Potential Role of the Gabapentinoids in the Prevention and Treatment of Acute and Chronic Postoperative Pain
Jørgen B Dahl and Ole Mathiesen

Brain Changes Related to Chronic Pain: Implications for Pain Extinction Training
Herta Flor, Martin Diers, Helena Knotkova, and Ricardo Cruciani

Update on the diagnosis and management of complex regional pain syndromes
Maike Stengel, Andreas Binder, Gunnar Wasner, and Ralf Baron

Oral Transmucosal Fentanyl Citrate for Cancer Breakthrough Pain: A Case Report
Giovambattista Zeppetella
Advances in Pain Management is supported by an educational grant from Cephalon.
1. We are aiming to provide practical information for pain specialists, including anesthesiologists, neurologists, oncologists, general physicians, and primary care physicians. How would you rate the information presented in this issue?

<table>
<thead>
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<th>Strongly agree</th>
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a) The technical quality of information included in *ADVANCES IN PAIN MANAGEMENT* was acceptable: 1 2 3 4 5

b) The information was relevant to my practice: 1 2 3 4 5
c) The information was presented clearly: 1 2 3 4 5
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1. We are aiming to provide practical information for pain specialists, including anesthesiologists, neurologists, oncologists, general physicians, and primary care physicians. How would you rate the information presented in this issue?
Dear Colleagues,

Welcome to the third issue of Advances in Pain Management.

In our first leading article, Drs Dahl and Mathiesen (Glostrup University Hospital, Glostrup, Denmark) explore the use of gabapentinoids and their potential in treating acute and chronic postoperative pain. This article discusses the mechanisms of action of the gabapentinoids and the conflicting results observed for immediate postoperative pain and chronic postoperative pain treatment.

In the second article, Drs Flor, Diers, Knotkova, and Cruciani (University of Heidelberg, Mannheim, Germany, and Beth Israel Medical Center, and Albert Einstein College of Medicine, New York, NY, USA) discuss the changes that occur to the brain during states of chronic pain and evaluate the consequences that these alterations have for the pharmacological, stimulatory, and behavioral management of chronic pain.

In the third article of the issue, Drs Stengel, Binder, and Baron (Universitätsklinikum Schleswig-Holstein, Kiel, Germany) review the methods used in the diagnosis of complex regional pain syndromes and the various treatment options that are presently available.

This issue also includes a case report on a patient’s experience of oral transmucosal fentanyl citrate for breakthrough cancer pain, which follows on from Dr Zeppetella’s article in issue 1, highlights from the 26th American Pain Society annual meeting, and a synopsis and critique of recently published scientific findings from several key areas of pain management.

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 two issues of what we believe will be an exciting and useful new journal in this developing field.

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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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Potential Role of the Gabapentinoids in the Prevention and Treatment of Acute and Chronic Postoperative Pain

Jørgen B Dahl, PhD and Ole Mathiesen, MD
Department of Anesthesia and Intensive Care Medicine, Glostrup University Hospital, Glostrup, Denmark

Acute postoperative pain is a combination of nociceptive pain and inflammatory pain resulting from peripheral and central neuronal sensitization, which includes an upregulation of the α2δ-1 subunit of the voltage-gated calcium channels found in the dorsal horn neurons. In addition, a neuropathic component is likely, as damage to neural tissue is inevitable in most surgical procedures. Gabapentin and pregabalin bind to the α2δ-1 subunit of voltage-dependent calcium channels, resulting in a reduced influx of calcium at nerve terminals. During the immediate perioperative period, the gabapentinoids may be expected to downstage the physiological, central sensitization processes induced by nociception and inflammation. Consequently, the gabapentinoids are thought to be able to “protect” the patient from the influence of central neuronal hyperexcitability, and the ensuing clinical allodynia (pain induced by stimuli that are not normally painful), and hyperalgesia (increased pain sensitivity) that may amplify early postoperative pain. Furthermore, gabapentin and pregabalin may relieve the symptoms associated with central sensitization in chronic postoperative neuropathic pain. In recent years, substantial clinical evidence has accumulated to show that the gabapentinoids are effective anti-hyperalgesics in the treatment of acute postoperative pain and that they may enhance the pain-relieving effects of other analgesics. However, results from studies of the prevention and treatment of chronic postoperative pain disagree. Future studies should explore the effects of “protective premedication” with combinations of various anti-hyperalgesic and analgesic drugs for postoperative analgesia. Adv Pain Manage 2007;1(3):82–90.

Mechanisms of acute and chronic postoperative pain
Surgery leads to nociceptive pain due to noxious, incisional, mechanical, thermal, or chemical stimulation of the skin and subcutaneous tissues, as well as the neural and visceral structures that are involved in the surgical procedure [1,2].

Soon after surgery is initiated, nociceptive pain is accompanied and augmented by inflammatory pain. Inflammatory mediators are released in the wound and adjacent tissues, resulting in a reduction in the threshold of local nerve endings (peripheral sensitization). In addition, central neurons becomes hyperexcitable owing to the afferent barrage of impulses from the wound, which subsequently leads to an exaggerated response by these neurons to normal sensory inputs (central sensitization) (Fig. 1) [1–3].

Acute postoperative pain is driven by input that is amplified by sensitized peripheral and central neurons. Although the hyperexcitability of the neuronal structures involved may outlast the original stimuli, the changes are generally reversible and normal receptivity of the system will eventually be re-established when the wound heals [2]. Accordingly, changes due to nociceptive and inflammatory pain have been compared with alterations to the “software” of the system [2], signifying that they may be “reformatted” back to normal. In contrast, alterations to the system “hardware” may lead to permanent changes in the processing of information. This can happen in patients who undergo surgery, if nerves are injured during the procedure. Not only can a neuropathic pain component develop immediately during the surgical procedure, but it may also persist in the absence of any peripheral stimulus or inflammation [2].

In summary, acute postoperative pain is a combination of nociceptive and inflammatory pain resulting from peripheral and central amplification mechanisms that include an upregulation of the α2δ-1 subunit of voltage-gated calcium channels [2]. In addition, a neuropathic component is likely, because damage to neural tissue is inevitable in most surgical procedures, leading to the spontaneous firing of injured nerve endings and subsequently adding to the increased pain sensitivity experienced in the early postoperative period [2].
The clinical consequences of peripheral and central sensitization, as well as peripheral nerve damage, are primary and secondary hyperalgesia, where “primary hyperalgesia” denotes increased pain sensitivity at the site of tissue damage and “secondary hyperalgesia” signifies increased pain sensitivity in the normal skin surrounding the site of tissue damage. Patients experience allodynia, hyperalgesia, spontaneous pain, and increased sensitivity in tissues adjacent to the wound [2,4]. These can lead to unprovoked pain at rest and intensified pain during movement, which may affect the ability of the patient to recover and mobilize after the operation [1].

Iatrogenic neuropathic pain due to nerve damage during surgery is probably the most important cause of chronic postoperative pain, a type of pain estimated to be present in up to 10–50% of individuals after common operations, and believed to be severe in approximately 2–10% of these patients [2].

**Mechanism of action of the gabapentinoids in acute and chronic postoperative pain**

Several hypotheses have been proposed for the gabapentinoids’ analgesic mechanism of action [5–8]. Gabapentin and pregabalin both bind to the α2δ-1 subunit of the voltage-dependent calcium channel, resulting in a reduction in the influx of calcium at nerve terminals. In turn, this reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P [5]. This mechanism has been consistently observed across a wide range of studies and probably accounts for the majority of analgesic activity that is seen using these compounds [5–8]. Pregabalin is structurally related to...
gabapentin and the two drugs are largely indistinguishable in terms of their pharmacological profile. However, in contrast to gabapentin, pregabalin has linear pharmacokinetics, and its binding affinity for the α\textsubscript{2}δ-1 subunit is six-times more potent than that of gabapentin [5].

The mechanism of action of the α\textsubscript{2}δ ligands differs from that of traditional "antinociceptive" drugs. The α\textsubscript{2}δ ligands have minimal effects on the release of physiological transmitter, but significantly inhibit sensitized or "abnormal" release [5]. Gabapentin has been reported to possess anti-hyperalgesic and anti-allodynic, but not anti-nociceptive, properties in animal models of surgical pain [9–10]. Furthermore, both gabapentin [11–14] and pregabalin [15] have been shown to reduce secondary hyperalgesia in a number of clinical models of inflammatory pain. In a recent and elegant study using functional magnetic resonance imaging in normal volunteers, Iannetti et al. studied gabapentin-induced modulation of brain activity in response to nociceptive mechanical stimulation of normal skin and capsaicin-induced secondary hyperalgesia [16]. The findings of that study showed that gabapentin had a measurable antinociceptive effect, but a stronger and more robust anti-hyperalgesic effect. This supports the concept that gabapentin is more effective in modulating nociceptive transmission when central sensitization is present [16].

Consequently, the α\textsubscript{2}δ ligands either have no or a limited effect on acute nociception per se, but they are effective in conditions where tissue injury or inflammation have induced sensitization in central neurons. Accordingly, it has been suggested that the gabapentinoids may be "ideal drugs that act selectively on pathophysiological systems" [17].

Our current knowledge of acute and chronic pain mechanisms, combined with the unique mechanism of action of the α\textsubscript{2}δ ligand, and the anti-hyperalgesic effects demonstrated in preclinical and clinical studies, provides a rationale for the use of gabapentin and pregabalin in postoperative pain treatment.

During the immediate perioperative period, the gabapentinoids are expected to downregulate the physiological sensitization process (or the “software” component of the alterations) induced by nociception and inflammation, which should reduce the influence of central neuronal hyperexcitability on early postoperative pain.

It is not clear if unrelieved perioperative pain may lead to persistent pain due to nociception-induced structural modifications of the central pain pathways. However, if most chronic postoperative pain states are due to direct peripheral nerve damage (or alterations of the “hardware” of the system) [2], it is not believed that administration of perioperative gabapentinoids (or other analgesic treatment modalities) should be able to preempt chronic postoperative pain. However, gabapentin and pregabalin may relieve the symptoms associated with a subsequent neuropathic pain state.

Clinical studies

Search criteria

Relevant double-blind, randomized controlled trials were identified by performing Medline (www.ncbi.nlm.nih.gov/PubMed/1966–2007), Cochrane Library (www.thecochranelibrary.com) and Google Scholar (www.scholar.google.com) searches, without language restrictions. The free text combinations used included the search terms: “gabapentin”, “pregabalin”, “postoperative pain”, “postoperative analgesia”, “chronic postoperative pain”, “chronic pain”, and “neuropathic pain”. Additional articles where sought by reviewing the reference list of retrieved reports and relevant reviews. The last search was performed March 2007.

Acute postoperative pain

Gabapentin

The first study looking into the effect of gabapentin on postoperative pain was published in 2002 [18]. In this double-blind, placebo-controlled investigation, 70 patients were randomized to receive a single dose of oral gabapentin 1200 mg or placebo, 1 h before radical mastectomy. Patients were followed 4-h postoperatively, and received patient-controlled morphine at doses of 2.5 mg to induce analgesia. The results of the study showed that gabapentin significantly reduced total morphine consumption from a median of 29 to 15 mg. Pain during movement was significantly reduced from 41 to 22 mm on a 100-mm visual analogue scale (VAS) 2-h postoperatively, and from 31 to 9 mm 4-h postoperatively. No significant differences between the groups were observed with regard to pain at rest or side effects [18].

Since this study, gabapentin has been evaluated in a large number of surgical procedures, including abdominal hysterectomy [19–24], lumbar discectomy [25–29], orthopedic surgery [30–33], and various other procedures (Table 1) [34–42]. Furthermore, a number of systematic reviews and meta-analyses have been undertaken that utilize data from the original studies on pain scores, total analgesia consumption, and side effects over a 6–24-h period [43–46]. The various meta-analyses have included data retrieved from between seven and 23 randomized, placebo-controlled trials [43–46].

In the meta-analysis conducted by Ho et al., which comprised records from 16 controlled studies of different surgical procedures, a single preoperative dose of gabapentin 1200 mg was demonstrated to reduce 24-h

Jørgen B Dahl and Ole Mathiesen
cumulative opioid consumption by 28 mg, a finding that was deduced from three valid trials [45]. Based on data from six and four studies, respectively, both early (6 h: –17 mm) and late (24 h: –11 mm) postoperative pain intensity scores (VAS 0–100 mm) were significantly reduced. A subgroup analysis of data from studies where gabapentin was administered at doses <1200 mg, showed reduced pain intensity and reduced cumulative 24-h opioid consumption, whereas combined data from studies where multiple doses were administered perioperatively were found to be inconclusive. Pooled data on the adverse effects from all the analyzed studies showed that patients who received gabapentin experienced less vomiting (number needed to treat [NNT]=11) and less pruritus (NNT=15) compared with placebo. In addition, the incidence of sedation was increased with gabapentin (number needed to harm=8). There were no statistically significant differences between the groups regarding the incidence of nausea, dizziness, urinary retention, constipation, or respiratory depression [45].

In the most recent review of gabapentin in postoperative pain management, 23 valid, randomized, placebo-controlled studies were identified [46]. A qualitative analysis demonstrated that of these 23 studies, 16 reported data on 24-h opioid consumption. In 12 of these 16 studies, opioid consumption was significantly reduced in those patients with gabapentin compared with placebo. Pain scores at rest 6 h after surgery were reduced in 12 of the 23 trials. Nineteen of the 23 studies reported a 24-h pain score at rest, which was reduced in 10 of these trials [46]. This review focused particularly on procedure-specific results, i.e. those aimed at obtaining a meta-analysis of records from identical surgical procedures [46]. An analysis of data from five trials of abdominal hysterectomy demonstrated that cumulative 24-h opioid consumption (~13 mg) and early (4–6-h), but not 24-h, pain scores, were significantly reduced with gabapentin. Furthermore, nausea, but not vomiting, dizziness, or sedation, was significantly reduced compared with placebo. Likewise, three trials of spinal surgery demonstrated that cumulative 24-h opioid consumption (~31 mg) and early and late pain intensity at rest were significantly reduced following active treatment. Neither nausea, vomiting, dizziness, nor sedation were affected by gabapentin in these trials [46].

In summary, 24-h supplemental analgesic consumption and/or early (4–6-h) or late (24-h) postoperative pain intensity were reduced in the majority (83%) of the published, placebo-controlled trials of gabapentin in postoperative pain. No firm conclusion can be drawn with regard to adverse effects. Nausea, vomiting, and pruritus were reduced in some meta-analysis of combined data whereas sedation was increased in other subsets of studies.

**Pregabalin**

So far, only two placebo-controlled studies have evaluated pregabalin for the treatment of acute, postoperative pain (Table 2). In a study by Hill et al., 300 mg pregabalin administered once postoperatively resulted in improved pain relief for 2–12 h after surgery compared with placebo, whereas pregabalin at a dose of 50 mg was ineffective [47]. Reuben et al. administered pregabalin 150 mg 1 h before and then 12 h after surgery to patients undergoing a spinal fusion operation [48]. These patients consumed less patient-controlled morphine and experienced less postoperative pain after 24 h compared with placebo.

**Gabapentin and pregabalin in combination with other analgesics**

Due to their unique mechanism of action, the gabapentinoids may be expected to have additive or even synergistic effects with other analgesics used to treat postoperative pain.

Several investigations have addressed this issue. In a study in human volunteers, gabapentin enhanced the acute analgesic effect of morphine, and the plasma concentration of gabapentin was increased when morphine was administered concomitantly [49]. Two studies have demonstrated that a combination of gabapentin and the cyclooxygenase-2 (COX-2) inhibitor rofecoxib is marginally superior to either single agent for postoperative pain relief after elective abdominal hysterectomy (Table 3) [21,22]. Perioperative administration of a combination of celecoxib and pregabalin improved analgesia and caused fewer side effects than either drug administered alone after spinal fusion surgery [48]. Furthermore, combinations of gabapentin and lornoxicam [39] and of gabapentin and rofecoxib [42] have been shown to reduce the need for supplemental opioids compared with lornoxicam and rofecoxib alone. In a recent study it was demonstrated that acetaminophen enhanced the analgesic effect of gabapentin after abdominal hysterectomy [24]. Finally, premedication with gabapentin decreased tourniquet-related pain and improved the quality of anesthesia and postoperative analgesia during and after hand surgery when patients were put under intravenous regional anesthesia with local anesthetics [33]. In contrast, preoperative gabapentin (800 mg) did not augment postoperative analgesia in patients given interscalene brachial plexus blocks for arthroscopic shoulder surgery (Table 3) [32].

In summary, several studies have demonstrated that a combination of gabapentin or pregabalin with either morphine, COX-2 inhibitors, non-steroidal anti-inflammatory drugs, acetaminophen, or local anesthetics, may enhance the postoperative analgesic effect compared with the drug on its own.
Table 1. Randomized, placebo-controlled studies of gabapentin in the treatment of acute, postoperative pain.

<table>
<thead>
<tr>
<th>Ref</th>
<th>Surgical procedure/ N. gabapentin/placebo</th>
<th>N. Gabapentin/placebo</th>
<th>Gabapentin dose (mg)</th>
<th>Effect on (24 h) analgesic consumption</th>
<th>Effect on early (4–6 h) pain score</th>
<th>Effect on late (24 h) pain score</th>
<th>Comments</th>
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<td></td>
<td>Single-dose 1200 mg pre-operatively</td>
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<td>[18]</td>
<td>Radical mastectomy 31/34 1200</td>
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<td>N/A</td>
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<td>[27]</td>
<td>Lumbar discectomy or spinal fusion 25/25</td>
<td>↓↓</td>
<td>1200</td>
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<td>ns Vomiting reduced with gabapentin</td>
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<td>[30]</td>
<td>Arthroscopic anterior cruciate ligament repair 20/20 1200</td>
<td>↓</td>
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<td>ns Dizziness increased with gabapentin</td>
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<td>[40]</td>
<td>Lower extremity plastic surgery 20/20 1200</td>
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<td></td>
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<td>ns Dizziness increased with gabapentin</td>
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<td>[39]</td>
<td>Laparoscopic sterilization 38/38 1200</td>
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<td>ns ns ns Significantly more patients needed morphine in the control group</td>
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<td>[41]</td>
<td>Thyroid surgery 37/35 1200</td>
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<td>[33]</td>
<td>Hand surgery 20/20 1200</td>
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<td>[26]</td>
<td>Lumbar discectomy 4 x 20/20 300, 600, 900, 1200 (four groups)</td>
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<td>Single-dose &lt;1200 mg pre-operatively</td>
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<td>[31]</td>
<td>Major orthopedic surgery 2 x 15/15 800–1200 mg</td>
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<tr>
<td>[32]</td>
<td>Arthroscopic shoulder surgery 27/26 800 mg</td>
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<td>[37]</td>
<td>Nefrectomy 2 x 20/20 Pre and postincision groups, 600 mg</td>
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<td>[25]</td>
<td>Lumbar discectomy 28/28 300 mg</td>
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<td>[35]</td>
<td>Laparoscopic cholecystectomy 153/153 300 mg</td>
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<td>Sedation and PONV increased with gabapentin</td>
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<td></td>
<td>Multiple-dose</td>
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<td>[19]</td>
<td>Abdominal hysterectomy 39/32 1200 mg pre-operatively + 600 mg x 3 on first postoperative day</td>
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<td>[38]</td>
<td>Pulmonary lobectomy 25/25 1200 mg pre-operatively + 600 mg x 2 for 4 postoperative days</td>
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<td>Vomiting reduced with gabapentin</td>
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Adverse effects of the gabapentinoids in acute postoperative pain

In general, both gabapentin and pregabalin have been well tolerated in clinical trials of neuropathic pain, with the most commonly reported adverse being somnolence, dizziness, ataxia, and fatigue [3]. Gabapentin does not reduce gut motility in rats [50], which is a major side effect of opioids in postoperative patients.

As emphasized previously, no firm conclusion can be drawn with regard to adverse effects from the meta-analyses of postoperative pain that have been published so far, despite the fact that rather large doses of gabapentin and pregabalin have been administered [45,46]. It should be noted, though, that patients in the immediate postoperative period are exposed to side effects not only from postoperative analgesics, but from the anesthesia and surgery itself, which may have masked adverse effects caused by gabapentinoids [18,19]. In addition, most studies were not powered to investigate side effects per se.

It is interesting that adverse effects, such as dizziness, have been significantly increased in some studies of ambulatory surgery [36,42] and consequently, the benefits of reduced pain and opioid intake may be overshadowed by the drawbacks created in this clinical setting.

Chronic postoperative pain

Chronic post-surgical pain is defined as pain with a duration of >2 months that has developed after a surgical procedure, where other causes, such as disease recurrence or the presence of a pre-existing pain syndrome, have been excluded [51]. Only a few clinical studies have evaluated the gabapentinoids within this definition of chronic postoperative pain.

Three studies have investigated gabapentin in the treatment or prevention of post-amputation pain, and the results have been found to be discordant [52–54]. In a crossover study, 14 patients attending a multidisciplinary pain clinic with phantom limb pain received a daily dose of placebo or gabapentin treatment, which was titrated in increments of 300–2400 mg, or the maximum tolerated dose, for 6 weeks. Gabapentin resulted in significantly reduced pain intensity scores compared with placebo [52]. However, in another study with a similar design, which included 24 patients, no significant effect of gabapentin was demonstrated [53]. In a recent investigation of parallel-group design, gabapentin was administered in the first 30 days after amputation, but it did not reduce the incidence or intensity of post-amputation pain at 30 days or 6 months after surgery, compared with placebo [54].

In a study by Serpell et al., gabapentin titrated to a maximum of 2400 mg/day, if required, was found to be
more efficacious than placebo in treating various neuro-pathic pain syndromes [55]. However, only a fraction of patients included in the overall efficacy analysis had clear post-traumatic neuralgia, which made interpreting the results difficult [55].

Finally, three studies of perioperative gabapentin administration have investigated analgesic efficacy beyond the immediate postoperative period [23,56,57]. In one study, 60 patients scheduled for abdominal hysterectomy were randomized to receive gabapentin 400 mg every 6 h. Treatment started 18-h preoperatively and continued for 5 days postoperatively. The results of the study showed no effect of gabapentin on immediate pain, but did show decreased pain in the surgical area 1-month postoperatively [23]. In two other studies [56,57], perioperative gabapentin was investigated together with local anesthetics as part of a multimodal analgesic regimen. In both breast surgery [56] and abdominal hysterectomy [57], a reduction in postoperative morphine usage, as well as pain for >1 month postoperatively, was reported. However, it should be noted that these studies [23,56,57] do not adhere to Macrae’s definition [51] of chronic postoperative pain as pain with a duration of ≥2 months. Two of the studies investigated a combination of gabapentin and local anesthetic versus placebo [56,57], which makes the interpretation of the effect of gabapentin per se difficult.

In summary, a limited number of studies using gabapentin have investigated its preventive effect on late postoperative pain [23,54,56,57] or its effect on established chronic postoperative pain [52–55]. Results are discordant, and three of the positive studies [23,56,57] do not adhere to the contemporary definition of chronic postoperative pain.

Summary, conclusions, and recommendations
Central sensitization induced by tissue injury has been suggested to play an important role in post-injury pain, and this hypothesis offers new targets for novel analgesic approaches [58]. The gapapentinoids have demonstrated promising effects as anti-hyperalgesics, or “co-analgesics” [59], in clinical studies of immediate postoperative pain that cover a wide range of different surgical procedures. However, results from prevention and treatment of chronic postoperative pain are conflicting.

Based on the available clinical evidence, preoperative administration of a single dose of gabapentin 800–1200 mg is recommended to reduce pain and opioid requirement in the immediate postoperative period after major (non-ambulatory) surgical procedures. Future studies should explore multiple dose regimens and the effects of “protective premedication” [3] with combinations of various antihyperalgesic and analgesic drugs for postoperative analgesia.

The preventive consequence on late postoperative pain and the effect on established chronic postoperative pain, still need to be established. Data on pregabalin in postoperative pain treatment are still too sparse to permit firm recommendations

Disclosures
Dr Jørgen Dahl has received an unrestricted research grant from Pfizer, Denmark. Dr Ole Mathiesen has no financial relationships to disclose.
Table 3: Randomized, placebo-controlled studies of combinations of gabapentinoids and other analgesics in the treatment of acute, postoperative pain.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>Combination regimens</th>
<th>Overall effect on analgesic consumption</th>
<th>Overall effect on pain</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>[21] Abdominal hysterectomy</td>
<td>Placebo vs. gabapentin vs. rofecoxib vs. gabapentin + rofecoxib</td>
<td>Gabapentin + rofecoxib &gt; rofecoxib = gabapentin &gt; placebo</td>
<td>Gabapentin + rofecoxib &gt; rofecoxib = gabapentin &gt; placebo</td>
<td>Effects on analgesic consumption more consistent than effects on pain score</td>
</tr>
<tr>
<td>[22] Abdominal hysterectomy</td>
<td>Placebo vs. gabapentin vs. rofecoxib vs. gabapentin + rofecoxib</td>
<td>Gabapentin + rofecoxib = rofecoxib = gabapentin &gt; placebo</td>
<td>Gabapentin + rofecoxib = rofecoxib = gabapentin &gt; placebo</td>
<td>Effects of combination regimens more consistent than effects on pain score</td>
</tr>
<tr>
<td>[48] Spinal surgery</td>
<td>Placebo vs. pregabalin vs. celecoxib vs. pregabalin + celecoxib</td>
<td>Pregabalin + celecoxib &gt; pregabalin &gt; celecoxib &gt; placebo</td>
<td>Pregabalin + celecoxib &gt; pregabalin = celecoxib &gt; placebo</td>
<td>Effects on analgesic consumption more consistent than effects on pain score</td>
</tr>
<tr>
<td>[39] Laparoscopic sterilization</td>
<td>Placebo vs. lornoxicam vs. lornoxicam + gabapentin</td>
<td>Lornoxicam = lornoxicam + gabapentin</td>
<td>Lornoxicam = lornoxicam + gabapentin</td>
<td>Effects on analgesic consumption more consistent than effects on pain score</td>
</tr>
<tr>
<td>[24] Tonsillectomy</td>
<td>Placebo vs. acetaminophen vs. acetaminophen + gabapentin</td>
<td>Acetaminophen + gabapentin &gt; acetaminophen</td>
<td>Acetaminophen + gabapentin &gt; acetaminophen</td>
<td>Effects of combination regimens more consistent than effects on pain score</td>
</tr>
<tr>
<td>[33] Hand surgery</td>
<td>Placebo vs. acetaminophen vs. acetaminophen + gabapentin</td>
<td>Acetaminophen + gabapentin &gt; acetaminophen</td>
<td>Acetaminophen + gabapentin &gt; acetaminophen</td>
<td>Effects of combination regimens more consistent than effects on pain score</td>
</tr>
<tr>
<td>[32] Arthroscopic shoulder surgery</td>
<td>Placebo vs. acetaminophen vs. acetaminophen + gabapentin</td>
<td>Acetaminophen + gabapentin &gt; acetaminophen</td>
<td>Acetaminophen + gabapentin &gt; acetaminophen</td>
<td>Effects of combination regimens more consistent than effects on pain score</td>
</tr>
</tbody>
</table>
References


An increase or decrease of sensory input into the brain leads to adaptive changes in the primary sensory and motor areas. Plastic changes have been associated with plastic changes on multiple levels of the nervous system [1]. In patients with amputations, analysis of primary somatosensory cortex changes has shown that the input from neighboring areas occupies the region that formerly received input from the now amputated limb [2–4]. These changes are mirrored in the motor cortex [5–8]. Interestingly, reorganizational changes were found only in amputees with phantom limb pain after amputation, and not in amputees without pain. This suggests that pain may contribute to the changes observed and that the persisting pain might be a consequence of the plastic changes that occur. Studies carried out in human upper-extremity amputee patients, displacement of the lip representation in the primary motor and somatosensory cortex was positively correlated with the intensity of phantom limb pain, and was not present in pain-free amputee patients or healthy control subjects. In addition, in the patients with phantom limb pain, but not in the pain-free amputee patients, imagined movement of the phantom hand was shown to activate the neighboring face area [8]. This co-activation probably occurs because of the high level of overlap of the hand, arm, and mouth representations. Similar observations have been made in patients with complex regional pain syndrome (CRPS). In these patients, the representation of the affected hand tended to be smaller compared with that of the unaffected hand and the individual digit representations had moved closer together [9–13]. The extent of the pathological changes in the cortical representations correlated with the intensity of pain [11,14], but was additionally related to a degradation of sensibility in the affected hand.

Hyperexcitability and chronic pain
In addition to cortical reorganization, general cortical hyperexcitability has been observed in chronic neuropathic pain syndromes [5,10,15–20]. For example, Larbig et al. presented pain-relevant and -irrelevant words to subjects and found enhanced late visual potential amplitudes on the encephalogram results of the amputee patients with pain, but not on those of the amputee subjects without phantom limb pain or healthy control patients [16]. Karl et al. found significantly higher P300 amplitudes in amputee subjects with pain compared with amputee subjects without pain and healthy controls in a visual oddball paradigm, suggesting that there is a higher magnitude of non-specific cortical excitability in amputee patients with pain and a reduced excitability in amputee subjects without pain [17].

This article reviews the evidence supporting plastic changes in the primary sensory and motor areas as well as areas involved in affective and cognitive processing during states of chronic pain. The authors discuss how these memory traces that are related to pain are built and how they may be extinguished using behavioral, stimulatory, and pharmacological methods. Recent scientific evidence shows that chronic pain is accompanied by plastic changes occurring on multiple levels of the nervous system. This review focuses on brain changes related to the experience of chronic pain in humans and will elucidate consequences for the pharmacological, stimulatory, and behavioral treatment of chronic pain. Advanced imaging methods have made it possible to study brain changes in response to pain and to determine how alterations in the brain might contribute to the experience of chronic pain. Adv Pain Manage 2007;1(3):91–5.
Schwenkreis et al. found a significant reduction in intracortical inhibition in both hemispheres in CRPS patients compared with healthy control subjects [10]. In upper- and lower-limb amputees, results of transcranial magnetic studies demonstrated an elevated excitability of the motor system at the site ipsilateral to the stump [5,15,21]. Motor-evoked potentials were elicited at lower intensities in those muscles immediately proximal to the site of amputation compared with the homologous muscle on the unaffected side. Transcranial magnetic stimulation also recruited a higher percentage of the motor neuron pool in the muscle on the side on the stump than on the unaffected side. These results suggest that the excitability of the motor system that projects into the muscle immediately above the amputation was increased. Cortical hyperexcitability was reported by Tinazzi et al. in patients with right primary trigeminal neuralgia and no clinical signs of trigeminal deafferentation [19]. It has been shown that increased behaviorally relevant input related to non-neuropathic pain can lead to changes in the cortical map [22–24]. For example, Flor et al. reported a close association between pain chronicity and enhanced excitability and map expansion of the back representation in the primary somatosensory cortex in patients with non-neuropathic back pain [22]. The back representation expanded and shifted more towards the leg representation the longer the pain persisted. Similar changes were reported by Giesecke et al. using functional magnetic resonance imaging [24]. Enhanced representations of painful stimulation were found in patients with fibromyalgia. The results showed that a large proportion of areas of the brain responded to painful stimulation of a standard value as well as higher activation intensities [23].

**Activation in areas associated with the affective and cognitive processing of pain**

Recent evidence has focused on the affective and cognitive processing of pain and how this might be altered during chronic pain. In a study by Witting et al. brain correlates of allostynia in patients with allostynia related to neuropathic pain were examined [25]. In this study, the authors conducted positron emission tomography and observed that allostynia was related to enhanced ipsilateral insular and orbitofrontal activation, as well as a lack of contralateral primary somatosensory cortex activation, which the authors explained was due to a stronger emotional load and higher computational demands in the processing of a mixed sensation of brush and pain. Orbitofrontal activation is probably related to mechanisms of descending pain modulation, but it might additionally be involved in anticipatory anxiety related to pain [26]. Similarly, in trigeminal neuralgia, allostynia activated not only areas in the primary sensory pathway, but also the basal ganglia and the frontal cortex [27]. Schweinhardt et al. observed a relationship between allostynia and caudal insular activity in pain patients [28]. In CRPS patients, hyperalgesia was associated with enhanced activation in all pain-relevant areas, including the primary and secondary somatosensory cortex.

In amputee patients, Willoch et al. used hypnosis to induce painful phantom sensations [29]. They observed activation in areas such as the insula and the anterior cingulate cortex – regions that have been identified as being important in the processing of affective pain components. However, the influence of the effort to create the specific sensation in the hypnotic condition cannot be controlled in this type of study. In a study in which acute and chronic pain intensity were altered simultaneously, it was observed that chronic pain intensity changes covaried with prefrontal activation whereas acute pain intensity changes covaried with insular activation, suggesting the existence of different processing modes for acute and habitual pain [30].

**Potential mechanisms underlying plastic changes of the brain in pain**

Potential mechanisms of plasticity related to pain include the unmasking of previously present but inactive excitatory synapses and the growth of new connections (known as “sprouting”). Immediate plasticity can be seen in humans and suggests that a reorganization of sensory pathways occurs very soon after amputation, probably owing to the unmasking of ordinarily silent inputs or dendritic sprouting rather than sprouting of new axon terminals [31,32]. An unmasking of latent excitatory synapses can be caused by an increased release of excitatory neurotransmitters, an increased density of postsynaptic receptors, changes in conductance of neuronal membrane, decreased inhibitory inputs, or removing inhibition from excitatory input [33,34]. However, the evidence thus far is pointing to the removal of inhibition from excitatory synapses as the major contributor to unmasking. The crucial element in this process is the decrease in inhibition that is induced by γ-aminobutyric acid (GABA). GABA is the most important inhibitory neurotransmitter in the brain and GABAergic neurons represent approximately one-third of the neuronal population in the motor cortex. Alterations in GABAergic inhibition can induce rapid changes in cortical excitability. It has been demonstrated that drugs to enhance GABAergic inhibition (for example, lorazepam) can increase intracortical inhibition [35,36], but they do not affect the motor threshold, suggesting that reduced intracortical inhibition is most likely mediated by GABA, while changes in the motor threshold have another underlying mechanism. As proposed
by Chen et al., a reduction to the motor threshold might involve enhancement of cortico-cortical connections [15]. Since drugs that block voltage-gated sodium channels increase the motor threshold [37], it is possible that the proposed enhancement in cortical connections could be mediated by voltage-gated sodium channels. In fact, by using models of spinal cord injury, Waxman and Hains reported a substantial calcium channel-mediated upregulation of activity in supraspinal pathways [38]. Structural changes, revealed by voxel-based morphometry [39] and magnetic resonance spectroscopy [40,41], suggest that neuronal loss and cell death was induced in chronic pain. However, the relationship of these changes to pain severity has not yet been documented.

Birbaumer et al. applied regional anesthesia to upper-limb amputee patients to treat phantom limb pain and observed a very rapid reversal of somatosensory cortical reorganization in those who experienced substantial pain relief, but not in those whose feeling of pain remained unchanged [42]. This suggests that a rapid modulation of cortical plasticity and pain is possible even in chronic pain states.

**Extinction training: a new approach in pain management**

If ongoing pain is associated with abnormal crosstalk from other brain regions in addition to enhanced peripheral input, then alterations to the respective brain region or the peripheral input should alter the brain map as well as the perception of pain. The prevention of somatosensory pain memories – that is learning-induced alterations of the map in the somatosensory cortex and associated brain regions [43,44] – is an important task in pain management and there at least four possible approaches have been suggested:

- Chronic pain must be prevented as early as possible by pharmacological and psychological interventions in order to keep pain memories from being established.
- Cortical reorganization related to amputation increased nociceptive input could be further prevented by using pharmacological agents that are known to impair cortical reorganization.
- Chronic states of pain could be reversed by using training procedures that are known to influence cortical reorganization.
- Pharmacological substances that are important for reorganization could be counteracted by the use of antagonists.
- Stimulation methods such as transcranial magnetic stimulation or transcranial direct current stimulation that can alter cortical excitation and inhibition could be used in the prevention of somatosensory pain management.

**Pharmacological intervention**

The prevention of phantom limb pain might be possible by using pharmacological agents that are known to prevent or reverse cortical reorganization. Among these substances, GABA agonists, N-methyl-D-aspartic acid (NMDA) receptor antagonists, and anticholinergic substances seem to be the most promising. A double-blind, placebo-controlled study that used the NMDA receptor antagonist memantine in the perioperative phase during amputations, reported a decrease in the incidence of phantom limb pain from 72% to 20% 1 year after amputation [45].

**Stimulation**

In amputee patients with chronic pain, stimulation-related procedures were found to be effective. Intense input into the cortical amputation zone by the use of a myoelectrical prosthesis, for example, was found to reduce both cortical reorganization and phantom limb pain [46]. Thus, extensive training with a myoelectrical or sensorimotor prosthesis appears to be useful in reducing phantom limb pain. For patients who the use of a prosthesis is not possible, sensory discrimination training might be beneficial. In one study, electrodes were closely spaced over the amputation stump in a region where stimulation excites the nerve that supplies the amputated portion of the arm. Patients then had to discriminate the frequency and location of the stimulation in an extended training period that lasted 90 min/day over a 2-week period. Substantial improvements to both two-point discrimination and phantom limb pain were demonstrated in the trained patients. These improvements were accompanied by changes in cortical reorganization, indicating a normalization of the shifted mouth representation [47]. These findings are in line with other evidence that suggests that behavioral training can have massive effects on cortical representations. Direct modifications of cortical activity by a brain–computer interface – for example, feedback of slow cortical potentials, somatosensory evoked potentials or fields, electroencephalogram rhythms, or blood flow changes related to the experience of pain – have been investigated [48,49].

In some patients pain elevation was achieved by electrical stimulation with electrodes implanted over the motor cortex that modulated cortical excitability [50,51]. Although positive results were reported with this method, the risk for complications limits its use. Recently, non-invasive techniques such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation were proposed as suitable alternatives to achieve pain relief. Both techniques have been applied to several hundred subjects (including patients and healthy volunteers) worldwide and no significant side effects have been reported.
Imagery and mirror training
Moseley used a tripartite program to analyze patients with CRPS [57]. This program consisted of: a hand laterality recognition task (a pictured hand was to be recognized as left or right); imagined movements of the affected hand; and mirror therapy (patients were asked to adopt the hand posture of both hands shown on a picture in a mirror box while watching the reflection of the unaffected hand). After 2 weeks’ treatment, pain scores were found to be significantly reduced. In addition, McCabe et al. found a reduction in pain ratings during and after mirrored visual feedback of movement of the unaffected limb in CRPS patients [58]. These studies suggest that modification of input into the affected brain region may alter pain sensation.

Behavioral training
Patients who demonstrate a large degree of pain behavior and are highly incapacitated by their pain should profit from operant behavioral treatment. The goals of this treatment are: a decrease in pain behaviors in the effort to extinguish pain; an increase in activity levels and healthy behaviors in the work place; leisure and family time; medication reduction and management; and a change in the behavior of the patient’s significant others [59]. The overall goal of treatment is to reduce disability by reducing pain and increasing healthy behavior of the patient. Medication is switched from an “as needed” basis to a fixed time schedule, whereby medication is given at certain times of the day to avoid negative reinforcement learning. Similar principles are applied to enhance activity and reduce inactivity and invalidity. This approach has been found to be effective in patients with chronic back pain as well as other pain syndromes [60,61]. The cognitive–behavioral model of chronic pain emphasizes the role of cognitive, affective, and behavioral factors in the development and maintenance of chronic pain. The central purpose of cognitive–behavioral treatment is to reduce feelings of helplessness and uncontrollability and to establish a sense of control over the experience of pain. This is achieved by the modification of pain-eliciting and maintaining behaviors, cognitions, and emotions. The cognitive–behavioral approach teaches patients various techniques to effectively deal with episodes of pain. Pain-related cognitions are changed by cognitive restructuring and pain-coping strategies that increase self efficacy such as attention diversion, the use of imagery, or relaxation. Several studies have examined the efficacy of cognitive–behavioral pain management, which are considered a very effective treatment of chronic pain [61,62]. Both operant and cognitive–behavioral therapy can lead to a significant reduction in pain intensity. However, cognitive–behavioral therapy can improve cognitive and affective variables whereas operant treatments yield significant improvements in physical functioning and behavioral variables [61].

Combined behavioral and pharmacological interventions
Behavioral treatments that focus on the extinction of pain behaviors and the acquisition of healthy behaviors can also alter the brain processes related to pain. In anxiety disorders, it has been shown that exposure to the anxiety stimuli with or without additional pharmacological intervention can alter the brain processes related to stimuli that are relevant to the disorder [63]. The partial NMDA receptor agonist D-cycloserine has been found to be effective in enhancing the extinction of aversive memories and has been used as an effective adjunct to exposure treatment in two studies [64,65]. In addition, cannabinoids have been identified as important modulators of extinction [66,67] and might be interesting compounds for extinction training. The different approaches have been summarized in Table 1. Since pain seems to generally increase excitability, substances that decrease excitation such as gabapentin and pregabalin would seem indicated as enhancers of extinction. As extinction is context-specific, it is important for training to cover as wide a variety of behaviors as possible, in as many different environments as possible, along with the use of stress and pain episodes to aid relapse prevention. In addition, cognitive and emotional aspects of pain need to be targeted.

### Table 1. Treatments that can enhance the extinction of pain memories.

- Partial NMDA receptor antagonists
- Calcium channel blockers
- Cannabinoids
- Opioids
- Transcranial magnetic stimulation
- Operant extinction training

NMDA: N-methyl-D-aspartic acid
Conclusion

Although recent scientific evidence has shown that chronic pain leads to changes in many brain regions, the responsiveness of pain to plastic changes opens the door for new intervention methods that rely on stimulation, behavioral training, or pharmacological interventions to prevent maladaptive memory formation or enhance extinction.

Disclosures

Drs Flor, Diers, Knotkova, and Cruciani have no financial interests to disclose.

References

Update on the Diagnosis and Management of Complex Regional Pain Syndromes

Maike Stengel, MD, Andreas Binder, MD, and Ralf Baron, PhD
Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany

Complex regional pain syndrome (CRPS) is clinically characterized by pain, abnormal regulation of blood flow and sweating, edema of the skin and subcutaneous tissues, active and passive movement disorders, and trophic changes of the skin, appendages of skin, and subcutaneous tissues. CRPS patients exhibit changes that occur in the somatosensory systems processing noxious, tactile, and thermal information, in the sympathetic systems innervating skin (i.e. blood vessels, sweat glands) and in the somatomotor system. CRPS is classified into type I (previously known as reflex sympathetic dystrophy) and type II (formerly causalgia). The current criteria of CRPS I and II are based mainly on the patient's history and a careful physical examination. There is currently neither a diagnostic gold standard nor an objective test procedure for CRPS. However, some diagnostic tests can add valuable information to confirm the diagnosis, although the absence of abnormal results does not disprove the presence of CRPS. So far, few evidence-based treatment regimens are available for CRPS. Treatment of the individual patient is thus empiric, using techniques that have evidence-based efficacy in other neuropathic conditions. Treatment should be immediate, and most importantly directed towards restoration of full function of the affected extremity. This objective is best attained in a comprehensive, interdisciplinary setting with particular emphasis on pain management and functional restoration. Adv Pain Manage 2007;1(3):96–104.
sensitivity value combined with a fair specificity (e.g. 0.85 vs. 0.60; Table 1). For research purposes, however, it is much more important to have a high specificity in order to perform studies in a precisely diagnosed population (e.g. 0.7 vs. 0.96; Table 1).

### Epidemiology

In a population-based study on CRPS I published in 2003, Sandroni et al. reported an incidence of approximately 5.5 per 100,000 person-years at risk and an occurrence of approximately 21 per 100,000 person-years [10]. Thus, CRPS I develops more often than CRPS II. Estimations suggest incidences rates for CRPS I of 1–2% after fractures, 12% after brain lesions, and 5% after myocardial infarction [11]. Incidence rates for CRPS II are estimated to be 1–5% after peripheral nerve injury [12]. However, these brain lesion and myocardial infarction figures are relatively high and must be interpreted with care because of the lack of uniform diagnostic criteria in the past. Females are more often affected by CRPS than males, with a female-to-male ratio ranging from 2:1 to 4:1. The condition shows a distribution over all ages, with a mean age peak of 37–50 years.

### Standardized diagnostic tests

The current criteria for CRPS I and II are based mainly on analysis of the patient’s history and a careful physical examination. Neither a diagnostic gold standard nor an objective test procedure exist for CRPS. However, some diagnostic tests can add valuable information to confirm the diagnosis, although the absence of abnormal results does not disprove the presence of CRPS (Table 2).

### Plain radiographs and X-ray bone densitometry

Endosteal and intracortical excavation, subperiosteal and trabecular bone resorption, and spotty and localized bone demineralization or osteoporosis have been thought to be specific signs of CRPS, but are only observed in chronic stages of the condition. A comparative study showed that radiography had a lower sensitivity (73% vs. 97%) and specificity (57% vs. 86%) than three-phase scintigraphy in early post-fracture CRPS [13].

### Bone scintigraphy

Osseous changes are common in CRPS. Therefore, three-phase bone scintigraphy can provide valuable information [14]. Homogenous unilateral hyperperfusion in the perfusion (30 s post-injection) and blood-pool (2 min post-injection) phases is characteristic, and will help to exclude differential diagnoses (e.g. osteoporosis due to inactivity). At 3 h post-injection, the mineralization phase will show increased

#### Table 1. Revised diagnostic criteria for CRPS

<table>
<thead>
<tr>
<th>Clinical signs and symptoms:</th>
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<tbody>
<tr>
<td>1. Positive sensory abnormalities:</td>
</tr>
<tr>
<td>• Spontaneous pain</td>
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<tr>
<td>• Mechanical hyperalgesia</td>
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<tr>
<td>• Thermal hyperalgesia</td>
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<tr>
<td>• Deep somatic hyperalgesia</td>
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<tr>
<td>2. Vascular abnormalities:</td>
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<tr>
<td>• Vasodilatation</td>
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<tr>
<td>• Vasoconstriction</td>
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<tr>
<td>• Skin temperature asymmetries</td>
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<td>• Skin color changes</td>
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<td>3. Edema, sweating abnormalities:</td>
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<tr>
<td>• Swelling</td>
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<tr>
<td>• Hyper- or hypohidrosis</td>
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<td>4. Motor and trophic changes:</td>
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<tr>
<td>• Motor weakness</td>
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<tr>
<td>• Tremor</td>
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<tr>
<td>• Dystonia</td>
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<tr>
<td>• Coordination deficits</td>
</tr>
<tr>
<td>• Nail and hair changes</td>
</tr>
<tr>
<td>• Skin atrophy</td>
</tr>
<tr>
<td>• Joint stiffness</td>
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<tr>
<td>• Soft tissue changes</td>
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</table>

Diagnosis of CRPS:

1. Clinical use: One or more symptom in three or more of the categories AND one or more signs in two or more categories. Sensitivity 0.84 Specificity 0.60

2. Research use: One or more symptom in each category AND one or more signs in two or more categories. Sensitivity 0.70 Specificity 0.96

CRPS: complex regional pain syndrome.
unilateral periarticular tracer uptake (Fig. 2). Pathological uptake in the metacarpophalangeal or metacarpal bones is thought to be a highly sensitive and specific marker of CRPS [13,15]. While there is currently no gold standard with which to compare bone scintigraphy, it is useful in ruling out pain syndromes of other origin. It should be noted that bone scintigraphy only shows significant changes during the subacute period (up to 1 year). In addition, the value of this test in children seems to be of less value than in adults, showing a higher variability and, interestingly, often decreased diffuse uptake. Therefore, it should mainly be performed in children to rule out other etiologies [16].

Magnetic resonance imaging
Magnetic resonance imaging scans have demonstrated changes in joints (joint effusion) and soft tissues in CRPS with a high sensitivity but a very low specificity [17]. Bone marrow edema is inconsistent in the acute phase and is never present in chronic stages.

Research tests
Quantitative sensory testing
Bedside testing (e.g., for allodynia and hyperalgesia) should be part of the physical examination to confirm the diagnosis of CRPS. In addition, it is practical to administer standardized psychophysical tests of the thermal, thermal pain, and vibratory thresholds to assess the function of large, small myelinated, and unmyelinated afferent fibers. Impairment of warm and cold sensation, as well as of heat pain, is common in patients with CRPS [18]. Abnormal results have also been observed for CRPS patients on other detailed sensoric tests, including those for static and dynamic allodynia, pin-prick allodynia, heat and mechanical hyperalgesia, and temporal summation [19]. Although no characteristic sensoric pattern has been identified in CRPS so far, it is useful to determine and quantify the individual signs of each patient and to document successful responses to treatment.

Autonomic function tests
Autonomic function testing comprises infrared thermometry, infrared thermography, the quantitative sudomotor axon reflex test (QSART), the thermoregulatory sweat test (TST), and laser Doppler flowmetry. Skin temperature differences can be assessed easily by infrared thermometry or thermography [20]. These differences are dependent on the environmental conditions, can change dynamically within minutes, and are most prominent in thermomoderate environments. Skin temperature side differences at rest (22–24°C room temperature, 30 supine position for 30 min) of <2°C show a poor sensitivity of 32%, but a specificity of 100%. Under controlled thermoregulation, temperature side differences of >2.2°C achieve a sensitivity of 76% and a specificity of 100% [21,22]. Therefore, in an attempt to assess the maximum asymmetry and improve sensitivity in clinical practice, repeat measurements should be carried out at the beginning, during, and at the end of the patient’s visit.

In a study of 21 patients with CRPS, an enhanced sudomotor output was demonstrated on the QSART and the TST in the affected limb compared with the contralateral limb within a mean disease duration of 5 weeks [23]. At a mean duration of 94 weeks, TST findings remained pathological whereas the QSART showed no side differences. Our group used laser Doppler flowmetry to assess the vascular reflex response in 25 patients with CRPS I [21]. By controlled whole-body cooling and warming, the sympathetic vasoconstrictor activity was altered and the cutaneous blood flow in the upper or lower extremities was monitored simultaneously. We demonstrated three different vascular regulation patterns in

<table>
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<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>Plain radiograph (only chronic stages)</td>
<td>73</td>
<td>57</td>
</tr>
<tr>
<td>Bone scan (only acute stages)</td>
<td>97</td>
<td>86</td>
</tr>
<tr>
<td>Quantitative sensory testing</td>
<td>high</td>
<td>low</td>
</tr>
<tr>
<td>Temperature differences (during sympathetic stimulation)</td>
<td>76</td>
<td>93</td>
</tr>
<tr>
<td>Magnetic resonance imaging (e.g. skin, joints)</td>
<td>91</td>
<td>17</td>
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CRPS I. Firstly, in short-term CRPS, the so-called “acute” phase: with a mean disease duration of 4 months, the affected limb shows higher skin perfusion values than the contralateral limb. Secondly, in patients with a mean history of 15 months of CRPS, the “intermediate” phase, in which the affected limb shows either higher or lower skin perfusion than the contralateral limb. Thirdly, in patients with a mean CRPS duration of >28 months, the “chronic” phase, the affected limb shows lower perfusion of the skin on the affected side. Subsequently, skin temperature was altered in a corresponding manner in all phases.

Neurogenic inflammation
In the fluid of artificially produced skin blisters, significantly higher levels of proinflammatory mediators and vasoactive substances, such as interleukin-6, tumor necrosis factor-α, tryptase, and endothelin-1, have been observed in the involved extremities of patients with CRPS I as compared with the uninvolved extremities, whereas nitrate/nitrite levels have been shown to be reduced [24–26]. This sort of test might become a diagnostic tool in the future; however, these findings have been shown to persist after pain and signs of CRPS I improved, questioning the direct relation between clinical signs and symptoms and proinflammatory cytokines [27].

Skin biopsies
One hypothesis is that CRPS I is caused by persistent minimal nerve injury, particularly distal degeneration of small-diameter axons. To investigate this, Oaklander et al. examined the affected sites and matching contralateral limbs of 18 adult patients with CRPS I, and a control group of seven adults with chronic leg pain and prior surgeries related to trauma or osteoarthritis [28]. Quantitative mechanical and thermal sensory testing was performed, followed by a quantification analysis of epidermal neuritic densities in skin biopsies. Axonal densities were diminished at the CRPS-affected sites of 17 of 18 subjects, by an average of 29%. Control subjects had no painful-site neurite reductions. However, the relevance of these findings to distinct pathophysiological mechanisms remains unclear [29].

Sympathetically maintained pain
On the basis of experience and recent clinical studies, the term “sympathetically maintained pain” was redefined: neuropathic pain patients presenting with similar clinical signs and symptoms can clearly be divided into two groups by the negative or positive effect of selective sympathetic blockade, selective activation of sympathetic activity, or antagonism of α-adrenoceptor mechanisms [30]. Pain that is relieved by specific sympatholytic procedures is considered sympathetically maintained pain. Thus, sympathetically maintained pain is now defined as a symptom or underlying mechanism in a subset of patients with neuropathic disorders, not a clinical entity. The positive effect of sympathetic blockade is not essential for diagnosis of CRPS. On the other hand, the only way to differentiate between sympathetically maintained pain and “sympathetically independent pain” is to test the efficacy of a correctly applied sympatholytic intervention [3].

Differential diagnosis
Due to the lack of a gold standard in the diagnosis of CRPS, the risk of over-diagnosing must be taken into account. In order to differentiate CRPS from other neuropathic and pain syndromes, a detailed history and physical examination according to the aforementioned specifications are mandatory.

Post-traumatic neuralgia
It is important to recognize that many post-traumatic neuropathy patients have pain but do not have the full clinical picture of CRPS II. In these cases, in contrast to CRPS II patients, pain is located largely within the innervation territory of the injured nerve. Although these patients often describe their pain as burning, they exhibit a less complex clinical picture than patients with CRPS II and do not show marked swelling or progressive spread of symptoms. The cardinal symptoms are spontaneous burning pain, hyperalgesia, and mechanical – especially cold – allodynia. These sensory symptoms are confined to the territory of the affected peripheral nerve, although allodynia may extend beyond the border of nerve territories for some centimeters. Spontaneous and evoked pain are felt superficially, not deep inside the extremity, and the intensity of both is independent of the position of the extremity. Patients with post-traumatic neuropathy occasionally obtain relief with sympatholytic procedures, although much less often than those with CRPS.

Following the IASP classification, it is possible to use the term “post-traumatic neuralgia” for this type of neuropathic pain (pain within the innervation territory of a lesioned nerve). However, the new definition of CRPS II also includes the statement that symptoms may be limited to the territory of a single peripheral nerve. Therefore, the term CRPS II could be applied to these localized post-traumatic neuropathies, even though they are different syndromes with different underlying mechanisms, highlighting an inherent weakness of this definition of CRPS II.

Other differential diagnoses
Neuropathies (e.g. diabetic polyneuropathy) may also present with spontaneous pain, skin color changes, and motor deficits, but are distinguished by their symmetrical
MAIKE STENGEL, ANDREAS BINDER, AND RALF BARON

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Distribution and the patient's history. Furthermore, all kinds of inflammations and infections (e.g. rheumatism or phlegmonous conditions) might induce intense unilateral skin warming. Unilateral arterial or venous occlusive diseases can cause unilateral pain and vascular abnormalities and must be excluded in the diagnosis of CRPS. Repetitive artificial occlusion of the blood supply to one limb (as in the psychiatric factitious disorders) might induce secondary structural changes of the blood vessels with consecutive abnormalities in perfusion and, therefore, mimic CRPS symptoms and signs.

**Therapy for CRPS**

A lack of understanding of the underlying pathophysiological abnormalities and an absence of objective diagnostic criteria result in inherent difficulties in conducting clinical trials of therapeutic modalities for CRPS. Therefore, only a few evidence-based treatment regimens are currently available. In fact, four literature reviews of outcome studies found discouragingly little consistent information regarding the pharmacological agents and methods available for the treatment of CRPS [31–34].

**Pharmacological therapy**

**Opioids**

Opioids are clearly effective in the treatment of postoperative, inflammatory, and cancer-related pain. The use of opioids in CRPS has not been studied. In other neuropathic pain syndromes, compounds such as tramadol, morphine, oxycodone, and levorphanol clearly have analgesic properties compared with placebo [35]. However, there are no long-term studies of oral opioid use in the treatment of neuropathic pain, including CRPS. Nonetheless, even without solid scientific evidence, the expert opinion of pain clinicians is that opioids can and should be used as part of a comprehensive pain treatment program. Given that some patients with neuropathic pain may obtain considerable pain relief with these agents, opioids should be prescribed immediately if other medications do not achieve sufficient analgesia.

**Antidepressants**

Tricyclic antidepressants have been intensely studied in other neuropathic pain conditions, but not in CRPS. There is solid evidence that serotonin and noradrenaline reuptake inhibitors (e.g. amitriptyline) and selective noradrenaline blockers (e.g. desipramine) produce pain relief in patients with diabetic or post-herpetic neuropathy. The effectiveness of selective serotonin reuptake inhibitors in the treatment of neuropathic pain states is still uncertain. Only one of four studies performed so far showed a significant pain reduction in patients with painful diabetic neuropathy [36]; no studies have been performed in CRPS patients. With regard to sodium channel blocking agents, lidocaine (lignocaine) administered intravenously is effective in the treatment of CRPS I and II for both spontaneous and evoked pain [37]. Carbamazepine has not been tested in CRPS.

**γ-aminobutyric acid agonists**

Intrathecally administered baclofen has been shown to be effective in the treatment of dystonia in CRPS patients in one study [38]. No other trials of γ-aminobutyric acid agonists for the treatment of CRPS have been published, and there is no evidence for an analgesic effect of baclofen, valproic acid, vigabatrin, or benzodiazepines in CRPS or other neuropathic pain conditions.

**Gabapentin**

Two studies have demonstrated promising preliminary evidence for an analgesic effect of gabapentin in patients with CRPS [39,40]. In addition, a randomized, double-blind, placebo-controlled trial found that gabapentin had a mild effect on pain and a good effect on sensory deficit symptoms in CRPS I [41]. Gabapentin is effective in the treatment of painful diabetic neuropathy and post-herpetic neuralgia [42].

**Steroids**

Orally administered prednisone, at 10 mg three times daily, has been clearly demonstrated as effective at improving the entire clinical status (up to 75%) of acute CRPS patients (<13 weeks) [43]. No evidence has been obtained with regard to the efficacy of other immunomodulating therapies, such as immunoglobulins or immunosuppressive drugs, for the treatment of CRPS.

**N-methyl-D-aspartate receptor blockers**

Clinically available compounds that are demonstrated to have N-methyl-D-aspartate receptor blocking properties are effective in the treatment of painful diabetic neuropathy, but are not effective for post-herpetic neuralgia or central pain. Therefore, these agents may offer new options for the treatment of CRPS.

**Calcium-regulating drugs**

Calcitonin administered intranasally three times daily has been demonstrated to significantly reduce pain in CRPS patients [44]. Intravenous clodronate 300 mg daily and alendronate either 7.5 mg/day intravenously or 40 mg/day orally have been shown to effect a significant improvement in pain, swelling, and movement range in acute CRPS patients [45–47]. The mode of action of these compounds in CRPS is unknown.
Free radical scavengers
Recently, a placebo-controlled trial was performed to investigate the use of the free radical scavengers dimethyl sulfoxide (DMSO) 50% topically or N-acetylcysteine (NAC) orally for the treatment of CRPS I [48]. Both drugs were found to be equally effective; however, DMSO seemed to be more favorable for warm and NAC more useful for cold CRPS I. The results of that study were negatively influenced by the fact that the included patients had a long disease duration. A previous trial of DMSO failed to show a positive effect of the drug in the treatment of CRPS [49]; however, another study in a small population of CRPS patients showed DMSO to be more effective than regional blocks with guanethidine [50]. Transdermal application of the \( \alpha_2 \)-adrenoceptor agonist clonidine, which is though to prevent the release of catecholamines through a presynaptic action, may be helpful when small areas of hyperalgesia are present [51].

Interventional therapy at the sympathetic nervous system level
Currently, two therapeutic techniques are used to block sympathetic activity:

- Injections of a local anesthetic around sympathetic paravertebral ganglia that project to the affected body part (sympathetic ganglion blocks).
- Regional intravenous application of guanethidine, bretylium, or reserpine (which all deplete noradrenaline line in the post-ganglionic axon) to an isolated extremity blocked with a tourniquet (intravenous regional sympatholysis).

There are many uncontrolled surveys in the literature reviewing the effect of sympathetic interventions in CRPS, in which approximately 70% of patients report full or partial responses [52]. However, the efficacy of these procedures is still a subject of controversy [32,53]. In fact, the specificity and long-term results, as well as the techniques used, have rarely been adequately evaluated.

One controlled study in patients with CRPS I found that sympathetic ganglion blocks with local anesthetic had the same immediate effect on pain as a control injection with saline [54]. However, after 24 h, patients in the local anesthetic group were markedly improved compared with the control group, indicating that evaluating the efficacy of sympatholytic interventions is best carried out after 24 h. With these data in mind, the aforementioned uncontrolled studies must be interpreted cautiously. Only 10 of the 24 studies reviewed by our group assessed the long-term effects of these interventions. A meta-analysis of studies assessing the effect of local anesthetic sympathetic blockade in the treatment of CRPS failed to draw a conclusion concerning the effectiveness of this procedure, mainly due to small sample sizes [55].

Surgical sympathectomy
There is only limited evidence regarding the efficacy of thoracoscopic or surgical sympathectomy. Four open-label studies have reported some long-lasting benefits in the treatment of both CRPS I and II [56–59]. The most important independent factor in determining a positive outcome of sympathectomy is a time interval of <12 months between the inciting event and the procedure [56,58]. An irreversible sympathectomy may be effective in selected cases. Owing to the risk of developing adaptive supersensitivity, even on nociceptive neurons, and subsequent increase and prolongation of pain, these procedures should not be recommended on a broad indication basis.

Stimulation techniques and spinal drug application
Transcutaneous electrical nerve stimulation may be effective in some cases and has minimal side effects. One randomized study found that epidural spinal cord stimulation was effective in the treatment of selected chronic CRPS patients [60]. Interestingly, these patients had previously undergone unsuccessful surgical sympathectomy.

Physical and occupational therapy
It should be stressed that clinical experience clearly indicates that physiotherapy is of utmost importance in CRPS patients to achieve recovery of function and rehabilitation. Standardized physiotherapy has been shown to produce long-term relief in terms of both pain and physical dysfunction in children [61].

Physical and, to a lesser extent, occupational therapy are able to reduce pain and improve active mobility in CRPS I patients [62]. Lymph drainage provides no benefit when applied together with physiotherapy in comparison with physiotherapy alone [63]. Patients who initially have less pain and better motor function are likely to benefit from physical therapy to a greater degree than other patients [64]. Physical therapy for the treatment of CRPS has been shown to be both more effective and less costly than either occupational therapy or control treatment [65].

Recent studies have demonstrated that the combination of hand laterality recognition training, imagination of movements, and mirror movements reduces pain and disability in CRPS patients [66]. Thus, physiotherapy, occupational therapy, and attentional training have become an important part of successful therapy for CRPS patients.
Psychological therapy
Although there is evidence of a psychological component of CRPS, only one study has addressed the efficacy of psychological treatment for patients with the condition. A prospective, randomized, single-blind trial of cognitive–behavioral therapy was conducted, together with physical therapy of different intensities, in children and adults and demonstrated a long-lasting reduction of all symptoms in both arms [67]. Fear of injury or re-injury by moving the affected limb is thought to be a possible predictor of chronic disability. In a small group of patients, graded exposure therapy was found to successfully reduce pain-related fear, pain intensity, and consecutively disability [68].

Therapy guidelines
Treatment for CRPS should be immediate and, importantly, directed toward restoration of full function of the extremity (see treatment algorithm, Fig. 3). This objective is best attained in a comprehensive, interdisciplinary setting with particular emphasis on pain management and functional restoration [69]. Pain specialists should include neurologists, anesthesiologists, orthopedic surgeons, physiotherapists, psychologists, and general practitioners.

The severity of the disease determines the therapeutic regimen. The reduction of pain is the precondition with which all interventions have to comply, meaning that no therapeutic approach for CRPS may be painful. In the acute stage of CRPS, when the patient still suffers from severe pain at rest and during movement, it is usually impossible to carry out intensive active therapy. Painful interventions, particularly aggressive physical therapy, at this stage often lead to deterioration. Therefore, immobilization and careful contralateral physical therapy should be the acute treatment of choice, and intense pain treatment should be initiated immediately.

The first-line analgesics and co-analgesics for CRPS are opioids, tricyclic antidepressants, gabapentin, and carbamazepine. In addition, corticosteroids should be considered if inflammatory signs and symptoms are predominant. Sympatholytic procedures, preferably sympathetic ganglion blocks, should identify the component of the pain that is maintained by the sympathetic nervous system.

To achieve the best outcome, a series of treatments should be initiated. Calcium-regulating agents should be used in cases of refractory pain. If resting pain subsides, first passive physical therapy, and subsequently active isometric used in cases of refractory pain. If resting pain subsides, first active isotonic training should be performed in passive physical therapy, and subsequently active isometric training. If inflammatory signs and symptoms are predominant. Mazepine. In addition, corticosteroids should be considered initiated immediately.

Calcium-regulating agents should be prescribed if inflammatory signs and symptoms are predominant. Pain specialists should include neurologists, anesthesiologists, orthopedic surgeons, physiotherapists, psychologists, and general practitioners.

To achieve the best outcome, a series of treatments should be initiated. Calcium-regulating agents should be used in cases of refractory pain. If resting pain subsides, first passive physical therapy, and subsequently active isometric training should be performed in combination with sensory desensitization programs until restitution of complete motor function. Psychological treatment must flank the regimen to strengthen coping strategies and discover contributing factors. In refractory cases, spinal cord stimulation and epidural clonidine could be considered. If refractory dystonia develops, intrathecal baclofen application is worth considering. Regarding the pharmacological treatment we advise the reader to check for indication and approval himself, since these items vary between countries.

Conclusion
CRPS are clinically characterized by pain, abnormal regulation of blood flow and sweating, edema of skin and subcutaneous tissues, active and passive movement disorders and trophic changes of skin. The diagnosis can be made by taking the medical history and a careful neurological examination in consideration of the diagnostic criteria for CRPS. Further diagnostic tests like bone scintigraphy and quantitative sensory testing can be helpful, but are not obligatory. The therapy of CRPS should be multidisciplinary and should include pharmacological treatment as well as physical, occupational, and psychological therapy.

Disclosures
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References
Figure 3. Treatment algorithm for complex regional pain syndromes.

**Psychological pathway**
- Pain coping skills
- Biofeedback, relaxation training
- Cognitive–behavioral therapy

**Rehabilitation pathway**
- Physiotherapy
- Occupational therapy
- Interventional pain management (sympathetic blocks)

**Severity of CRPS**
- **Severe**
  - Intense pain at rest and during movements
  - Intense pain management
  - Immobilization
  - Contralateral physiotherapy
  - If SMP-sympathetic blocks
- **Moderate**
  - No pain at rest, but pain during movements
  - Pain management
  - Physiotherapy and occupational therapy up to pain threshold
- **Mild**
  - No pain at rest and no pain during movements
  - Intense physiotherapy and occupational therapy

**Diagnosis CRPS**
- Start treatment as early as possible

**SMP?**

**Relapse**
- Repeat pathway

**Neurostimulation (e.g., spinal cord stimulation)**
- Epidural clonidine

CPRS: complex regional pain syndrome; SMP: sympathetically maintained pain. Modified with permission from [70].


Oral Transmucosal Fentanyl Citrate for Cancer Breakthrough Pain: A Case Report

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Medical Director, St Clare Hospice, Hastingwood, Essex UK

This report gives an account of the experience of a patient with esophageal cancer who was initially taking morphine to prevent breakthrough pain (BTP). The patient found that morphine was not satisfactory for treating BTP episodes and so was placed onto a regimen of oral transmucosal fentanyl citrate. This case study demonstrates the potential of oral transmucosal fentanyl citrate for the management of BTP. Adv Pain Manage 2007;1(3):105–7.

The term “breakthrough pain” (BTP) has been used to describe a phenomenon whereby pain intensity suddenly increases to break through the background pain that is otherwise controlled by a fixed schedule “around-the-clock” (ATC) opioid regimen [1]. BTP in patients with cancer is common, with prevalence rates among those with advanced disease reported as ranging from 23% to 90% [2]. A typical BTP episode is characterized by a fast onset, is often very severe, usually reaches a peak intensity within a few minutes, and can last an average duration of approximately 30 min [3–5]. Two types of BTP exist: incident pain, which can be precipitated by predictable volitional factors such as movement or unpredictable non-volitional factors such as bladder spasm; and spontaneous pain, which occurs in the absence of a specific trigger and can be unpredictable and occur at random.

The management of BTP aims to reduce the frequency and severity of the pain and the basic principles are:

- General assessment.
- Lifestyle changes.
- A modification of the pathological processes.
- Management of the reversible causes.
- Pharmacological and non-pharmacological symptomatic management of BTP.

The pharmacological symptomatic management of BTP often involves the use of supplemental doses of medication that are known as “rescue medication”. The ideal rescue medication should be efficacious, have a rapid onset of action, a relatively short duration of effect, and minimal adverse effects. Normal-release, also known as immediate release, opioids are the mainstay approach for patients who are receiving an oral or transdermal ATC opioid regimen, but the onset and duration of action of most oral opioids may not be suitable for treating many BTP episodes [6], as illustrated in the following case study.

Case Study
A 65-year-old man with esophageal cancer was referred to a palliative outpatient service for pain control. At assessment he was taking modified-release morphine 200 mg twice daily for background pain and 60–90 mg normal-release morphine for BTP; although background pain was well controlled, some episodes of BTP were not. On further questioning he was able to identify two separate BTPs: one was predictable and associated with eating, whilst the other was unpredictable and spontaneous. Both were retrosternal dull pains associated with his primary cancer. Each pain had slightly different characteristics (Table 1).

When taking normal- or immediate-release morphine the patient reported that the rescue medication took approximately 25 min to have an effect. Although this was acceptable for predictable pains (as he took rescue medication 30 min before meals) it was unsatisfactory for spontaneous BTPs. He tried varying the dose of morphine between 60 and 90 mg, but this had no significant benefit and instead he developed troublesome adverse effects, indicating that the lack of effect was not due to inadequate dose titration, but possibly due to the rate of onset of morphine-induced analgesia.

The patient agreed to switch to oral transmucosal fentanyl citrate (OTFC) and he was commenced on 200 μg when required and instructed that if this was not effective to increase the dose in accordance with a predetermined titration schedule (Fig. 1). Over the next 2 days he found that OTFC 600 μg improved his spontaneous BTP episodes within 10–15 min, which he considered a significant improvement.
compared with his previous rescue medication. He decided to use normal-release morphine for incident pain and OTFC for spontaneous pain as he felt this gave him better control. After 2 weeks the dose of OTFC required further titration to 1200 μg, and he remained on this combination for a further 5 months until his condition deteriorated and he was no longer able to use oral medication.

**Discussion**

BTP is a heterogeneous phenomenon; experience of it is different for each individual and, as illustrated by this particular subject, can additionally vary within an individual. Despite the self-limiting nature of BTP, its impact can be significant and can cause effects such as reduced functional ability, low mood, negative impact on social relations, reduced enjoyment of life, poor sleep patterns, and can influence their ability to work [8]. Therefore, a comprehensive assessment is imperative. There are currently no validated tools to assess BTP, although most studies have characterized it according to location, severity, temporal characteristics, relationship to regular analgesia, precipitating factors, predictability, pathophysiology, etiology, and palliative factors [8]. Applying these characteristics to the patient revealed two separate episodes of BTP, each requiring its own management plan.

The patient was prescribed normal-release morphine as rescue medication. However, commonly used oral opioids can take approximately 30 min to produce an analgesic effect, which is too slow for many BTP episodes [6,9], and which this patient found unsatisfactory for his spontaneous BTP. The dose of rescue medication is often 10–15% of the patient’s around the clock analgesia; the practice of using a fixed dose is based largely on anecdotal observations and given that BTP may vary in etiology, intensity, and duration, it is possible that the effective doses of rescue medication may vary in addition, although in this particular case, changing the dose did not make a significant difference to the onset of analgesia.

Rescue medication is sometimes given prophylactically for predictable pain, although adverse effects may become problematic due to the effects of the medication that persist long after the pain has resolved. There is some evidence to suggest that methadone has a faster onset of action [10]; however, its use is complicated by complex pharmacokinetics and pharmacodynamics. Recently, new formulations that deliver a lipophilic opioid, fentanyl, directly through mucous membranes have been developed in an effort to provide a more rapid onset of analgesic effect.

OTFC is a fentanyl-impregnated lozenge applied to and absorbed across the buccal mucosa. The lozenge can provide pain relief within minutes and is indicated in cancer-related BTP in patients using ATC opioids for background pain. Peak effects occur within 20–30 min after administration, approximately one-quarter of the total dose is rapidly absorbed from the buccal mucosa and becomes immediately available, and the approximate one-third that remains becomes systemically available, giving a total bioavailability of 50%. A number of trials have confirmed the efficacy, safety, and tolerability of OTFC, including two randomized controlled studies and a long-term follow-up study [11–14].

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**Table 1. Characteristics of incident and spontaneous esophageal pain.**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Incident</th>
<th>Spontaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily frequency</td>
<td>3 (1–4)</td>
<td>5 (3–8)</td>
</tr>
<tr>
<td>Precipitant</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Predictability</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden</td>
<td>Gradual</td>
</tr>
<tr>
<td>Time to peak intensity (min)</td>
<td>5–15</td>
<td>10–15</td>
</tr>
<tr>
<td>Intensity (NRS)</td>
<td>5–7</td>
<td>5–9</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>30–40</td>
<td>30–60</td>
</tr>
</tbody>
</table>

NRS: numeric rating scale; pO₂: partial pressure of oxygen.
The results of clinical trials suggest that the successful rescue dose cannot be predicted from the ATC opioid dose, therefore, it is recommended that each patient be titrated to a successful dose that produces adequate analgesia and minimal adverse effects.

Successful management of BTP not only requires a comprehensive assessment, good communication, and education, but depends on efforts to encourage patients and caregivers to participate in the treatment plan; indeed, patients may sometimes choose not to use their rescue medication [15]. The individual in this case study found OTFC easy to use, the titration schedule simple, and so he soon found a successful dose. Interestingly, he chose to continue with both opioid preparations as rescue medication. He felt the choice of the two opioids gave him more control of his pain, and at a time when patients with progressing disease feel they are losing control, it is important, where possible, to restore the aspect of patient control.

Some patients may report difficulty using OTFC either because of untreatable xerostomia or poor coordination or dexterity and an alternative option may be required. Recently, the efficacy of a fentanyl buccal tablet, using an effervescent drug delivery system to enhance absorption, has been demonstrated in a placebo-controlled study of opioid-tolerant patients with cancer-related BTP [16]. As expected, the study demonstrated an onset of effect that was more rapid than that of oral therapy. The formulation has been licensed in the US and is currently being reviewed by the regulatory authorities in Europe. Other transmucosal sublingual, buccal, inhaled, and intranasal formulations, containing fentanyl, are in development.

Summary
The successful management of cancer pain depends on a comprehensive assessment that must take into account background pain and BTP. BTP is a heterogeneous phenomenon that is different for each patient, typically comes on quickly, lasts as long as 1 h, and feels much like background pain, except that it may be more severe. This case study illustrates that patients may experience multiple BTPs that can vary in frequency, intensity, rate of onset, duration, and predictability. Subsequent pharmacological management of pain may require a combination of preparations depending on the characteristics of the BTP.

Disclosure
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References
**NEUROPATHIC PAIN**

Multimodal approaches to the management of neuropathic pain: The role of topical analgesia

de Leon-Casasola OA.


Neuropathic pain results from various disorders and can be challenging to treat. This article discusses the role of topical analgesics in the treatment of neuropathic pain, and provides evidence, obtained from clinical trials, for the use of specific topicals in the treatment of neuropathic pain from various origins. Research findings suggest that α-adrenergic agonists, N-methyl-D-aspartic acid antagonists, local anesthetics, tricyclic antidepressants, and counterirritants can be successfully used in their topical formulations to treat patients with neuropathic pain.

Many topical agents are commonly used for the treatment of neuropathic pain. For example, amitriptyline and doxepin (from the class of tricyclic antidepressants), and amantadine, dextromethorphan, ketamine, and orphenadrine (all N-methyl-D-aspartic acid (NMDA) antagonists) have been used in an off-label manner to treat neuropathic pain despite data being either unavailable or from poor-quality and small-sample-size clinical trials.

The author of this article summarizes the clinical data that are available on the different classes of topical analgesics and evaluates evidence on their use in the treatment of neuropathic pain:

- **α-Adrenergic agonists**: transdermal clonidine and topical clonidine cream have been shown to be effective in patients with chronic pain and hyperalgesia due to diabetic neuropathy and orofacial pain. Patients receiving topical clonidine had better relief than patients receiving placebo in all described trials. However, the sample size in all trials was small, ranging from 12 to 17 subjects.

- **NMDA antagonists**: the author of this article points out that there is no published literature that would support the use of topical amantadine, dextromethorphan, or orphenadrine for the treatment of neuropathic pain. However, there are case reports and studies on healthy volunteers, suggesting that further study of ketamine gel or ointment is warranted. It has been proposed that topical ketamine targets peripheral opioid receptors as well as the sodium and potassium channels.

- **Local anesthetics**: efficacy of lidocaine in the transdermal patch formulation for treating neuropathic pain has been well documented in randomized, controlled trials. In addition, another therapy, eutectic mixture of local anesthetics (EMLA), has been studied for the treatment of neuropathic pain. In patients with post-herpetic neuralgia, repeated daily application of EMLA resulted in a significant reduction of pain.

- **Tricyclic antidepressants**: topical formulations of doxepin and amitriptyline have shown efficacy in various neuropathic pain states. Amitriptyline provides pain relief via multiple pharmacological mechanisms, including inhibition of norepinephrine and serotonin reuptake, blocking NMDA and α2-adrenergic receptors, and partially blocking sodium and potassium channels. Transdermal delivery of amitriptyline results in a significant dose-dependent analgesic effect.

- **Counterirritants**: some counterirritants, such as, capsaicin, have only shown limited success in patients with neuropathic pain. Topical formulations of capsaicin did not show efficacy in patients with human immunodeficiency virus related pain or in patients with distal polyneuropathy. However, capsaicin cream was found to be beneficial in patients with diabetic peripheral neuropathy, osteoarthritis, and post-herpetic neuralgia.

Further study of these agents will reveal their potential in neuropathic pain treatment.

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Histaminergic involvement in neuropathic pain produced by partial ligation of the sciatic nerve in rats

Huang L, Adachi N, Nagaro T et al.

Previous studies have shown that the histaminergic system is involved in somatic and visceral pain perception and that histamine receptors play an important role in acute pain. However, the role of the histaminergic system in neuropathic pain is yet to be clarified. The objective of this study was to determine the changes to histamine metabolism in an animal model of neuropathic pain. The results showed histaminergic activity to be significantly increased in the presence of neuropathic pain, and demonstrated that histaminergic receptors play a role in this condition.

In the human body, histaminergic neural fibers regulate the release of non-histaminergic neurotransmitters through histamine heteroreceptors located on non-histaminergic nerve endings. The histaminergic system is a part of the neuronal network that regulates various processes, including nociception. H2 histamine receptors mediate somatic and visceral pain perception, and stimulation of these receptors aggravates acute pain. H2 and H3 histamine receptors are also involved in nociception. H2 receptor antagonists and H3 receptor agonists have been shown to have an antinociceptive effect in the treatment of acute nociceptive pain; however, the role of the histaminergic system in neuropathic pain has not yet been clarified. Thus, the aim of the present study was to determine the changes in the histamine metabolism in neuropathic pain, and to determine the effects of various histaminergic ligands on neuropathic pain. The authors’ animal model experiments were done in male rats that had neuropathic pain induced by partial ligation of the sciatic nerve. The procedure had a controlled design – some animals received the real ligation and some received only sham surgery. Changes in the histamine metabolism were studied in the rat striatum, which contains a dense distribution of histamine receptors. Results showed that although the extracellular concentration of histamine did not differ between ligated animals (i.e. animals with neuropathic pain) and sham surgery-operated animals, the level of histaminergic activity was significantly higher in the former. In addition, blockade of H1 receptors in the rat brain significantly increased their pain threshold (i.e. produced an antinociceptive effect), suggesting that the activation of H2 receptors may enhance neuropathic pain. Local application of an H2 receptor antagonist increased the nociceptive threshold whereas systemic administration had the opposite effect.

This study has demonstrated that the histaminergic system is involved in neuropathic pain. However, the specific role of the H3 receptor and the mechanism underlying its function in the modulation of neuropathic pain needs to be clarified in future studies.

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Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain

Slatkin NE, Xie F, Messina J et al.

Short-acting opioids are currently the treatment of choice for breakthrough pain; however, many patients experiencing breakthrough pain do not receive adequate pain relief from this therapy. This study evaluated a new opioid formulation, the fentanyl buccal tablet (FBT), for the treatment of breakthrough pain in patients with chronic cancer pain who are tolerant to opioid treatment. The trial consisted of an open-label dose-titration phase and a double-blind treatment phase and the results showed that FBT had a rapid onset and sustained effect, and was efficacious and well tolerated.

In this double-blind, randomized, placebo-controlled study, the authors evaluated the use of the fentanyl buccal tablet (FBT) for the treatment of breakthrough pain in patients with chronic cancer-related pain who were opioid-tolerant. This study was carried out at 30 outpatient treatment centers across the US. An open-label dose-titration phase was performed in which patients were randomly assigned to one of 18 double-blind dose sequences that were used to treat 10 breakthrough pain episodes. Patients were expected to complete this phase in approximately 7 days. Patients rated their breakthrough pain episodes on an 11-point pain intensity (PI) scale just before taking the drug and at specific, clinically relevant time intervals after administration. PI differences (PIDs) were calculated and the primary efficacy variable was calculated as the sum of the PIDs over the first 60 min (SPID60). Secondary efficacy measures were also calculated and included PIDs and pain relief (PR) for a period of up to 2 h.

A total of 129 patients were enrolled into this study and, of these, 87 patients identified an effective FBT dose and were...
entered into the double-blind phase. Of the 87 patients, 75 completed the study and 78 were evaluable for efficacy.

The results demonstrated that SPID₆₀ for FBT was significantly more favorable than placebo (p<0.0001). The secondary efficacy measures of PIDs and PR showed a greater reduction in PI following FBT administration compared with placebo, even after 10 min. The difference in PID between FBT and placebo was maintained for 2 h. The adverse effects (AEs) reported were similar to those seen in patients on opioid treatment and included nausea, fatigue, and dizziness. During the study, 83 of 125 (66%) patients reported such AEs.

In conclusion, this study demonstrated FBT to be effective and well tolerated, with a rapid onset of action in opioid-tolerant patients with chronic cancer pain and breakthrough pain.

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Fentanyl buccal tablet for the relief of breakthrough pain in opioid-tolerant adult patients with chronic neuropathic pain: a multicenter, randomized, double-blind, placebo-controlled study
Simpson DM, Messina J, Xie F et al.

SODIUM CHANNEL BLOCKERS

Sodium channel blockade may contribute to the analgesic efficacy of antidepressants
Dick IE, Brochu RM, Purohit Y et al.

Opioid-tolerant men and women (aged 18–80 years) who experienced chronic persistent neuropathic pain for ≥3 months as well as incidents of breakthrough pain were included in this multicenter, randomized, double-blind, placebo-controlled study. In the open-label dose-titration phase, the authors randomly assigned patients to one of three prespecified double-blind treatment sequences consisting of nine tablets (six of the effective dose of fentanyl buccal tablet [FBT] and three of placebo) that were to be taken by the patient to treat nine consecutive breakthrough pain experiences. This part of the study lasted 21 days. Patients rated their perception of each breakthrough pain episode, as well as other outcomes, on an 11-point pain intensity (PI) scale just prior to administration of the drug and then at specific time intervals after the initiation of treatment. Primary (calculated using the sum of the PI differences [PIDs] over the first 60 min [SPID₆₀]) and secondary efficacy measures were analyzed and a safety and tolerability profile was compiled based on the adverse events reported by the patient or recorded by the study’s investigators.

In the evaluated patients, 80 of 102 patients (78%) received an effective dose of FBT in the open-label dose-titration phase and 79 of these progressed to the double-blind phase. Of these 79 patients, 77 (97%) completed the study and 75 (95%) were evaluable for efficacy. Results showed that SPID₆₀ was significantly greater when FBT was used to treat breakthrough pain, compared with placebo. In addition, FBT was found to have a greater efficacy than placebo, producing a greater reduction in PID 10 min after administration, which was sustained throughout the 2-h observation period. Moreover, subjects were almost four times less likely to use opioid supplementation when taking FBT compared with placebo. Adverse events were reported in 64 of 102 (63%) patients, the most common being nausea, dizziness, somnolence, and vomiting. These events were reported more frequently during the dose-titration phase than in the double-blind phase.

Overall, in the opioid-tolerant patient population in whom a more effective FBT dose was identified, FBT was shown to have a rapid-onset of analgesia and was effective and well tolerated in the management of breakthrough pain.

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Tricyclic antidepressants have shown efficacy in the treatment of neuropathic pain whereas the newer generation of antidepressants, the selective serotonin reuptake inhibitors (SSRIs); (fluoxetine and zimelidine), have not shown to be effective in the treatment of neuropathic pain.

Tricyclic antidepressants interact with several molecular targets in order to relieve neuropathic pain, but this may not be linked to a single molecular mechanism. Previous trials with various agents showed that drugs with efficacy against neuropathic pain often acted as sodium channel blockers. Thus, sodium channel blockade may be one of the putative mechanisms underlying the antihyperalgesic efficacy of tricyclic antidepressants.

In this study, the authors compared the potency of nine antidepressants, which include the tricyclic antidepressants as well as SSRIs, to block the sodium voltage-gated channel Na1.7 subtype, which is preferentially expressed in nociceptive neurons. The following antidepressants were used in the study: amitriptyline, desipramine, fluoxetine, imipramine, maprotiline, mianserin, nortriptyline, paroxetine, and zimelidine. The authors used a protocol designed to approximate the affinity of the drug for the inactivated state of the Na1.7 channel. The study design allowed the authors to make direct comparisons between different antidepressants and other sodium channel blockers.

Sodium currents were examined using a whole-cell voltage clamp on primary sensory neurons that had been isolated from mice dorsal root ganglia, and the steady-state affinities of agents in the resting and inactivated state of the Na1.7 channel were calculated. The authors of the study found that the tricyclic antidepressants that are efficacious in the treatment of post-herpetic neuralgia or diabetic neuropathy exhibit affinities for the inactivated state of the Na1.7 channel within the range of therapeutic plasma concentrations. In contrast to tricyclic antidepressants, the SSRIs fluoxetine, mianserin, paroxetine, and zimelidine had affinities outside their therapeutic ranges. Of note, SSRIs are generally considered ineffective for treating neuropathic pain. The results of this study indicate that there is a correlation between the Na1.7-blocking potency of antidepressants and their efficacy in the treatment of neuropathic pain.

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**Relationship between the firing frequency of injured peripheral neurons and inhibition of firing by sodium channel blockers**

Ritter AM, Ritchie C, Martin WJ.

Using two rat models of nerve injury, L5 spinal nerve section and sciatic nerve section, the authors studied the effect of two intravenously administered sodium channel blockers, lamotrigine and lidocaine, on spontaneous activity in primary afferent neurons. As many sodium channel blockers exhibit a use-dependent block of sodium current, the authors hypothesized that lidocaine and lamotrigine would more readily inhibit neurons that fire at higher frequencies. The results showed that within each model, higher frequency of firing did not translate to a more effective block. This finding indicates that the efficacy of sodium channel blockers depends on the nature of the injury and the pattern of resulting neuronal activity rather than the frequency of firing.

The authors of this study examined the ability of lidocaine and lamotrigine, two potent sodium channel blockers, to inhibit spontaneous activity in two rodent models of nerve injury. The two models, spinal L5 nerve section and sciatic nerve section, differ in the proximity of the lesion to the cell body, the location of where the spontaneous neuronal activity originates, and the pattern of firing. Tonic firing, which is thought to originate in the cell body, predominates in the L5 section, whereas high-frequency bursting, which is highly likely to originate in the neuroma, is observed in the sciatic nerve section. Based on findings of previous studies, the authors predicted that lidocaine and other sodium channel blockers that act as frequency-dependent sodium channel blockers would more effectively block neurons at high frequencies. To test the hypothesis, the spinal L5 nerve section or sciatic nerve section was performed in 42 male adult rats, and electrophysiological extracellular recordings were taken from 18 and 37 neurons in the spinal nerve section and sciatic nerve section model, respectively. The results revealed that inhibiting the firing that was induced by intravenous application of sodium channel blockers (lamotrigine or lidocaine) was longer lasting in the sciatic nerve section model. However, within each model, a higher frequency of firing did not result in a more effective block. The authors additionally found a strong negative correlation between frequency and inhibition in the spinal L5 nerve section model. In the sciatic nerve section model, only neurons firing in rhythmic bursts were inhibited. This finding indicates that the efficacy of sodium channel blockers depends on the nature of the injury and the pattern of resulting neuronal activity, rather than on the frequency of firing. This study contributed to a better understanding of the conditions under which sodium channel blockers are effective in animal models of nerve injury, and these findings may translate to a better understanding of the circumstances that sodium channel blockers canBlockers. **ADVANCES IN PAIN MANAGEMENT Vol 1 No 3 2007**
Blockers can be therapeutically useful in patients with neuropathic pain.

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**NOVEL THERAPIES**

GW406381, a novel COX-2 inhibitor, attenuates spontaneous ectopic discharge in sural nerves of rats following chronic constriction injury


Although cyclooxygenase-2 (COX-2) inhibitors are generally ineffective for the treatment of allodynia- and hyperalgesia-associated neuropathic pain, GW406381, a novel COX-2 inhibitor, has been shown to reduce allodynia, hyperalgesia, and the generation of spontaneous neural activity in a rat model of neuropathic pain induced by chronic constriction of sural nerves. Results of this study indicate that COX-2 may play an important role in neuropathic pain, but that only some COX-2 inhibitors are effective in reverting the symptoms associated with neuropathic pain.

The purpose of this study was to determine the effect of oral GW406381, a novel cyclooxygenase-2 (COX-2) inhibitor, on mechanical allodynia, hyperalgesia, and the generation of spontaneous ectopic discharge in the sural nerve of rats with chronic constriction injury. The effect of GW406381 was compared with that of rofecoxib, a well-known COX-2 inhibitor.

The results showed that GW406381, but not rofecoxib, significantly reversed the decrease in paw withdrawal thresholds as assessed using von Frey filaments and the paw pressure test in adult male rats with constriction injury induced by ligation of the sciatic nerve. Furthermore, in GW406381-treated rats, the proportion of sural nerve fibers exhibiting spontaneous activity was significantly lower than in the rofecoxib- or vehicle-treated rats. Findings from this study suggest that COX-2 may play a significant role in the maintenance of neuropathic pain following nerve injury, but that only certain COX-2 inhibitors are effective in this paradigm. These findings can contribute to a better understanding of the mechanisms underlying the development and maintenance of neuropathic pain. In clinical settings, mechanical and thermal alldynia, hyperalgnesia, and spontaneous ongoing pain are typical symptoms of neuropathic pain, and are very often resistant to available treatment. The fact that oral GW406381 can reverse the symptoms associated with neuropathic pain following nerve injury is a promising finding that deserves further investigation in future studies.

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Does thalidomide have an analgesic effect? Current status and future directions


This article reviews the role of the neuromodulator thalidomide in the treatment of neuropathic pain. The author describes neuroimmune modulation in the context of neuropathic pain, and explains how insights into neuroimmune modulation may help researchers to better understand the mechanisms of persistent pain. This article describes the evidence from both animal and human studies for the analgesic effect of thalidomide. However, despite its analgesic efficacy, the use of thalidomide is substantially limited by its neurotoxic and teratogenic effects. A new analogue of thalidomide, lenalidomide, may represent a safer variant of the immunomodulator for the treatment of persistent pain.

It has been shown that some patients with intractable pain who were resistant to conventional therapy experienced substantial pain relief when treated with immuno modulators such as thalidomide. Findings from animal studies suggest that the analgesic effect of thalidomide involves inhibition of tumor necrosis factor-α which, together with interleukin-1β initiates neuropathic pain. Evidence for the analgesic effect in humans is mainly based on case reports, case-report series, and abstracts. Available results suggest that thalidomide can be effective in the treatment of complex regional pain syndrome (CRPS). In reviewed case reports, the dose of thalidomide varied from 50 to 300 mg/day. Thalidomide therapy resulted in substantial pain relief in some CRPS patients, but it did not work for others. Although the drug was poorly tolerated by many patients, those who responded experienced a substantial relief of CRPS symptoms. It is important to note that the patients selected in reviewed studies were mostly treatment resistant had severe symptoms, and responded poorly to conventional therapy. In addition, there is limited evidence for the beneficial effects of thalidomide in polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes syndrome, also known as POEMS, and for the treatment of radiculopathy and headaches.
However, despite its analgesic efficacy, the use of thalidomide is substantially limited by its neurotoxic and teratogenic effects. This fact initiated efforts to synthesize compounds that are structurally and pharmacologically related to thalidomide, in the hope that they would be less teratogenic. A new structural and functional analogue of thalidomide, lenalidomide, is representative of a second generation of immunomodulatory drugs. The relevant analgesic mechanisms of action include inhibition of proinflammatory cytokine secretion and an increased level of anti-inflammatory cytokine secretion from peripheral blood mononuclear cells, inhibition of the expression of cyclooxygenase inhibitor-2 (COX-2) but not COX-1, and inhibition of cell proliferation in some cell lines. In a multicenter study of CRPS patients, lenalidomide provided significant pain relief. These findings indicate that lenalidomide, a functional analogue of thalidomide, may provide a safe and meaningful therapy for CRPS.

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MISCELLANEOUS

Natural history of pain following herpes zoster

This longitudinal, naturalistic study assessed the pathway of pain in a sample of 94 patients diagnosed with herpes zoster who were considered to be at high risk for developing post-herpetic neuralgia (PHN). At 6 months following the onset of rash, a total of 30 patients met the study criteria for PHN and two had clinically meaningful pain intensity.

Based on findings that show older age and higher initial pain intensity as significant risk factors for post-herpetic neuralgia (PHN), this current study evaluated the course of pain following herpes zoster (HZ) onset in patients at high risk for developing PHN. Patients aged ≥50 with severe pain intensity after rash onset were those at high risk for developing PHN.

To qualify for the study, patients had to have experienced severe average daily pain that was ≥20/100 on the visual analogue scale for the past 48 h. Oral analgesic use was permitted. Using a definition of PHN from prior studies [1], if pain was present for the past 48 h at 6 months after rash onset then:

- Patients with daily pain ≥0/100 met criteria for PHN.
- Patients with daily pain ≥3/100 met criteria for “clinically meaningful” PHN.

At 6-month follow-up, the main study outcomes (pain, impact of pain, coping, and life stress) showed that:

- 30 patients (32%) met criteria for PHN.
- Two patients met criteria for clinically meaningful PHN.
- The impact of pain, coping, and life stress levels were not significantly or clinically different between groups.

Assessments at 2–6 weeks (visit 1), 6–8 weeks (visit 2), 3 months (visit 3), and 6 months (visit 4) after rash onset showed that the rate of pain attenuation was similar in both the PHN and non-pain groups.

This study had multiple strengths, for example, the use of empirically based diagnostic criteria for PHN, a longitudinal design to identify the trajectory of pain, and sampled a selection of patients, which included those who were vulnerable to developing PHN. The study could have benefited from further elaboration into the rationale for the timing of assessments (e.g. were timings based on PHN course?). To qualify, patients had to have severe pain (e.g. >20/100); however, it is unclear whether this cut-off was high enough to capture patients either at “high-risk” for developing PHN or those at clinically meaningful PHN. The proportion of patients with low, moderate, and severe pain at each time point requires more discussion. Follow-up studies should explore whether patients with moderate to severe pain intensity at study entry are more likely to develop clinically meaningful pain compared with patients with low pain intensity. Future investigations with sufficient variability in pain intensity or other risk factors for PHN may be needed to compare subgroups of patients at high, medium, and low risk for developing clinically meaningful PHN.

Given the low levels of pain observed at 6-month follow-up, it is unclear how representative the final sample is of the overall PHN population. The use of a non-random sample in this study may limit the potential of the findings to be applied to the general population. Of 1003 HZ patients screened for the study, 94 patients completed all four visits. It is possible that the inclusion criteria for the study were too narrow, the feasibility of the methods was too limited, or the rates of significant pain following HZ were simply low.


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CLINICAL REVIEWS

Pathogenesis, diagnosis, and treatment of lumbar zygapophysial (facet) joint pain
Cohen SP, Raja SN.

This current review describes the etiology, assessment, and treatment of lumbar zygapophysial (LZ) joint pain. Common sources of LZ pain include aging-related changes in the caudal facet joints, comorbid osteoarthritis, and degenerative disc disease. Common ways to diagnose LZ pain is with local anesthetic (LA) blocks of the posterior spinal nerve rami and intra-articular injections. Following first-line pharmacotherapy and physical therapy, second-line therapies include intra-articular steroid injections and radiofrequency denervation. Surgical modalities, in particular arthrodesis, lack efficacy in this setting.

Lumbar zygapophysial (LZ) joint pain and facet injections for the treatment of LZ pain are common in the US, but there are mixed results regarding appropriate assessment and intervention methods. The current article reviews LZ pain in the literature, as well as the anatomical correlates, pathogenesis, epidemiology, diagnosis, and treatment. LZ joints (for example, facet joints [FJs]) are a major cause of low back pain (LBP). LZ pain was first documented a century ago, and the term “facet syndrome” emerged in the literature in 1933. While a seminal report by Mixter and Barr [1] postulated that lumbar disc rupture was the cause of LBP, not LZ joints, Shealy [2,3] showed that fluoroscopically guided radiofrequency facet denervation alleviated LZ-induced back pain. According to the authors of this study “lumbar FJs form the posterolateral articulations connecting the vertebral arch of one vertebra to the arch of the adjacent vertebra…dual innervation from medial branches arising from posterior rami at the same level and one level above the z-joint” are received. Each joint contains a fibrous capsule with sympathetic efferent fibers. Inflammatory cytokines are present in FJ cartilage and synovial tissue. The cause of LZ pain is mainly due to injury or wear through a lifetime of repetitive use. Risk factors for LZ pain include spondyloolisthesis, degenerative disc disease (DDD), and age. DDD followed by the development of comorbid osteoarthritis is known to cause LZ pain. Rates of LZ range between 5% and 90% depending on the diagnostic modalities, criteria used and the age of the population. Problems with the data from published studies arises because many studies exclude patients with neurological signs or symptoms due to disc herniation and those with failed back syndromes. A systematic review of the data suggests that the lumbar FJs cause persistent LBP in up to 15% of patients. Two examples of widely used diagnostic techniques for the treatment of LZ pain are low-volume intra-articular or medial branch blocks. However false-positive rates are high due to placebo responses, the use of sedation and LA, and the effects related to injectate dispersion.

The evidence gives mixed results for the treatment for LZ pain, with evidence for, and against, intra-articular steroid injections and radiofrequency denervation of medular branches innervating the FJs.


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Increased plasma substance P and CGRP levels, and high ACE activity in migraineurs during headache-free period
Fusayasu E, Kowa H, Takeshima T et al.

The purpose of the study was to examine the mechanisms underlying migraine headache. The authors determined the plasma levels of three chemical substances that may play a role in migraine – substance P (SP), calcitonin gene-related peptide (CGRP), and angiotensin converting enzyme (ACE) – in migraineurs with aura and without aura during a non-headache period, and compared these with levels in healthy control subjects. The results showed elevated levels of SP and CGRP, and an increase in ACE activity in both groups of patients compared with control subjects. These results indicate a significant role of all three substances in the trigeminovascular nociceptive mechanisms associated with migraine.

The mechanisms underlying migraine headaches have not yet been fully determined. However, numerous research findings support the hypothesis that unknown triggers can activate perivascular trigeminal axons; these release vasoactive neuropeptides (e.g. substance P [SP], calcitonin gene-related peptide [CGRP], or neurokinin A) that could cause neurogenic inflammation, which may spread to adjacent tissue. Consequently, these activated trigeminovascular fibers that transmit nociceptive information to the nucleus caudalis and higher brain centers. Results from recent studies indicate that CGRP, SP, and angiotensin converting enzyme (ACE) may play a role in these nociceptive processes that are associated with the development of migraine.
The aim of the study was to compare levels of SP, CGRP, and ACE activity in migraine patients, during a migraine-free period, with those in healthy control subjects. One-time blood samples taken from cubital veins were obtained from 41 migraineurs with aura (MA), 54 migraineurs without aura (MO) and 52 healthy control subjects, and the levels of SP and CGRP, as well as ACE activity were determined. The authors found significantly elevated levels of SP and CGRP in both groups of migraine patients, compared with control subjects. Furthermore, the activity level of ACE was significantly increased in migraineurs. The highest level of ACE activity was seen in the MA group, and although ACE was lower in the MO group, it was still significantly higher than in the control subjects. The data suggest that SP, CGRP, and ACE are compounds associated with the pathophysiological mechanisms of migraine, and that elevation of the levels of SP, CGRP, and ACE activity is not related to the presence of acute pain associated with migraine because increased plasma levels of these compounds were found in migraineurs during a migraine-free period.

However, these findings have some limitations: the data were obtained from a one-time measurement of plasma concentrations, which may not accurately reflect the true status; and the authors did not determine the origin of SP, CGRP, and ACE in the blood samples. The studied substances may not necessarily originate from the central nervous system, and thus their links to the mechanisms of migraine are questionable.

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The relationship between cytokines and pain/depression


This review article describes the critical role of proinflammatory cytokines (PICs) in modulating pain and depression via peripheral and central immune activation. Mediated by the immune system, PICs activate glial cells that trigger a “sickness response”, which can lead to pain and depression. New and innovative interventions for neuropathic pain and depression may aim to reduce PIC cellular activity. Examples of such treatment options include etanercept, infliximab, propentofylline, nonsteroidal anti-inflammatory drugs, and selective serotonin re-uptake inhibitors, as well as other agents.

Proinflammatory cytokines (PICs) are proteins released by the immune system during the acute phases of a host organism’s responses to infection, inflammation, and foreign agents. PICs include three molecules: tumor necrosis factor-α, interleukin-1 (IL-1), and IL-6, all of which trigger an organism’s “sickness response”. Sickness responses involve a cluster of responses including adaptive and pathological, which comprises physiological, behavioral, and hormonal responses. Sickness responses (for example, those that happen during the flu) serve to enhance survival. They involve fever, conservation of energy and activity, amplified pain, melancholy, anhedonia, and lethargy. Sickness responses are central to understanding relationships among PICs, pain, and depression. PICs are associated with the onset, maintenance, and recurrence of depression in both healthy and medically ill populations, possibly via PIC-induced increases in serotonin uptake and deficits in serotonin systems and can influence indications such as depression, wasting, and fatigue due to a modified monoamine availability and other endocrine processes [1]. Of note, antidepressants administered prophylactically may protect patients receiving interferon-α therapies from developing depression. Allosthenia and hyperalgesia commonly occur during sickness responses. Patients with inflammatory and non-inflammatory neuropathies have been shown to have elevated levels of cytokines, a result of enhanced PIC receptor expression in peripheral sensory nerve fibers, spinal root nerves, and dorsal root ganglia. As a result, certain PIC antagonists appear to have analgesic properties. PICs that may prevent and attenuate neuropathic pain include propentofylline, fish oil, melatonin, and gene therapies. Examples of PIC-related treatments for depression include etanercept, infliximab, IL-6 antibodies, fish oil, physical activity, and selective serotonin reuptake inhibitors.

Overall, this review provides compelling conceptual and empirical evidence for PIC-induced links between chronic pain and depression. Mediated by immune responses, PICs trigger “sickness responses” leading to pain and depression. Whereas sickness responses appear to be adaptive in the acute injury phase, central and peripheral activation may persist in a maladaptive feedback loop, ultimately leading to chronic pain, depression, and disability. Central nervous system PICs are activated by glial cells while peripheral PICs appear to trigger glial cells following an immune stimulus — a process that suggests bidirectional central and peripheral relationships. Additional naturalistic and longitudinal studies on the connection between PICs, pain, and depression are needed.

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Clinical Reviews

Primary and secondary hyperalgesia can be differentiated by postnatal age and ERK activation in the spinal dorsal horn of the rat pup

The purpose of this study was to determine the changes in primary and secondary hyperalgesia that were induced by a chemical stimulation of C fibers at different postnatal ages. This was done using a quantitative model that took electromyography recordings from anesthetized rat pups at the age of 3, 10, and 21 postnatal days. Results showed that primary hyperalgesia could be induced at all postnatal ages, whereas secondary hyperalgesia was present at the age of 10 and 21, but not 3, postnatal days. The authors of this study showed that age-related differences in secondary hyperalgesia are linked to the activity of extracellular signal-regulated kinase. Findings from this study could contribute to a better understanding of age-related alterations in nociceptive processing.

A full understanding of the developmental changes occurring in primary and secondary hyperalgesia through the postnatal period is important for pain management in pediatric patients. The authors of this study used an electromyographic model in rats of different ages (3, 10, and 21 postnatal days old) to evaluate the developmental changes occurring in primary and secondary hyperalgesia. Hyperalgesia was induced by mustard oil or capsaicin, and was measured using electromyography flexion reflex recordings. Results from the experiment showed that while primary hyperalgesia was present at all ages, secondary hyperalgesia developed only at 10 and 21 postnatal days. It did not develop at the age of 3 postnatal days. Further analysis revealed that this finding is linked to differences in activation of extracellular signal-regulated kinase (ERK). The results showed that development of secondary hyperalgesia is dependent on phosphorylation of ERK in the spinal cord and that the magnitude and spatial distribution of phosphorylated ERK expression parallels the degree of secondary hyperalgesia. At the age of 3 postnatal days, ERK was present in the dorsal horn, but capsaicin produced minimal ERK activation. In contrast, at the age of 21 postnatal days, capsaicin induced the expression of phosphorylated ERK in the superficial dorsal horn through several lumbar segments, which was consistent with the spread of secondary hyperalgesia.

The findings obtained in this study are valuable for their potential clinical implications. The authors point out that laboratory studies of the reflex responses to nociceptive stimulation are important for investigating developmental changes in nociceptive processing, quantifying responses to injury, and establishing age-related changes in analgesic efficacy, which can all contribute to better pain management in neonates and infants.

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Activity-dependent slowing of conduction velocity in uninjured L4 C fibers increases after an L5 spinal nerve injury in the rat

Previous findings have revealed that alterations to the function of uninjured afferents may play an important role in the development of neuropathic pain following nerve injury. The purpose of this study was to determine whether the action potential conduction properties of unlesioned L4 C fibers are altered following injury to the adjacent L5 spinal nerve. Using the spinal nerve ligation (SNL) model in rats, the authors showed that after SNL of L5, but not after a sham surgery, activity-dependent slowing and supranormal conduction in uninjured L4 C fibers were significantly enhanced. This indicates that the excitability of uninjured afferents is altered following a nerve injury.

The mechanisms underlying neuropathic pain after nerve injury are not yet fully understood. However, it has been shown that after a nerve injury, unmyelinated nociceptive afferents in an uninjured nerve can develop spontaneous activity. Moreover, previous results have indicated that activity-dependent slowing of conduction (i.e. a decrease in conduction velocity after repetitive stimulation) may be altered following nerve injury. The purpose of this study was to determine whether the action potential conduction properties of unlesioned L4 C fibers are altered following injury to the adjacent L5 spinal nerve. The authors used a model based on spinal nerve ligation (SNL) developed by Kim and Chung [1] to perform blinded experimental procedures (real SNLs of the L5 spinal nerve versus sham surgery) in male rats and mice. The experiments were followed by electrophysiological recordings taken from C fibers in the uninjured L4 spinal nerve. Results revealed two distinctive populations of C fibers: a “nociceptor” population with a large activity-dependent slowing; and “non-nociceptor” C fibers with a smaller degree of activity-dependent slowing. Additional experiments in two animals revealed that when sympathectomy was performed 1 week before, SNL decreased the number of fibers in the non-nociceptive population. However, after SNL, activity-dependent slowing in both
populations of C fibers in the uninjured L4 nerve was enhanced (i.e. the conduction velocity significantly decreased) and the authors consequently assessed how quickly the conduction velocity recovered from slowing after the repetitive stimulation. The results showed no significant difference in recovery time in animals with SNL versus those receiving sham surgery (93 s vs. 112 s, respectively). When the SNL model is applied to mice instead of rats, results revealed similar changes in the activity-dependent slowing of C fibers.

This is the first study investigating the changes to the conductive properties that can be induced by nerve injury in activity-dependent uninjured C fibers. The findings can contribute to a better understanding of the role of injured and uninjured afferents in the development of neuropathic pain.


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Daily fatigue in women with osteoarthritis, rheumatoid arthritis, and fibromyalgia
Zautra AJ, Fasman R, Parish BP et al.

The authors of this prospective, longitudinal study investigated the psychosocial and physical correlates of fatigue experienced in women with chronic pain disorders. Results showed that fatigue levels differed between people and by pain diagnosis. Fibromyalgia patients reported the highest level of fatigue compared with rheumatoid arthritis and osteoarthritis patients. In all pain diagnoses, a lack of positive mood was a stronger predictor of fatigue severity than depression, pain intensity, sleep disturbance, or negative affect.

Fatigue is common in chronic pain, with approximately 40% of patients with osteoarthritis (OA) and rheumatoid arthritis (RA) and 74% of fibromyalgia patients (FMS) reporting fatigue. However, fatigue characteristics may vary among OA, RA, and FMS patients due to differences in pain etiology and interpersonal characteristics such as depression, insomnia, and disability. Across studies, negative affect (NA) for example distress, sadness, and anger has been demonstrated as a primary determinant of fatigue. However, the role of positive affect (PA) needs more investigation. The authors of this study evaluated the role of PA and NA, as well as other potential correlates of fatigue, in 255 women with physician-diagnosed OA, RA, and FMS.

Data was collected from patients’ paper diaries and laptop computers for a period of 30 days. At day 30, multilevel analyses showed that fatigue had significant within- and between-person differences:

- FMS patients reported a higher degree of overall and greater daily fluctuation in fatigue compared to OA and RA patients.
- The analysis of fatigue in FMS patients’ variability showed that within-person differences in daily fatigue showed significantly more variance in fatigue than between-person differences (70% vs. 30%, respectively).
- A lack of PA was the best overall predictor of daily fatigue. An interaction effect for type of pain diagnosis and PA showed that FMS patients reported the lowest PA.
- Analyses of fatigue correlates showed that daily increases in fatigue were significantly associated with decreases in PA beyond the contribution of other important variables such as pain, depression, sleep quality, and NA.

The determinants and moderators of fatigue require clarification. This study involved a fine-grained analysis of fatigue patterns and its correlates. FMS patients had the highest variability in daily fatigue levels while OA patients had the lowest. Intrapersonal differences characterized by deficits in PA were strongly associated with fatigue, particularly in FMS patients. The strengths of this study include the longitudinal design and measurement of fatigue correlates, the use of multilevel techniques to analyze variability in fatigue, and the strategies that were used for promoting adherence with patient diary completion. Although this quality study provides useful data, the daily “moment-to-moment” interaction of PA and fatigue was not assessed. This study may have benefited from multiple daily repeated assessments to order to clarify the temporal and causal relationships between PA and fatigue, as well as reciprocal relationships between these variables.

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Highlights from the 26th American Pain Society 2007

Washington, DC, USA, May 2–7, 2007

The 26th Annual Scientific Meeting of the American Pain Society was held at the Washington Convention Center, Washington, DC, USA from May 2–7 2007. A total of 1400 delegates representing a variety of disciplines from 29 different countries attended this year’s conference. The main themes focused on the diagnosis, treatment, and management of acute, chronic cancer, non-cancer, and recurrent pain. Some of the studies that are relevant to Advances in Pain Management are highlighted here.

Management of breakthrough pain

D Simpson et al. (Cephalon, Inc., Frazer, PA, USA) presented a meta-analysis of two randomized, placebo-controlled, double-blind studies of fentanyl buccal tablet (FBT). One of these studies was composed of opioid-tolerant patients with chronic neuropathic pain and the other was carried out in patients with chronic low back pain.

The current treatment of choice for chronic pain patients suffering from breakthrough pain (BTP) and patients with chronic non-cancer pain who experience episodic exacerbations of severe pain are the short-acting opioids. However, BTP intensity can peak before the onset of analgesia from short-acting opioids. Therefore, BTP treatments require a rapid onset of action and FBT has the potential to provide this.

The studies analyzed had identical trial designs: patients who identified an effective dose of FBT during the titration phase were entered into a second, double-blind, phase to treat nine episodes of BTP. Patients rated their BTP episodes on an 11-point pain intensity (PI) scale. The PI differences (PIDs) between each timepoint and pretreatment were calculated and the sum of all the PIDs in the first 60 min (SPID60) gave the primary efficacy measure. The SPID60 results significantly favored FBT compared with placebo (p<0.0001 for both studies) and FBT had a notable effect on PIDs compared with placebo after only 10 min, an effect that was sustained over 2 h.

In conclusion, this meta-analysis showed that FBT was effective for treating BTP in two populations of opioid-tolerant patients.

L Montague et al. (University of Michigan, Ann Arbor, MI, USA) conducted a comparative study in a racially diverse population of cancer patients that examined the racial differences in BTP characteristics and its impact on quality of life. Data was collated from subjects with breast, prostate, colorectal, or lung cancer (at stage III or IV) or multiple myeloma (stage II, III, or IV) who presented with BTP episodes. In this study, patients carried out an initial assessment and follow-up surveys at 3 and 6 months that analyzed the severity of consistent pain and BTP, the depressed affect and active coping ability, as well as the patients’ health-related quality of life.

A total of 96 individuals (75% white, 66% female, mean age=56.3±10.3 years) were analyzed and results measured on the Center for Epidemiological Studies Depression Scale showed that the subjects experienced psychological distress; however, there were no racial differences in depression prevalence. In addition, there were no significant differences between race for the duration, quality, or location of pain flares, but the non-white Americans (the minority patients) did tend to experience a greater number of pain flare types than white Americans. Although it was not significant (p=0.8), minority subjects tended to report poorer outcomes on measures of health-related quality of life. These results provide information that can be used in the future for health policy and clinical practice.

An analysis of three studies that looked into the efficacy and tolerability of FBT in treating patients with BTP was presented by D Taylor et al. (Cephalon, Inc., Frazer). FBT has recently been approved for the treatment of BTP in opioid-tolerant patients with chronic cancer pain and is additionally being investigated for use in patients with chronic non-cancer pain.

There were 548 patients enrolled on these three studies who filled in a medication preference questionnaire either 1 month after in an open-label study or upon completion of one of two randomized, double-blind studies. The patients were opioid-tolerant with chronic non-cancer pain and complained of between one and four BTP episodes per day as a result of pain conditions such as neuropathic pain, low back pain, headache, osteoarthritis, or traumatic injury. These patients were using fixed doses of opioids in order to manage persistent pain.
The results showed that most (89%) patients experiencing breakthrough and persistent pain preferred FBT to the supplemental opioid they were using before. Feedback from patients concluded that FBT had a more rapid onset of analgesia, was easier to administer, and more convenient to use compared with their previous opioid treatment.

**Opioid treatment and associated GI symptoms**

Chronic pain is commonly treated with opioid analgesics; however, this treatment can cause adverse gastrointestinal (GI) side effects, with constipation being one of the most commonly reported. The authors of this study reported on the results from the OPIOID (Opioid Patterns Indicating Opioid-Induced Bowel Dysfunction) survey, an online US survey carried out to describe patient-rated severity of constipation-associated GI symptoms in patients taking opioids for non-cancer-related chronic pain. Participants of this study, by S. Cook et al. (GSK, Research Triangle Park, NC, USA) were adults recruited from research panels and were representative of the US population. The subjects in this study used opioids ≥4 days/week for a minimum of 1 month.

A total of 723 patients reported that they experienced constipation incidents. Symptom severity was assessed using a five-point scale (0=absent, 4=very severe) by the two-item Patient Assessment of Constipation Symptom (PAC-SYM) questionnaire over a period of 2 weeks. Straining or squeezing to pass bowel movements was rated by the highest proportion of subjects as being of moderate or greater severity (77%, severity score=2–4).

The findings from the PAC-SYM questionnaire were used in the OPIOID survey to indicate that a large number of patients on opioid treatment experienced moderately severe, or worse, GI symptoms.

One side effect resulting from opioid treatment is opioid-induced bowel dysfunction (OBD). The PROBE (Patient Reports of Opioid-related Bothersome Effects) survey was a web-based cross-sectional survey that was carried out in 161 chronic pain subjects from all over the US to characterize the prevalence, frequency, and severity of OBD side effects and give an indication of how these symptoms affect quality of life (QoL) and activities of daily life (ADL). In addition, this study, presented by T. Bell et al. (GSK, Research Triangle Park) investigated whether these parameters were influenced by the duration and frequency of the opioid therapy.

Individuals in the study were asked to rate their GI side effects on a scale of 0–4 while on opioid treatment in addition to their QoL and ADL. The sample was split into sub-groups according to the frequency and duration of treatment. GI symptoms such as constipation (the most common side effect), bloating, decreased appetite, and reflux were experienced and had similar frequencies and severities in each opioid frequency/duration subgroup. Most individuals with constipation claimed there was a degree of negative impact on QoL and ADL.

These results suggest that many patients on opioid therapy experience GI adverse events, regardless of how often or the duration at which they administer opioid medication. GI side effects tend to persist with increasing duration of opioid intake, suggesting that patients do not develop tolerance to the adverse effects of opioids.

**Opioid therapy**

K. Simpson et al. (Seacroft Hospital, Leeds, UK) reviewed the case notes from >1500 patients with long-term pain. First of all, all cancer patients were omitted and the authors found that of those remaining more than one-third (n=517) were taking at least one opioid. Each subject’s social context, any physical disability due to persistent pain, and the effect of pain on employment were noted for the study. The authors analyzed the prescribed opioids, duration of therapy, adjuvant therapies, and any associations that were found to be related to stopping opioids.

It was found that 29% of patients were prescribed codeine, 16% took morphine, and 2% administered oxycodone. There were 10% of patients who used transdermal fentanyl or buprenorphine.

Results showed that 51% of patients who had their employment affected by pain experienced nociceptive pain and >44% of all subjects consulted a pain physician after 1–5 years. The results also showed that 64% of subjects used opioids for >12 months and 8% took them for <3 months. It was found that a proportion (30%) of individuals stopped administering opioids because of a lack of efficacy – only 8% of these patients administered opioids alone and >91% took their opioid therapy with another agent.

The successful treatment of chronic, non-cancer pain involves monitoring patients who are taking opioid treatments and subsequently identifying those who may show signs of opioid misuse. The principle of this study by R. Jamison et al. (Brigham and Women’s Hospital, Boston, MA, USA) was to create and validate a patient self-assessment measure. As a result, the Current Opioid Misuse Measure (COMM) was developed for use in chronic pain subjects who were on long-term opioid therapy.

The 40-item COMM underwent empirical evaluation with 227 patients who were taking opioids for non-cancer pain. The COMM was developed with the help and expertise of pain management and addiction specialists across the US.

Fifty-five individuals were recruited to test 1-week test–retest reliability of COMM. They were all evaluated...
using alpha COMM, the prescription drug-use questionnaire interview, and they had to submit a urine sample for toxicology screening purposes.

The 17-item COMM seemed to effectively measure opioid abuse, demonstrating good internal consistency and test-retest reliability. In order to assess the capability of COMM to pick up on changes to patient status, 86 subjects were followed and reassessed after 3 months. To cross validate COMM, 250 new recruits (all chronic pain patients) were assessed. Psychometric properties were found to be retained, indicating that COMM is a robust self-report measure that can be used to analyze opioid abuse.