2000–6. The source of this positive policy change largely continues to be state healthcare regulatory boards (i.e. medical, osteopathic, and pharmacy) that adopted policies encouraging pain relief, palliative care, or end-of-life care.

**Discussion**

Since the year 2000, when the PPSG began evaluating state policies, there has been a notable improvement in the extent that the policies encourage effective pain management and the appropriate use of opioid analgesics. Advocates in many states have successfully used the Evaluation Guide and Progress Report Card to identify policy language in need of change and have promoted its repeal, or have adopted positive regulatory policy.

While unrelieved pain is being recognized as a significant public health problem, it is occurring at the same time as the increasing crisis of pain medication abuse and diversion. Efforts to prevent prescription medication abuse can have the undesirable and unintended consequence of restricting access for legitimate medical purposes. It remains important to effectively address the risks for pain medication abuse and diversion without impeding patient care. Recent policies issued by state medical boards promote such a perspective, conforming to the principle of Balance [48]. The policies support pain management practices that monitor whether the medication is being used for the reason it is prescribed, as well as gauging treatment effectiveness by improvements in patient functioning. This approach to prescribing controlled substances for pain helps accomplish the dual objective of enhancing public health (through effective patient pain relief) and protecting public safety (through minimizing the possibility of medication abuse or diversion) [23].

Although some policy improvement resulted from efforts to repeal state legislative barriers, the primary reason for positive change over time occurred because medical, osteopathy, and pharmacy regulatory boards adopted policies about pain management. In the past 6 years, 17 state regulatory boards adopted policies based on the Federation’s models designed to encourage better treatment of pain and to address practitioners’ fear of investigation and discipline [45]. A further five states developed board policies for which neither of the Federation’s models were the source [45]. In addition, four states approved joint policy statements relating to the use of controlled substances for pain relief; these are collaborative efforts by several regulatory boards, such as medicine, osteopathy, pharmacy, and nursing, which emphasize the importance of multidisciplinary pain treatment and communicate positive messages to a variety of healthcare licensees [45]. Furthermore, some medical boards have created programs to share their pain management policy with their licensees, and have developed sections on their websites that provide information to licensees about the use of controlled substances to treat pain [57]. The frequency of policy creation and educational initiatives demonstrates that many regulatory boards are serious about confronting unrelieved pain.

Despite the significant positive policy adoption in recent years, state advocates now face the challenge of eliminating many outdated negative provisions from statutes, some of which were adopted >30 years ago. Although states can endorse stricter laws than federal policy, undue restrictions are not a necessary part of drug control or professional practice laws. Since the year 2000, there has been a 60% increase in positive provisions, compared with only a 13% reduction in negative provisions during the same period [45]. As a result, the repeal of negative provisions from statutes seems to be receiving less attention than efforts of professional licensing boards to adopt positive policies. A particular challenge remains for states that have a considerable number of both positive and negative provisions. There must be

**Table 4. Number of states at each grade level: 2000, 2003, and 2006.**

<table>
<thead>
<tr>
<th>Grade level</th>
<th>2000</th>
<th>2003</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D+</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>C+</td>
<td>13</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>B</td>
<td>11</td>
<td>13</td>
<td>20</td>
</tr>
<tr>
<td>B+</td>
<td>1</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
efforts in these states to reduce the number of restrictive or ambiguous provisions in legislation in order for grade improvement to occur.

The issue of state drug control and professional practice policies is becoming a more frequent part of the dialogue when conceptualizing what can be done to improve pain management for people with chronic cancer or non-cancer conditions. For example, statutorily mandated advisory councils are multidisciplinary committees (typically composed of legislative, regulatory, and healthcare appointees) created to enhance pain management at the state level. Historically, such committees have focused on educational initiatives for healthcare professionals or the general public, but in recent years they have additionally begun to examine the quality of policies in their states and to design strategies to repeal barriers. Furthermore, activities of state pain initiatives are expanding to address barriers present in healthcare laws and regulations. This evolving approach clearly connects the dots among state policy, professional practice, and patient care.

Similar to any single factor, positive policy change is not usually sufficient in itself to enhance pain management. However, improving state policy is a necessary complement to the many ongoing state-level efforts designed to educate healthcare professionals about the appropriate use of pain medications and to inform the general public about the availability of pain treatment options. Most importantly, improving state policy will remove restrictions and can enhance appropriate access to pain medications for people who experience moderate to severe pain during the course of their illness and beyond. State policy barriers must not stand in the way of patients achieving effective pain relief and an improved functioning and quality of life.

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References


Successful Treatment of Painful Glossopharyngeal Neuropathy with Pregabalin: A Case Report

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This report describes a very unusual case of glossopharyngeal neuralgia that transformed into a more constant neuropathic pain, which was responsive to treatment with pregabalin. Pregabalin is not a firstline drug for the treatment of neuralgia and it has only been documented by a single case report. This case further suggests the potential use of this drug for varied types of neuropathic pain. Adv Pain Manage 2007;1(2):67–9.

Glossopharyngeal neuralgia is a rare pain syndrome characterized by severe paroxysmal pain in the areas innervated by the glossopharyngeal nerve (cranial nerve IX [CN IX]). CN IX supplies motor and sensory fibers to the tongue, soft palate, pharynx, and parotid gland [1]. Neuralgia, in this distribution, has an incidence of approximately 0.7/100,000 per year, is usually unilateral, and generally occurs in the left side of the face [2]. Although idiopathic in most cases, it can be caused by demyelinating plaques (multiple sclerosis), nerve compression from tumors (cerebellopontine angle), peritonsillar abscess, or vascular lesions, including arterial malformations of the carotid, vertebral, or posterior inferior cerebellar arteries [1]. Neuralgia can also be the presentation of Eagle syndrome, or compression of CN IX by the stylomastoid process [3].

Glossopharyngeal neuralgia can be treated pharmacologically or by surgical interventions. Published studies have identified numerous drugs that have been effective in anecdotal reports, including carbamazepine, baclofen, phenytoin, valproate, pimozide, and clonazepam [1]. More recent case reports have highlighted the use of newer antiepileptics including gabapentin, pregabalin, lamotrigine, and oxcarbazepine [4–7], and in addition, opioids may be of benefit in some patients. Furthermore, surgical approaches have been recommended for those patients refractory to medical treatment and include microvascular decompression or gamma knife surgery [8,9].

Some patients with neuralgic pains due to structural disease develop a constant component of the pain, which often continues to be punctuated by paroxysmal episodes of severe pain. Based on clinical experience, the treatment of these neuropathic pains usually proceeds as it would for the initial neuralgic pain.

We report a very unusual case of glossopharyngeal neuralgia that transformed into a more constant neuropathic pain due to dolichoectatic vertebral and basilar arteries, which was promptly responsive to treatment with pregabalin. The use of pregabalin to treat glossopharyngeal neuralgia has been noted previously in a single case report [5]. This current case further suggests the potential use of this drug for varied types of neuropathic pain and illustrates the course of a rare neuropathic pain.

Case

A 74-year-old man presented with right facial pain 5 years ago. The pain involved the right cheek, jaw, and mid-face, and extended into the tongue. The quality of the pain was sharp, shooting, stabbing, and at times burning. It occurred several times each day and each episode was a few seconds in duration.

The pain episodes became more frequent and severe. More than three years after onset, a continuous dysesthetic component developed. This constant pain progressively worsened. The pain was exacerbated by bending forward and chewing produced a sharp electrical sensation. The pain was lessened when he turned his head to the left and lowered his jaw. In addition, he reported some dribbling on the right side of his mouth, and therefore had to modify his diet to soft foods.

In the past, he had been treated with acetaminophen and ibuprofen, with only minimal relief. Application of a topical anesthetic to the affected area worsened the drooling...
and had to be abandoned. A trial with carbamazepine was aborted due to side effects.

The patient’s medical history was significant for hypercholesterolemia, coronary artery disease, and he had suffered a myocardial infarction in 1986 (he was aged 54 years). The patient’s psychiatric history was nothing out of the ordinary. Surgical history showed significant bowel obstruction in 1988, with subsequent perforation and surgical repair without long standing complications. His medications included ramipril, atorvastatin, and aspirin, which he was taking regularly without experiencing significant side effects.

At the time of admission to the pain practice, the right side of the patient’s face was mildly swollen. Neurological examination revealed severe hyperalgesia of the right mid-lower mandibular area, and oral mucosa in the base of the mouth and tongue without crossing over midline. The rest of the neurological exam was unremarkable. There was no tenderness of the tongue or oral mucosa and the temporomandibular joint had full range of motion bilaterally.

A magnetic resonance imaging scan was carried out and revealed focal high-grade narrowing of the left posterior cerebral artery proximally. Flow-related enhancement was noted throughout, with marked distortion, dilation, and elongation in the left and right arteries, and the basilar artery. Magnetic resonance angiography (MRA) showed arterial dolichoectasia with no abnormal mass enhancement or lesion, and normal venous sinuses.

A surgical approach to release the pressure from the nerve was proposed to the patient, but he preferred to undergo pharmacological trials first. Treatment was initiated with tramadol without any improvement. Although pregabalin is not a first-line drug for the treatment of neuralgias, the neuropathic component of the pain and the good tolerability, and positive clinical experience with pregabalin in our practice meant a trial with this drug was recommended to the patient. He was given pregabalin at a starting dose of 25 mg orally at night, which was quickly titrated to 50 mg twice daily. The pain declined dramatically. He was mostly pain-free. He had no side effects, with the exception of constipation. The right-sided facial swelling resolved and the face appeared symmetrical.

Following a period without pain, the patient stopped treatment with pregabalin. Pain with the same characteristics and distribution promptly recurred. Pregabalin was restarted and the pain subsided. Six months later, the patient is at the same dose of pregabalin, pain free, and without side effects.

Discussion

The patient developed a classic case of glossopharyngeal neuralgia, which transformed over a period of years to a continuous neuropathic pain. Imaging revealed the likely cause to be vertebrobasilar dolichoectasia with compression of CN IX. This anomaly has been associated with hemi-facial spasms and cranial nerve palsies via vascular compression of cranial nerves [10–12]. In dolichoectasia, the arteries can be angulated, tortuous, or dilated. The degree of vascular impingement on local structures varies [13]. The diagnosis can usually be established by MRA [14].

Although glossopharyngeal neuralgia is usually idiopathic, it is important to recognize the possibility of an underlying structural disease. Not all secondary neuralgias will transform to continuous dysesthesias, and clinicians should have a low threshold for appropriate imaging of even typical presentations of neuralgia in order to exclude structural etiologies. Primary therapy of the cause was not possible in this case, but in other situations, identification of the underlying cause may offer the potential for a curative intervention.

This rare pain syndrome responded dramatically to pregabalin and did so at a relatively low dose. Pregabalin is an anticonvulsant that has been shown to have analgesic properties in patients with painful diabetic peripheral neuropathy, postherpetic neuralgia, and several other syndromes [15]. It is structurally related to gabapentin, but has different pharmacokinetics [16,17]. Furthermore, it has been proposed that it acts by decreasing the release of glutamate, noradrenaline, and substance P via blockade of the α,δ subunit of voltage-gated calcium channels in the central nervous system [18].

Conclusion

This case suggests that pregabalin may be useful in the treatment of glossopharyngeal neuropathy caused by a structural lesion. Given its efficacy in varied types of neuropathic pain, pregabalin should be considered in patients with painful cranial neuropathies, including neuralgias.

Disclosures

The authors have no financial interest to disclose.

References


CLINICAL REVIEWS
Commentary and Analysis on Recent Key Papers

Clinical reviews were prepared by Lara Dhingra, Helena Knotkova, and Ricardo A Cruciani

NOVEL THERAPIES

Single-dose and steady-state pharmacokinetics of fentanyl buccal tablet in healthy volunteers
Darwish M, Kirby M, Robertson P Jr et al.

In this study, the investigators evaluated the safety and tolerability of a single dose of fentanyl buccal tablet and the steady state after multiple doses of fentanyl buccal tablets in normal volunteers. Subjects received one 400 μg fentanyl buccal tablet at the initiation of the study in order to determine the pharmacokinetics of a single dose. After day 4 of the study, and through to day 9 (end of study), steady-state pharmacokinetics were addressed by administering the subjects the same amount of the medication every 6 h. To avoid the effect mediated by fentanyl, all subjects were pretreated with 50 mg oral naltrexone, which was then administered every 12 h during the entire duration of the study. Due to this, data on efficacy and drug-mediated side effects were not available. Some side effects were observed and were probably related, but were not attributed, to the study drug. Multiple fentanyl determinations were carried out, which included the first dose to determine the peak plasma concentration, and multiple doses to determine the pharmacokinetic parameters once in steady state.

The sample included 24 subjects, age range 19–44 years, 20 males and four females, and a close to equal representation of black and white subjects.

Following multiple administrations, the peak plasma level of fentanyl was higher compared with the single-dose data. The higher than predicted levels suggest a certain degree of fentanyl accumulation.

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Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate
Darwish M, Kirby M, Robertson P Jr et al.

In a randomized, cross-over design study, 26 healthy volunteers received either:

- 400 μg fentanyl buccal tablet given transmucosally (the way that it was designed).
- 800 μg fentanyl buccal tablet given orally (for the purpose of comparison).
- 800 μg of oral transmucosal fentanyl citrate (the older formulation) given transmucosally.
- 400 μg of intravenous fentanyl.

Fentanyl is a well-known drug that has been synthesized and used for the management of pain for >40 years. Due to its lipophylicity it can cross mucosal barriers easily and reach peak blood levels more rapidly than other molecules such as hydromorphone or morphine. The authors of the current investigation conducted a study to compare the bioavailability of oral transdermal fentanyl citrate, a formulation that has been on the market for many years, with a new formulation called fentanyl buccal tablet. Fentanyl buccal tablet has been designed to achieve peak blood levels and alleviate pain more rapidly. This delivery system produces an effervescent reaction that facilitates fentanyl absorption through the oral mucosa.

Breakthrough pain is a challenging problem in the management of cancer and non-cancer pain, and consequently there is a tremendous effort underway to achieve better and more rapid pain relief. A drug that has received significant attention is fentanyl. Due to its lipophylicity it can cross mucosal barriers easily and reach peak blood levels more rapidly than other molecules such as hydromorphone or morphine. At present, there are several formulations being tested to this effect. In the current article, the authors present safety and tolerability data on a recently developed formulation of fentanyl used for breakthrough pain: fentanyl buccal tablet.
In order to prevent the effect caused by fentanyl, patients were pretreated with 50 mg of oral naltrexone. Minor side effects were observed in some subjects, but were attributed to the administration of naltrexone.

Intravenous fentanyl reached its peak plasma concentration more rapidly than any of the other forms of administration. Fentanyl buccal tablet given transmucosally was better absorbed compared with the other forms of administration (except intravenous) and reached peak concentrations more rapidly.

The absolute bioavailability of fentanyl was greater following transmucosal administration of fentanyl buccal tablet as compared with oral transmucosal fentanyl citrate. Approximately 30% lower doses of fentanyl buccal tablet than oral transmucosal fentanyl citrate would be required to achieve an equivalent plasma level of fentanyl. These differences must be taken into account when selecting dose regimens or switching between these formulations.

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Efficacy of complementary and alternative medicine therapies in relieving cancer pain: a systematic review

This systematic review evaluated 18 randomized controlled trials of complementary and alternative medicine (CAM) therapies for cancer pain. Although a significant benefit for acupuncture, support groups, hypnosis, and relaxation was found, no CAM therapies for cancer pain can be recommended due to a lack of high-quality trials to date.

Multiple studies show that patient preference for the use of complementary and alternative therapies (CAM) for cancer pain is growing. However, there is a lack of knowledge about the efficacy of CAM therapies in relieving cancer-related pain. Thus, this systematic review evaluated the quality of randomized controlled trials (RCTs) of CAM therapies for cancer pain.

In this current review, 18 RCTs were evaluated. Using a scoring criterion, two independent raters assigned a quality rating to each trial (e.g., high, good, intermediate, or low quality). The results showed that few trials were rated as high quality (Table 1). However, significant benefits for acupuncture, supportive psychotherapy, relaxation, hypnosis, and herbal therapy were found. Many trials were considered poor quality due to small sample sizes with no calculations for statistical power, poorly designed or absent control arms, no data on adverse effects, and brief intervention durations.

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Table 1. Quality rating and benefit assessment of trials using complementary and alternative therapies.

<table>
<thead>
<tr>
<th>Level of benefit</th>
<th>Quality rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant benefit</td>
<td></td>
</tr>
<tr>
<td>One acupuncture trial</td>
<td>Good</td>
</tr>
<tr>
<td>Two supportive psychotherapy trials</td>
<td>Good; intermediate</td>
</tr>
<tr>
<td>Two relaxation/guided imagery trials</td>
<td>Good; low</td>
</tr>
<tr>
<td>One hypnosis trial</td>
<td>Good</td>
</tr>
<tr>
<td>One herbal supplement therapy</td>
<td>Low</td>
</tr>
<tr>
<td>Post-intervention or short-term benefit</td>
<td></td>
</tr>
<tr>
<td>Two acupuncture trials</td>
<td>Low</td>
</tr>
<tr>
<td>One music therapy trial</td>
<td>Low</td>
</tr>
<tr>
<td>One herbal supplement therapy</td>
<td>Low</td>
</tr>
<tr>
<td>Two massage therapy trials</td>
<td>High; intermediate</td>
</tr>
<tr>
<td>Two healing touch intervention trials</td>
<td>Good; intermediate</td>
</tr>
<tr>
<td>No benefit</td>
<td></td>
</tr>
<tr>
<td>Two music therapy trials</td>
<td>Low</td>
</tr>
<tr>
<td>Two massage therapy trials</td>
<td>High; intermediate</td>
</tr>
</tbody>
</table>

Despite potential benefits for acupuncture, support groups, relaxation, hypnosis, and healing touch interventions, none can be recommended given the sparse data. One of the strengths of this review was its rigorous appraisal process for RCT evaluation. This article may have benefited from broader enrollment criteria that included trials for meditation, yoga, tai chi, and qigong.


Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain

The purpose of the study was to determine changes in cortical excitability in patients with chronic neuropathic pain at baseline and after repetitive transcranial magnetic stimulation (rTMS). The results showed that rTMS applied over the motor cortex at a frequency of 10 Hz restored intracortical inhibition in the motor cortex of the hemisphere contralateral to the affected hand.

Several previous studies have reported transient relief of neuropathic pain after applying repetitive transcranial
magnetic stimulation (rTMS) at 10–20 Hz over the primary motor cortex. The goal of the present study was to determine whether motor cortex rTMS could induce changes in excitability of the motor cortex with respect to pain relief. Twenty-two patients with chronic neuropathic pain located in one upper limb and 22 age-matched healthy controls underwent cortical excitability testing of various parameters at baseline and after sham or active rTMS at a frequency of 1 Hz or 10 Hz applied over the motor cortex. These included motor threshold at rest, amplitude ratio of motor evoked potentials at two intensities, cortical silent period (CSP), intracortical inhibition (ICI), and intracortical facilitation. The results showed that at baseline, CSP was shortened in both hemispheres in patients compared with healthy subjects. Moreover, CSP correlated with pain score. ICI was only reduced in the motor cortex hemisphere contralateral to the affected hand. After active rTMS at 10 Hz, but not at 1 Hz or sham, ICI in the hemisphere contralateral to the affected hand increased. The findings indicated that chronic neuropathic pain was associated with a loss of inhibition in the motor cortex, suggesting impaired γ-aminobutyric acidergic neurotransmission. The current study shows that rTMS at 10 Hz, applied over the motor cortex, can restore the defective intracortical inhibition associated with chronic neuropathic pain.

Identification of the alpha2-delta-1 subunit of voltage dependent calcium channels as a molecular target for pain mediating the analgesic actions of pregabalin

Field MJ, Cox PJ, Stott E et al.

Proc Natl Acad Sci USA 2006;103:17537–42.

Neuropathic pain represents a significant therapeutic challenge, and gabapentin has shown clinical efficacy in a wide range of neuropathic pain conditions. Pregabalin, the more potent new-generation compound, is the most widely studied agent in controlled clinical trials for neuropathic pain. This current article demonstrates that the analgesic action of pregabalin is mediated through the α2δ-1 subunit of voltage-gated calcium channels, and establishes this subunit as a target for pain control.

In the last decade, a number of putative mechanisms for the analgesic action of gabapentin and pregabalin have been postulated. Despite their structural similarity to the inhibitory transmitter γ-aminobutyric acid (GABA), neither pregabalin nor gabapentin bind to GABAA or GABAB receptors, nor do they interact with GABA-uptake transporters. In 1996, a gabapentin-binding protein was isolated, sequenced, and identified as the α2δ subunit of voltage-gated calcium channels (VGCCs). However, previous studies have not conclusively demonstrated the importance of the interaction of gabapentin and pregabalin with this protein. The purpose of the current study was to demonstrate the importance of the α2δ-1 subunit of VGCCs in the analgesic action of pregabalin. The authors used a gene-targeting technique to generate a mutant mouse, R217A, for this trial. Previous studies have shown that a mutation leading to the substitution of arginine at position 217 with alanine on the α2δ-1 protein prevented gabapentin from binding to that subunit. The aim of the present study was to demonstrate that pregabalin binding was similarly affected. The results showed that the mutation itself did not prevent the development of allodynia after nerve injury in the mutant mice, and that pain responses in these mutants were normal. However, pregabalin possessed no analgesic activity in the mutant mice against either chemically induced tonic pain or nerve injury-induced chronic pain. The mutation at position 217 prevented pregabalin from binding to the α2δ-1 subunit without affecting the level of protein expression. These data clearly demonstrate that the R217A mutation does not alter normal responses to noxious stimuli or significantly change the mechanisms underlying neuropathic pain in the R217A mutant mice. Furthermore, the data showed that it is the α2δ-1 subunit of VGCCs that provides a target for the analgesic action of pregabalin.

Sumatriptan alleviates pain in patients with trigeminal neuralgia

Kanai A, Suzuki A, Osawa S et al.


In order to determine the efficacy of sumatriptan to alleviate pain in patients with trigeminal neuralgia, the current authors conducted a placebo-controlled trial in 15 patients who had been suffering from painful paroxysms for at least 1 month.

A typical symptom associated with trigeminal neuralgia is a recurrent severe burning or shock-like pain of neuropathic origin in the eyes, lips, nose, scalp, forehead, and jaw. Carbamazepine, among other anticonvulsants, has been shown to alleviate this type of pain in approximately 40–80%
of patients. However, some patients do not respond to anticonvulsants or have unbearable side effects. Pain in migraine headaches, which also involve abnormalities of the trigeminal system, can be successfully managed with sumatriptan and other triptans acting on 5-hydroxytryptamine 1B/1D receptors. The present study, a placebo-controlled trial, investigated whether sumatriptan relieved pain in patients with trigeminal neuralgia. Fifteen patients who had been suffering from painful paroxysms for at least 1 month were enrolled. Each patient received 1 mL of saline subcutaneously as placebo, followed by subcutaneous sumatriptan, 3 mg in 1 mL of saline, 15 min later. This treatment was followed by a 1-week administration of oral sumatriptan (50 mg twice daily). The results showed that after treatment with placebo there were no significant changes in pain intensity, whereas following administration of subcutaneous and oral sumatriptan, visual analogue scale scores for pain while resting, touching, and talking decreased significantly. Adverse events involved fatigue (four patients) and nausea (two patients). No effect of sumatriptan on blood pressure or heart rate was observed in any of the participating patients. The authors concluded that for patients with trigeminal neuralgia, especially those who could not tolerate anticonvulsants, sumatriptan might provide a safe and efficient option in the treatment of trigeminal neuralgia-related pain.

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The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery

In this placebo-controlled, randomized trial, 80 patients who were scheduled for decompressive lumbar laminectomy with posterior spinal fusion were randomized to receive celecoxib, pregabalin, placebo, or a combination of pregabalin and celecoxib following oral medication 1 h before and 12 h after surgery. The results showed that administration of the combination of pregabalin and celecoxib in patients after spinal fusion surgery provided better analgesia and caused fewer side effects than either analgesic drug alone.

Celecoxib belongs to the class of cyclooxygenase-2 (COX-2)-specific nonsteroidal anti-inflammatory drugs (NSAIDs), whereas pregabalin is an α2δ subunit calcium channel ligand. These agents are two mechanically different types of analgesics that have demonstrated efficacy after a variety of surgical procedures. However, no previous study has evaluated the efficacy of administering pregabalin with an NSAID for postoperative analgesia. Eighty patients who were scheduled for decompressive lumbar laminectomy with posterior spinal fusion were randomized to receive the following oral medication:

- Two placebo capsules.
- Celecoxib 400 mg 1 h before surgery and celecoxib 200 mg 12 h after surgery.
- Pregabalin 150 mg 1 h before and 12 h after surgery.
- Celecoxib 400 mg and pregabalin 150 mg 1 h before surgery, and celecoxib 200 mg and pregabalin 150 mg 12 h after surgery.

Following surgery, all patients received morphine via patient-controlled analgesia. No other analgesic medication was given.

The findings of the study show that the combination of pregabalin and celecoxib resulted in a significant reduction in pain scores (pain at rest and with movement), as well as a reduction in morphine consumption during the first 24 h after surgery. Moreover, the combination was the only treatment that significantly reduced the incidence of nausea and excess sedation, suggesting that this specific drug combination could have wider clinical use in post-surgical settings.

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Ensuring pain relief for children at the end of life

The present article reviews, through a case-based presentation, pharmacological and non-pharmacological methods available for pain control in pediatric palliative care. The authors of the current study discuss recommended dosages and potential side effects of pain medications, and detect barriers to good pain control in children facing end of life.

The World Health Organisation analgesic ladder, delineated 15 years ago, is appropriate for use in children. It starts with using a non-opioid, which can include paracetamol, for the
management of mild pain, step 2 is represented by weak opioids (e.g. codeine), and step 3 uses opioids without a ceiling effect and is typically recommended for moderate-to-severe pain. The authors of the current study mention that some pain specialists recommend skipping step 2, as pain in most patients is well managed using just steps 1 and 3. Acetaminophen and nonsteroidal anti-inflammatory drugs can be used as adjuvants at any step.

The choice of medication that is best for a specific pediatric patient is influenced by multiple factors such as medical history, drug allergy or intolerance, preferred route of administration, half-life, and availability. The authors point out that opioids such as morphine, codeine, fentanyl, hydromorphone, oxycodone, and methadone can be safely used in children. The exception to safe opioid use is meperidine and mixed opioid agonist–antagonists (e.g. pentazocine and dezocine). For the majority of pediatric patients at the end of life, good pain relief while maximizing function is achievable. On occasion, in the setting of intractable pain or other distressing symptoms (e.g. breathlessness) it may not be possible to provide adequate pain relief without compromising the sensorium. The addition of a sedative to the analgesic may be required if all other options have been explored by palliative medicine specialists. The authors emphasize that good pain control can significantly improve the quality of life for children with life-threatening conditions.

The current review describes the fundamentals of opioid risk management. Critical public health issues are discussed, including current rates of prescription opioid abuse in the US, the role of regulatory agencies and healthcare providers in reducing abuse and diversion, and existing methods for risk management.

Recent advances in the development of opioid analgesics have been promising. However, the growing availability of long-acting opioids requires balancing of the analgesic benefits of opioid therapy for millions of pain patients with the potential risks of abuse and diversion. The authors discuss these complex issues, including the roles of key entities involved in pain care and abuse prevention.

Epidemiological data indicate that the medical use of opioids has risen dramatically from 1997–2002 (fentanyl by 200%, oxycodone by 400%). The problem of prescription opioid abuse and diversion has risen concurrently, with the proportion of drug abuse due to opioid abuse increasing from 5.8 to 9.9%.

Katz et al. highlight the importance of risk management, such as practices to reduce harm related to opioid therapy while preserving access to pain treatment. Key entities and policies responsible for risk management include:

- Federal agencies, such as the US Food and Drug Administration, Drug Enforcement Administration, Substance Abuse and Mental Health Administration, and National Institute on Drug Abuse.
- State laws that restrict the use of opioid therapy and regulate medical practice.
- Healthcare providers who implement best practices for pain management, including monitoring and addressing the risk of opioid abuse.
- Healthcare payors who absorb costs associated with opioid abuse and restrict authorization, quantities, and co-payments for opioid analgesics.
- The pharmaceutical industry, currently accountable for the safety of opioids throughout the “drug’s life cycle” and collaborating with the public sector to minimize risk.

Multiple national surveys assessing opioid abuse have been used, including “Monitoring the Future” in youths and young adults, and the “National Household Survey on Drug Abuse” in the general population. Additional methods to identify opioid abuse and diversion that have been implemented include:

- The “Drug Abuse Warning Network” – a surveillance system that monitors national trends in drug-related emergency department visits and deaths.
- The “Drug Evaluation Network System” – a database providing information on the number of patients admitted to addiction treatment programs.
- The “Treatment Episode Data Set” – records the characteristics of patients entering selected treatment facilities.

In order to improve patient management, effective screening tools aimed at assessing a patient’s risk potential for opioid misuse have been established. Interventions for abuse and diversion include educating providers on behavioral strategies for risk management and new drug formulations that deter abuse. At present, 22 states track controlled substances prescribed statewide using electronic databases, e.g. “Prescription Monitoring Programs”.

This current review provides a critical analysis of key issues in risk management. Standards of care for managing patients at risk for abuse require more dissemination. A challenge for
the public and private sectors will be to identify population-based objectives for reducing opioid abuse and the combinations of services needed for risk management.

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**Failing to plan is planning to fail: improving the quality of care with survivorship care plans**

Earle CC. 


With recent advances in cancer treatment, healthcare systems must respond to the needs of a new and rapidly growing population of cancer survivors. However, there are no formal guidelines for the delivery of follow-up healthcare in cancer survivors. This review summarizes recent recommendations from the Institute of Medicine on the provision of survivorship care.

Although the number of cancer survivors is increasing, national guidelines for the provision and coordination of follow-up care are lacking. The area of cancer survivorship has become a national priority as cancer survivors experience a variety of medical and psychosocial health problems, including neurocognitive and sexual impairments, infertility, chronic fatigue and pain, psychological distress, relationship difficulties, and employment and financial hardships. Recognizing that cancer survivors are at an increased risk for the development of second primary cancers, cancer recurrence, and long-term and late treatment effects, there has been a call for multidisciplinary care approaches. At present, guidelines for follow-up care for cancer survivors, including screening and surveillance, treatment of late medical effects, symptom management, genetic counseling, and health promotion, are under development. However, there is a lack of consensus among experts on strategies for long-term care.

Based on the Institute of Medicine’s (IOM’s) recent report, “Lost in Transition”, the following key components of a survivorship care plan are recommended:

- A treatment summary that includes a record of all disease-, medical-, and treatment-related characteristics presented to the survivor at discharge.
- A written follow-up care plan to monitor medical and psychosocial sequelae in survivors, including a designated coordinator who oversees the delivery of care from multiple providers.
- Ongoing surveillance as indicated for high-risk survivors.

Present barriers to survivorship care plans include a lack of communication systems and web-based approaches for conveying treatment summaries and follow-up plans among providers. In addition, there is a lack of data on current patterns of long-term care in survivors and factors influencing patient satisfaction and preferences for care. This review provides a useful summary of the IOM report, identifies unique needs and concerns among cancer survivors, and highlights areas for additional research. However, the review may have benefited from more information about various follow-up care models (e.g. shared-care models, nurse-led models, and specialized, multidisciplinary survivorship follow-up care clinics), and the advantages and disadvantages of these individual approaches.

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**Children’s self-reports of pain intensity: scale selection, limitations and interpretation**

von Baeyer CL. 


This review provides a rationale for the use of self-report scales to evaluate pain intensity in children and describes various assessment instruments. Methodological and conceptual issues associated with the use of different rating scales are discussed, including age-related developmental patterns affecting validity and interpretation.

Pain assessment in children can provide useful information on treatment response and efficacy, with studies showing that evaluation improves pain outcomes. However, the choice of an appropriate assessment tool is complex and involves consideration of developmental, socio-cultural, and behavioral factors. Thus, pain measurement in children presents unique challenges. This current review presents an overview of different instruments for pain assessment in children and considerations for tool-selection.

Based on their analysis, the authors of the current review recommend using the numerical, color visual analogue, faces, and pieces of hurt scales. Furthermore, they suggest that scales are most useful when combined with behavioral observations and reports from parents and providers. Sources of bias include the under- or over-endorsement of pain due to children’s knowledge deficits, the perceived negative consequences of reporting pain, and anchor effects. Despite potential barriers to validity and interpretation, pain intensity scales that are appropriate for specific age and development level are clinically meaningful and may optimize pain therapy in children.

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Groin pain in athletes
Macintyre J, Johson C, Schroeder EL.

Groin pain is highly prevalent in athletes; however, accurate identification of the cause of groin pain is complex. This comprehensive review describes the most common causes of groin pain, methods for differential diagnosis, and best practices for treatment.

Groin pain is frequently under-diagnosed or misdiagnosed in patients. It can be classified into three main categories: athletic, non-athletic, and musculoskeletal causes. Most groin pain in athletes occurs as a result of kicking or sudden changes in direction or speed. The most common sources are abductor muscle strain, osteitis pubis, and sports hernia.

Abductor strain or tendinopathy accounts for the majority of cases of groin pain in athletes. Strains of the abductor longus are most common and frequently recur. They can be managed using rehabilitative approaches that preserve range of motion and enhance strengthening and endurance. Tenotomy for chronic pain may be indicated when conservative pain management approaches fail.

The onset of osteitis pubis is usually progressive, with the site of pain in the symphysis, lower abdomen, proximal adductors, and genitals. Radiographic imaging and magnetic resonance imaging (MRI) may be useful. Treatments including ice, physical therapy, and nonsteroidal anti-inflammatory drugs are used, but these are not evidence-based. For severe cases, phototherapy, corticosteroid injection, curettage, and stabilization may be indicated.

Data on sports hernia (athletic pubalgia) is mixed, with some studies suggesting that they are rare and others that they are common. They are frequently caused by tissue damage in the external inguinal ring. MRI and radiographic imaging are non-specific, presenting challenges to diagnosis. Good clinical outcomes have been reported following multi-phase rehabilitation programs of strengthening and running. Surgical interventions include herniorrhaphy and adjunctive rectus abdominus repair.

Other causes of groin pain include stress fractures, sacro-iliac joint dysfunction, extra-articular snapping hip syndromes, intra-articular hip disorders, and nerve entrapments. Important points for assessment with these conditions include:

- Ruling out the presence of femoral neck fractures in athletes with stress fracture using a “hop test”.
- Identifying labral tears and femoroacetabular impingement in patients with intra-articular hip disorders.
- Establishing whether the pain may be secondary to nerve entrapment or lumbar radiculopathies, using electromyography, MRI, and diagnostic blocks for diagnosing nerve injury.

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Panic attacks after spinal cord stimulator implantation
Sheu R, Goloff M, Esteban S et al.
Anesth Analg 2006;103:1334–5.

The authors of this article report the case of a 45-year-old man who developed panic attacks following spinal cord stimulator implantation. Despite the absence of preoperative psychiatric risk factors, the patient experienced poor post-surgical adjustment, leading to stimulator removal. These clinical findings suggest panic disorder as a potential complication from surgery and highlight a need for enhanced provider awareness.

Psychological screening to evaluate patients who are candidates for spinal cord stimulator implantation is routine. The goal of screening is to evaluate the patients’ psychological status, understanding of implantation, and abilities to cope with the surgical plan. This current letter describes the case of a 45-year-old man who underwent spinal cord stimulator implantation in order to improve radicular low back and knee pain.

Based on limited pain relief from multiple treatment modalities, the patient was evaluated for a spinal cord stimulator trial. Routine psychological evaluation by a clinical psychologist revealed no significant psychiatric history or evidence of psychological distress. Following a 1-week spinal cord stimulator trial, the patient’s pain and physical function improved significantly. Subsequently, a dorsal column stimulator was implanted with lead tips at the T9–T10 level. Stimulation was verified in the lower back and lower limb, with an absence of stimulation in the chest or abdomen.

Two weeks following implantation, the patient developed cardiac symptoms (such as chest tightness), anxiety, and insomnia. The results of comprehensive cardiac testing, which included electrocardiogram, stress test, echocardiogram, and angiogram, were unremarkable. In the absence of cardiac symptoms, the patient was prescribed sertraline lansoprazole, metoprolol, and alprazolam for the treatment of panic disorder. He continued to use oxycodone extended-release and oxycodone with acetaminophen for his pain. Although his pain...
decreased with the stimulator, the patient reported negative cognitions that served to trigger panic symptoms. Anxiety did not improve with pharmacotherapy or with the stimulator turned off. At the patient’s request, the stimulator was removed. The panic symptoms resolved following removal.

Findings from this case suggest a need for increasing provider awareness of panic disorder as a potential complication of stimulator implantation, even in patients who have no psychiatric history. This case indicates that behavioral and psychosocial factors may complicate treatment response, adherence, and post-surgical adjustment and recovery. At present, there is a lack of empirical data on psychosocial outcomes following spinal cord stimulator implantation. Risk factors for psychological sequelae following implantation require investigation, and a greater understanding may improve clinical outcomes and assist in the comprehensive care of patients with pain.

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Pain-related catastrophizing in healthy women is associated with greater temporal summation of and reduced habituation to thermal pain

Catastrophizing has been identified as one of the primary behavioral determinants of pain severity and disability. The current report is the first known study to assess the relationship between catastrophizing and temporal summation of pain. Results showed that higher levels of catastrophizing were associated with a greater temporal summation of thermal pain in women. Findings suggest catastrophizing may affect pain processing by promoting central nervous system sensitization.

Catastrophizing has prominent effects on the level of pain that patients report. While positive coping attempts involve adaptive thoughts and behaviors to manage pain, catastrophizing involves negative ideations or intrusive thoughts that exaggerate pain intensity. Several findings highlight the role of catastrophizing on pain response, including:

- Greater pain-related catastrophizing is associated with higher pain ratings and lower pain tolerance.
- Catastrophizing is associated with central nervous system activation in areas of the brain implicated in the affective processing of noxious stimuli.

There is a lack of research on the relationships between temporal summation and catastrophization. Temporal summation is an index of central pain facilitation critical to pain processing and pain experience. It involves the following points:

- Successively administering a series of identical noxious stimuli that are increasingly painful although stimulus intensity is unchanged.
- Associations with acute and chronic pain, gender differences in pain, and disorders that include maladaptive sensitization to pain such as fibromyalgia.

Using a series of thermal pulses, the relationship between catastrophization and temporal summation was assessed in 38 women who were free of pain or psychiatric comorbidity. Three sets of 10 pulses lasting 0.5 s each were administered from a 38°C baseline, at temperatures of 47, 49, and 51°C. Each set was 2 min apart with an inter-pulse delay of approximately 2 s. Results from t-tests and non-parametric analyses showed that high catastrophizers were more likely to abort the procedure at the 51°C series and reported elevated levels of pain in each series.

Analyses of covariance showed that the interaction of catastrophization was significant for the 47 and 49°C series, but not the 51°C series. Furthermore, high catastrophizers reported greater summation of pain and reduced habituation to repetitive noxious stimuli.

These findings suggest that catastrophizing may facilitate sensitization in acute pain experience. However, the study is unable to clarify the mechanisms or pathways in pain processing. It is theorized that individual differences in catastrophizing impact pain processing at the neurophysiological and psychological levels via increased attention to pain and repetitive C-fiber stimulation from second-order neurons in the spinal cord. Future studies may evaluate whether catastrophizing is a mediator of pain and temporal summation, and whether this acute model can be applied to chronic pain experience. These preliminary findings are promising and may warrant behavioral interventions that modify catastrophizing to alter pain processing.

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The 23rd Annual Meeting of the American Academy of Pain Medicine (AAPM) was held at the Hilton New Orleans Riverside Hotel/Morial Convention Center in New Orleans, LA, USA. Approximately 1000 pain medicine physicians from across the country gathered at the AAPM to share information about up-to-date research, and the latest in patient care and regulatory issues that affect the practice of pain medicine. Discogenic pain, neuromodulation, and opioid therapy were among the focuses of the meeting.

This year’s “Decade of Pain Lecture” was dedicated to John Oakley, an AAPM member and internationally recognized leader in neuromodulation who died in 2006. A variety of fascinating presentations on the latest developments in a number of additional pain care topics were also featured.

Other highlights included the opening meeting of the New Orleans Pain Consortium, an important gathering of the State Organizational Liaison Initiative, a keynote address by Ronald M Davis (Henry Ford Health System, Michigan, MI, USA), president-elect of the American Medical Association (AMA), and the announcement of this year’s scientific poster winners.

As a symbol of the AAPM’s support for New Orleans, instead of giving the meeting faculty small gifts of appreciation for their participation, the AAPM made a US$2400 donation on behalf of the faculty to the New Orleans Area Habitat for Humanity. Speakers also received “rebirth” pins designed by a local jewelry artist, who donated a portion of the proceeds to a local charitable organization.

The “Decade of Pain Lecture”
Joshua P Prager (University of California, Los Angeles, CA, USA) celebrated the enormous strides made over the past 10 years in neuromodulation, the implanting of devices in the nervous system to control pain, movement dysfunction, and other central nervous system disorders. First established >40 years ago out of a belief that stimulating the dorsal column of the spinal cord could treat chronic pain syndromes, neuromodulation has evolved considerably as an indisputable therapy for controlling refractory pain conditions, often with fewer complications and side effects than conventional pain therapies.

Dr Prager was quoted saying that “during the past decade, intraspinal therapy for intractable pain has evolved into a useful clinical treatment.” Neuromodulation has demonstrated that effective changes can occur in the nervous system by application of targeted electricity or small amounts of medications. As microprocessor and battery technology advances, the tools used are becoming more practical, potent, and effective. Devices are now smaller and more robust, with a greater life span compared with just 3 years ago. Together with advanced imaging techniques, more is known about neuromodulation targets both before and after they are treated. Advances in spinal cord stimulation include implants using pacemaker technology and a more sophisticated use of rechargability, which allows access to pain targets not previously accessible. Advances in intraspinal drug delivery, including an increase in clinical indications and the advent of newer classifications of intrathecal medications, allow for this therapy to reach a wider range of patients with chronic pain.

Despite the progress, much work in neuromodulation remains to be done. In Dr Prager’s opinion, studies are needed to answer questions about efficacy in patients with non-cancer and neuropathic pain. Further investigation into combinations of medicines, which offer promise for even better treatment, is required. In addition, a system for delivering different medications at different rates needs to be developed.

Dr Prager’s lecture was dedicated to Dr Oakley, a leader in neuromodulation whose untimely death occurred in 2006. At a separate ceremony during the Annual Meeting, Dr Oakley was posthumously awarded the National Pain Foundation’s Ambassador of the Year Award for his contributions to pain medicine.
Speaker highlights
This year’s array of programs, symposiums, and lectures offered something for everyone. The following represents a summary of a number of these presentations that the present author found to be among the most interesting to ongoing pain research.

Multidisciplinary pain medicine
Treating chronic pain simply as a neurobiological issue will not work, according to a seminar by Steven Feinberg (Bay Area Pain and Wellness Center, Los Gatos, CA, USA), Elliot Krames (Pacific Pain Treatment Center, San Francisco, CA, USA), Albert Ray (Pain Medicine Solutions, Miami, FL, USA), and Herbert Rosomoff (The Rosomoff Comprehensive Pain Center at Douglas Gardens, Miami, FL, USA). Proper treatment, they said, requires that chronic pain (the disease) be seen as a biopsychosocial phenomenon, which requires the expertise of well-trained pain physicians, nurses, psychologists/psychiatrists, physical and occupational therapists, nutritionists, and others. This treatment team approach aims to restore the patients’ maximum abilities to gain control of their lives, improve their quality of life, and reduce the amount of future medical care that they will need. Treatment techniques should include anything that empowers patients to achieve these goals. Medications and invasive interventions have a role, but are no more than tools in the physician’s armamentarium. Ultimately, individuals who are successful in managing their chronic pain take charge of their lives and minimize interactions with the medical community. The speaker argued that the data clearly indicate that the multidisciplinary approach, where all necessary providers are gathered under one roof, is the most efficient, productive, and effective treatment approach.

Discogenic pain
Novel techniques for the treatment of discogenic pain were presented at a symposium entitled “Discogenic pain: minimally invasive and surgical solutions,” chaired by Leonardo Kapural (Cleveland Clinic, Cleveland, OH, USA). Among those described were thermal and novel radiofrequency techniques such as intradiscal biacuplasty and other intradiscal therapies, as well as surgical options such as fusion and artificial disc replacement. The panelists, including Nilesh Patel and Robert McLain (both from Cleveland Clinic), agreed that patient selection appears to be the key determinant of therapeutic success.

Evidence-based medicine
Jerome Schofferman (SpineCare Medical Group Inc., Daly City, CA, USA) coordinated a symposium called “Evidence-based practice and pay for performance.” With new information on the latest pain treatment breakthroughs constantly emerging from both reliable and unreliable sources, sorting out the true from the false has become particularly important for pain medicine physicians. The best approach may be something called evidence-based medicine (EBM) or evidence-based practice, which is defined as “medical care based on the best research, combined with a physician’s clinical expertise integrated with each patient’s unique values and circumstances.” EBM is a quality-improvement measure rather than a cost-reduction process. Nevertheless, long-term cost savings should be achieved as EBM seeks to identify the best treatment the first time around and avoid expensive salvage care. New technologies marketed without sufficient testing are avoided in favor of those that have been subjected to a prospective, randomized placebo-controlled trial with a large number of patients. Always embracing the latest technologies or always relying on the old ways of doing things is not serving the patients’ best interests, and EBM is an effort to find a middle ground that serves both the physician and the patient.

Law enforcement
According to Mark W Caverly (Department of Justice, Washington, DC, USA), the Drug Enforcement Administration (DEA) and the pain treatment community have common interests in the appropriate use of controlled substances for legitimate medical conditions. Speaking at a “Pain Medicine and Law Enforcement” symposium on the subject of the DEA’s relationship with pain physicians, Caverly discussed the balanced mission of the DEA, which is to prevent the diversion and abuse of pharmaceutical controlled substances while ensuring an adequate supply for legitimate medical needs in the usual course of professional practice.

Speaking at the same symposium on the topic of overcoming a physicians’ fear of drug law enforcement, David Joranson (University of Wisconsin, Madison, WI, USA) stated that he thought a physician’s fears of disciplinary action against those prescribing opioids for pain were exaggerated. He went on to say that many state boards have adopted more balanced pain management policies, but clinicians may not be aware of them. The key to reducing anxiety is good communication between clinicians, law enforcement agencies, and regulatory authorities (see also leading article on state laws and regulations governing the use of controlled substances to treat pain – pages 60–6).

Chronic pain management with opioids
A practical approach to effective communication with patients was addressed in the symposium “Chronic Pain Management with Opioids: strategies to improve communications between caregivers and patients,” chaired by Scott M Fishman.
(University of California Davis, CA, USA). The highlights included updates on pain assessment, clinical management requirements for using opioids to treat chronic pain, and opioid risk management. The program emphasized methods and tactics for communicating with patients and listening for remarks that can assist with optimal pain management. All of this year’s presentations and symposiums from the AAPM are available online at www.painmed.org.

New Orleans Pain Consortium
An organizational meeting of the New Orleans Pain Consortium was held to begin addressing chronic problems in the Louisiana pain care delivery system, problems that pre-dated, but were greatly exacerbated by, Hurricane Katrina. The multidisciplinary group, which included 25 participants from the initial meeting, is the brainchild of Education Committee Chairman, Michael Moskowitz (Mill Valley Pain, Mill Valley, CA, USA). The points discussed during the kickoff meeting included the difficulties facing pain physicians in the New Orleans area, a suggestion that an ad hoc committee be re-established for the purpose of addressing the problems within the state medical board, and a pledge of support from the AAPM to help the Consortium with planning meetings, attracting speakers, and garnering industry support for its goals. Dr Moskowitz stated that “solutions won’t be developed in a single afternoon, but with the creation of the Pain Consortium, these very real problems can begin to be addressed in the long term.”

State Organizational Liaison Initiative
A meeting was held by the AAPM State Liaison Initiative, which is a new project to provide direct communication with the AAPM leadership and representatives within every state in an effort to improve the Academy’s involvement with state and local issues. The Academy hopes that this process will allow it to support members in influencing local and state legislation and regulations, and to share this information with other regions. A number of important matters pertaining to the practice of pain medicine, and in particular, prescribing issues, are determined by state legislatures and medical boards. Unfortunately, it is difficult for AAPM to monitor many of these without input from physicians locally impacted by these changes.

Participation as a state liaison will require maintaining contact with local and state medical societies, particularly with any professional lobbyist, in order to keep the AAPM informed of any pending regulatory or legislative issues. Representatives are still needed from various states including Alaska, Arizona, Arkansas, Delaware, Georgia, Hawaii, Illinois, Indiana, Iowa, Kentucky, Maine, Maryland, Massachusetts, Montana, Nevada, North Carolina, North Dakota, Oregon, Pennsylvania, South Dakota, Tennessee, Vermont, Washington, Wisconsin, and Wyoming.

Keynote address
In his keynote address, one of the plenary sessions of the meeting, Dr Davis highlighted a number of key AMA initiatives – focusing, in particular, on the role that organized medicine plays in advocating a physician’s ability to deliver improved healthcare. This honored an annual tradition of having an AMA representative deliver the keynote address and highlights the close partnership between the two organizations. More information about the current AMA issues outlined by Dr Davis is available at www.ama-assn.org.

Conclusion
The AAPM 23rd Annual Meeting was a great success, providing diverse and interesting research updates on topics ranging from discogenic pain, neuromodulation, opioid therapy, and patient care, to regulatory issues that affect pain medicine. In addition, a number of poster presentations gave some exciting insights into existing pain issues.

We look forward to further advancements being presented at the AAPM 24th Annual Meeting, to be held on February 13–16, 2008, at Gaylord Palms Resort & Convention Center, Orlando, FL, USA.