SEARCH METHODOLOGY

The content of this feedback report refers only to the most relevant material located under each of the evidence headings and is drawn predominantly from author abstracts or research recommendations within guidelines. The question is posed in the context of the effectiveness of opioids analgesics in patients with hip and/or knee osteoarthritis. Further details of all the studies included in this report are shown in the appendix, sorted by report section and author name.

Criteria used (PICO):

Who? (population)
Patients with hip and/or knee osteoarthritis

What? (intervention/exposure/measure)
Opioid analgesics

Comparison
Placebo; No intervention

What is measured? What are the outcomes?
Pain; Function

Location and setting
Any

Exclusion Criteria
Non-English language guidelines, recommendations, systematic reviews, overviews and clinical opinions. However, non-English language primary research articles with English abstracts were included if relevant, see Section D: Primary Research.

Databases Searched
CINAHL; Cochrane Library; EMBASE; MEDLINE
Types of Study

RCTs specifically with an enriched enrolment, randomised withdrawal design.

Keywords searched

Search protocols were designed around the following terms: musculoskeletal pain, neuropathic pain and headache AND analgesics AND clinical trials AND enriched, withdrawal and discontinuation design (e.g. see Appendix 1 for MEDLINE protocol)

Date limits

None

Summary of available evidence

<table>
<thead>
<tr>
<th>EVIDENCE TYPE</th>
<th>INCLUDED IN FEEDBACK</th>
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<tbody>
<tr>
<td>A</td>
<td>Evidence Summaries</td>
</tr>
<tr>
<td>B</td>
<td>Systematic Reviews &amp; Meta-analyses</td>
</tr>
<tr>
<td>C</td>
<td>Clinical Trial Registries (Current and Closed)</td>
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<tr>
<td>D</td>
<td>Primary Research</td>
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<td>E</td>
<td>Overviews and expert opinions</td>
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<tr>
<td>F</td>
<td>Intellectual Property Office</td>
</tr>
</tbody>
</table>

RESULTS

A: Good Quality Evidence Summaries (including guidelines)

Not relevant to this report.

B: Systematic Reviews and Meta-analyses

See Appendix 2, Section B for details of reviews included in this section.

Five systematic reviews which specifically identified enriched enrolment, randomized withdrawal trials (EERW) were pertinent to this evidence review (see appendix 2.B.1). Each review had a different emphasis with regards pathology and/or analgesic:

- EERW trials of analgesics (Katz, 2009)
- EERW vs non-EERW trials of opioids for chronic non-cancer pain (Furlan, Chaparro, Irvin and Mailis-Gagnon, 2011)
- Buprenorphine versus fentanyl or morphine in patients with chronic moderate to severe pain. (Wolff, et al., 2012)
• Pregabalin and gabapentin in neuropathic pain (Straube, Derry, McQuay and Moore, 2008): the authors identified 7 RCTs which they considered had ‘partial enrichment’.
• Pregabalin for fibromyalgia (Straube, Derry, Moore and McQuay, 2010)

In addition, four systematic reviews were identified which may specifically identify clinical trials with an EERW design but require the methodology to be more closely scrutinized to clarify (see Appendix 2.2).

C: Clinical Trial Registries
Not relevant to this report.

D: Primary Research
See Appendix 2, Section D for details of studies included in this section.

D.1 RCTs with enriched enrolment, randomised withdrawal design

Fifty-seven RCTs utilising an enriched enrolment, randomised withdrawal design were identified concerning the treatment of chronic non-malignant pain conditions with analgesics (see appendix 2.D.1). These are listed alphabetically below by drug name:

• Intravenous adenosine in neuropathic pain (Lynch, Clark and Sawynok, 2003)
• AZD3582 (COX-inhibiting nitric oxide donator) or rofexocib in knee OA (Schnitzer, Kivitz, Lipetz, Sanders and Hee, 2005).
• Delta-9-tetrahydrocannabinol/cannabidiol oromucosal spray for central neuropathic pain (Langford, et al., 2013)
• Droxicam or diclofenac sodium hip and/or knee OA (Corts Giner and García Borrás, 1991)
• Etoricoxib or naproxen for rheumatoid arthritis [pain a secondary outcome] (Matsumoto, et al.,2002)
• Fentanyl buccal tablet for breakthrough pain associated with chronic neuropathic pain (Simpson, Messina, Xie and Hale, 2007) and in opioid treated patients with chronic low back pain (Portenoy, Messina, Xie and Peppin, 2007)
• Gabapentin for:
  o neuropathic pain syndromes (Serpell and Neuropathic Pain Study Group, 2002).
  o postherpetic neuralgia (Irving, et al., 2009; Rice, Maton and Postherpetic Neuralgia Study Group, 2001).
• Hydromorphone for chronic low back pain (Hale, Khan, Kutch and Li, 2010; Jamison, et al., 2013)
• Lacosamide for diabetic neuropathic pain (Wymer, Simpson, Sen, Bongardt and Lacosamide, 2009)
• Morphine sulphate and naltrexone hydrochloride ER for chronic moderate to severe hip and/or knee OA (Katz, Hale, Morris and Stauffer, 2010)
• Nabilone (adjuvant) in diabetic neuropathic pain (Toth, et al., 2012)
• Oxycodone
  o for moderate to severe OA pain (Friedmann, Klutzaritz and Webster, 2011)
  o with morphine as analgesia in induced cold pain (Grach, Massalha, Pud, Adler and Eisenberg, 2004)
- Oxycodone CR or oxycodone-acetaminophen for OA pain (Caldwell, et al., 1999)
- Oxytrex (oxycodone + ultralow dose naltrexone) for chronic low back pain (Webster, et al., 2006)
- Pregabalin for:
  - pain associated with fibromyalgia (Crofford, et al., 2005; Pauer, Atkinson, Murphy, Petersel and Zeiher, 2012)
  - neuropathic pain associated with lumbosacral radiculopathy (Baron, et al., 2010)
  - moderate to severe neuropathic pain (Hewitt, et al., 2011)
  - peripheral neuropathic pain (Gammaitoni, et al., 2013; Gilron, Wajsbro, Therrien and Lemay, 2011) and specifically moderate to severe pain (Jensen, et al., 2012)
  - postherpetic neuralgia (Dworkin, et al., 2003; Sabatowski, et al., 2004).
  - painful diabetic neuropathy (Lesser, Sharma, LaMoreaux and Poole, 2004) and specifically painful diabetic peripheral neuropathy (Rosenstock, Tuchman, Lamoreaux and Sharma, 2004).
- Rizatriptan for acute treatment of migraine [paediatrics] (Ho, et al., 2012)
- Tapentadol ER in painful diabetic peripheral neuropathy (Schwartz, et al., 2011)
- Tramadol for
  - OA pain (Burch, et al., 2007; Roth, 1998)
  - fibromyalgia (Russell, et al., 2000)
  - chronic low back pain (Schnitzer, Gray, Paster and Kamin, 2000; Vorsanger, Xiang, Gana, Pascual and Fleming, 2008)
  - OR gabapentin for painful idiopathic small fiber neuropathy (Ho, et al., 2009)
  - OR naproxen for knee OA (Schnitzer, Kamin and Olson, 1999)
- Transdermal buprenorphine for:
  - chronic pain [malignant and non-malignant origin] (Bohme and Likar, 2003; Sorge and Sittl, 2004).
  - persistent non-cancer-related pain (Landau, et al., 2007)
  - chronic low back pain (Miller, et al., 2013)
  - chronic moderate to severe low back pain (Steiner, Munera, Hale, Ripa and Landau, 2011; Steiner, et al., 2011; Yaras, et al., 2013)
- Transdermal buprenorphine + oral paracetamol versus oral codeine-paracetamol combination for hip and/or knee OA (Conaghan, O'Brien, Wilson and Schofield, 2011)
- Transdermal clonidine for diabetic neuropathy (Byas-Smith, Max, Muir and Kingman (1995)
- Topical lidocaine plaster/patch for post-herpetic neuralgia (Binder, et al., 2009; Galer, Rowbotham, Perander and Friedman, 1999).

In addition, seven RCTs were identified which may have an EERW design but require the methodology to be more closely scrutinized for clarification (see Appendix 2.D.2).

Conference abstracts of EERW-designed RCTs and other papers of possible interest are listed in Appendix 3.
E: Overviews and Expert Opinions
Not relevant to this report.

F: Intellectual Property Office
Not relevant to this report.

ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>bid</td>
<td><em>bis in die</em> i.e. twice a day</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>CR</td>
<td>Controlled release</td>
</tr>
<tr>
<td>DPN</td>
<td>Diabetic peripheral neuropathy</td>
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<tr>
<td>EERW</td>
<td>Enriched enrolment randomized withdrawal (EERW)</td>
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<tr>
<td>EQ-5D</td>
<td>EuroQoL-5 Dimension</td>
</tr>
<tr>
<td>ER</td>
<td>Extended release</td>
</tr>
<tr>
<td>GiT</td>
<td>Gastrointestinal Tract System</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
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<tr>
<td>IR</td>
<td>Immediate release</td>
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<tr>
<td>LBP</td>
<td>Low back pain</td>
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<tr>
<td>MSK</td>
<td>Musculoskeletal</td>
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<tr>
<td>NRS</td>
<td>Numerical Rating Scale</td>
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<tr>
<td>OA</td>
<td>Osteoarthritis</td>
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<td>OR</td>
<td>Odds ratio</td>
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<tr>
<td>ORL-1</td>
<td>Opioid receptor like -1</td>
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<tr>
<td>PR</td>
<td>Prolonged release</td>
</tr>
<tr>
<td>qid</td>
<td><em>quater in die</em> i.e. four times a day</td>
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<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid arthritis</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>SF-36</td>
<td>Short form 36</td>
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<tr>
<td>SMD</td>
<td>Standardised mean difference</td>
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<tr>
<td>TEAE</td>
<td>Treatment-emergent adverse event</td>
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<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
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<tr>
<td>WOMAC</td>
<td>Western Ontario and McMaster Universities Arthritis Index</td>
</tr>
</tbody>
</table>
References


APPENDIX 1

Searches
1  exp musculoskeletal pain/
2  exp back pain/
3  chronic pain/
4  headache/
5  neck pain/
6  exp neuralgia/
7  exp arthritis/
8  exp arthralgia/
9  Fibromyalgia/
10 ((musculoskeletal or back or chronic or neuropathic or neck) adj3 pain).ti,ab.
11 backache.ti,ab.
12 arthr*.ti,ab.
13 osteoarthr*.ti,ab.
14 OA.ti,ab.
15 (coxarthr* or gonarthr*).ti,ab.
16 (degenerative adj3 (joint or joints)).ti,ab.
17 fibromyalgia.ti,ab.
18 fibromyositis.ti,ab.
19 fibrositis.ti,ab.
20 FMS.ti,ab.
21 CWP.ti,ab.
22 headache*.ti,ab.
23 neuralgia*.ti,ab.
24 or/1-23
25 exp Analgesics/
26 exp Narcotics/
27 analgesic*.mp.
28 opiate*.mp.
29 opioid*.mp.
30 narcotic*.mp.
31 NSAID*.mp.
32 ((nonsteroidal or non-steroidal) adj (anti-inflammatory or antiinflammatory)).mp.
33 exp Cyclooxygenase 2 Inhibitors/
34 (COX-2 adj inhibitor*).mp.
35  (("cyclooxygenase 2" or "cyclo-oxygenase 2") adj inhibitor*).mp.
36  or/25-35
37  24 and 36
38  randomized controlled trial.pt.
39  controlled clinical trial.pt.
40  randomized.ab.
41  placebo.ab.
42  clinical trials as topic.sh.
43  randomly.ab.
44  trial.ti.
45  or/38-44
46  exp animals/ not humans.sh.
47  45 not 46
48  (enriched or enrichment or withdrawal or EERW or “discontinuation
design”).mp.
49  37 and 47 and 48
2.B.1: SRs specifying the inclusion of RCTs with EERW design

<table>
<thead>
<tr>
<th>Title</th>
<th>Abstract [The following text is verbatim]</th>
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<tbody>
<tr>
<td>Furlan, Chaparro, Irvin and Mailis-Gagnon (2011) A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain.</td>
<td>BACKGROUNDD: An enriched enrollment randomized withdrawal (EERW) design excludes potential participants who are nonresponders or who cannot tolerate the experimental drug before random assignment. It is unclear whether EERW design has an influence on the efficacy and safety of opioids for chronic noncancer pain (CNCP). OBJECTIVES: The primary objective was to compare the results from EERW and non-EERW trials of opioids for CNCP. Secondary objectives were to compare weak versus strong opioids, subgroups of patients with different types of pain, and the efficacy of opioids compared with placebo versus other drugs. METHODS: MEDLINE, EMBASE and CENTRAL were searched up to July 2009, for randomized controlled trials of any opioid for CNCP. Metaanalyses and meta-regressions were conducted to compare the results. Treatment efficacy was assessed by effect sizes (small, medium and large) and the incidence of adverse effects was assessed by a clinically relevant mean difference of 10% or greater. RESULTS: Sixty-two randomized trials were included. In 61 trials, the duration was less than 16 weeks. There was no difference in efficacy between EERW and non-EERW trials for both pain (P=0.6) and function (P=0.3). However, EERW trials failed to detect a clinically relevant difference for nausea, vomiting, somnolence, dizziness and dry skin/itching compared with non-EERW. Opioids were more effective than placebo in patients with nociceptive pain (effect size=0.60, 95% CI 0.49 to 0.72) and neuropathic pain (effect size=0.56, 95% CI 0.38 to 0.73). CONCLUSION: EERW trial designs appear not to bias the results of efficacy, but they underestimate the adverse effects. The present updated meta-analysis shows that weak and strong opioids are effective for CNCP of both nociceptive and neuropathic origin.</td>
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<tr>
<td>Katz (2009) Enriched enrollment randomized withdrawal trial designs of analgesics: focus on methodology.</td>
<td>OBJECTIVES: To systematically identify and critically assess clinical trials that use enriched enrollment randomized withdrawal (EERW) trial design as a methodology for assessing the effect of analgesics pain. METHODS: A comprehensive literature search was conducted through April 2007 in Medline and Embase to identify all randomized controlled trials that use EERW trial designs. Data were collected from relevant trials and tabulated. Results were categorized on the basis of study designs, preenrichment and postenrichment disposition, discontinuation rates, primary and secondary efficacy results, and respective P values. RESULTS: The literature search identified 2875 unique citations, most of which were deemed inappropriate for this analysis. The primary reasons for exclusion included inappropriate study design, no available abstract, not a clinical study, and therapeutic area not related to chronic pain. Eight EERW clinical trials of analgesics were identified. Half of the trials were in chronic low back pain, and 5 of 8 trials used an opioid as the active drug. Of the 8 trials, 5 used a parallel design and 3 used crossover designs. The primary efficacy parameter used was pain scores or time to discontinuation, and statistically and clinically significant effects in active treatments relative to placebo were observed after randomization in all trials. The median magnitude of effect was 1.7 on a 10-point scale. Time to exit was a more statistically powerful endpoint than mean pain intensity. DISCUSSIONS: EERW trials are an emerging type of study design that in certain settings may offer advantages over traditional trial designs in characterizing the effects of analgesic medications.</td>
</tr>
<tr>
<td>Straube, Derry, McQuay and Moore (2008) Enriched enrolment: Definition and effects of</td>
<td>AIMS: Enriched enrolment study designs have been suggested to be useful for proof of concept when only a proportion of the diseased population responds to a treatment intervention. We aim to investigate whether this really is the case in trials of pregabalin and gabapentin in neuropathic pain. METHODS: We defined 'complete', 'partial' and 'non-enriched' enrolment, and examined pregabalin and gabapentin trials for the extent of enrichment and for effects of enrichment on efficacy and adverse event outcomes. RESULTS: There were no studies using complete enriched</td>
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<tr>
<td>Enrichment and Dose in Trials of Pregabalin and Gabapentin in Neuropathic Pain. A Systematic Review.</td>
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<td><strong>Enrichment</strong> and dose in trials of pregabalin and gabapentin in neuropathic pain. A systematic review.</td>
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<td>The objective was to systematically assess efficacy and safety of buprenorphine patch versus fentanyl patch in patients with chronic moderate to severe pain.</td>
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<td>RESULTS: Significant benefit of pregabalin over placebo was seen for a variety of outcomes including mean pain and sleep scores, the proportion of patients achieving at least 50% pain relief and most of the individual domains of short-form 36. Only a minority of patients achieve moderate or substantial pain relief. The proportions of patients with any adverse event, somnolence or dizziness were also significantly greater with pregabalin than with placebo. There was no difference with regard to serious adverse events. A dose-response relationship was apparent for at least 50% pain relief and for adverse event outcomes. CONCLUSIONS: Pregabalin is effective in treating FM and is relatively safe. The size of therapeutic effect is similar to that with other recent interventions such as duloxetine and the combination of tramadol and paracetamol. Enriched enrolment randomized withdrawal design gives similar results to classical trial designs in FM.</td>
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<tr>
<th>Straube, Derry, Moore and McQuay (2010) Pregabalin in fibromyalgia: meta-analysis of efficacy and safety from company clinical trial reports.</th>
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<tr>
<td>OBJECTIVES: Meta-analysis of pregabalin trials in FM using company trial reports, which provide more detailed information about trials than published papers. FM is a common condition with a significant impact on quality of life. METHODS: Reports of five high-quality randomized trials (3808 patients) of pregabalin in FM were obtained from Pfizer. Four trials (2754 patients) were of classical trial design and one was an enriched enrolment randomized withdrawal design. Outcomes for meta-analysis from the four trials with classical design were pooled in an intention-to-treat analysis. RESULTS: Significant benefit of pregabalin over placebo was seen for a variety of outcomes including mean pain and sleep scores, the proportion of patients achieving at least 50% pain relief and most of the individual domains of short-form 36. Only a minority of patients achieve moderate or substantial pain relief. The proportions of patients with any adverse event, somnolence or dizziness were also significantly greater with pregabalin than with placebo. There was no difference with regard to serious adverse events. A dose-response relationship was apparent for at least 50% pain relief and for adverse event outcomes. CONCLUSIONS: Pregabalin is effective in treating FM and is relatively safe. The size of therapeutic effect is similar to that with other recent interventions such as duloxetine and the combination of tramadol and paracetamol. Enriched enrolment randomized withdrawal design gives similar results to classical trial designs in FM.</td>
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<td>OBJECTIVE: To systematically assess efficacy and safety of buprenorphine patch versus fentanyl patch in patients with chronic moderate to severe pain. METHODS: Fifteen databases were searched up to December 2010. Randomised and quasi-randomised trials assessing the efficacy in patients with chronic pain were included. Quantitative methods for data synthesis were used and two network meta-analyses were conducted. RESULTS: Fourteen unique trials (17 publications) were included. No head-to-head randomised trials of buprenorphine patch compared with fentanyl patch were identified. Therefore, less robust evidence from indirect comparisons was used. Results from a network meta-analysis of non-enriched designs (eight trials), using trials versus placebo and trials versus morphine for indirect comparisons, indicated that transdermal fentanyl, in comparison with transdermal buprenorphine, showed significantly more nausea (odds ratio [OR] 4.66, 95% confidence interval (CI) 1.07 to 20.39), a significantly higher number of treatment discontinuations due to adverse events (OR 5.94, 95% CI 1.78 to 19.87), and non-significant differences on all other outcomes, including pain measures. In comparison with morphine, transdermal buprenorphine had a significantly higher decrease of pain intensity (MD [mean difference] -16.20, 95% CI -28.92 to -3.48) while morphine caused more cases of constipation (OR 7.50, 95% CI 1.45 to 38.85) and a significantly higher number of treatment discontinuations due to adverse events (OR 5.80, 95% CI 1.68 to 20.11). All other outcomes showed non-significant differences between transdermal buprenorphine and morphine. The results were similar when also including six trials using enriched designs with the exception of more cases of vomiting for fentanyl (OR 17.32, 95% CI 4.43 to 67.71) and morphine (OR 15.85, 95% CI 3.92 to 64.13) compared to buprenorphine. CONCLUSIONS: The findings indicate comparability of transdermal buprenorphine and transdermal fentanyl for pain measures with significantly fewer adverse events (nausea and treatment discontinuation due to adverse events) caused by transdermal buprenorphine.</td>
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</table>
### Background

Antiepileptic drugs have been used in pain management since the 1960s; some seem to be especially useful for neuropathic pain. Lacosamide is an antiepileptic drug that has recently been investigated for neuropathic pain relief, although it failed to get approval for painful diabetic peripheral neuropathy from either the Food and Drug Administration or the European Medicines Agency. **OBJECTIVES:** To evaluate the analgesic efficacy and adverse effects of lacosamide in the management of chronic neuropathic pain or fibromyalgia. **SEARCH METHODS:** We searched the Cochrane Neuromuscular Disease Group Specialized Register (2011, Issue 4), CENTRAL (2011, Issue 3), MEDLINE (January 2000 to August 2011) and EMBASE (2000 to August 2011) without language restriction, together with reference lists of retrieved papers and reviews. **SELECTION CRITERIA:** We included randomised, double-blind studies of eight weeks duration or longer, comparing lacosamide with placebo or another active treatment in chronic neuropathic pain or fibromyalgia. **DATA COLLECTION AND ANALYSIS:** Two review authors independently extracted data for efficacy and adverse events and examined issues of study quality, including risk of bias assessments. Where possible, we calculated numbers needed to treat to benefit from dichotomous data for effectiveness, adverse events and study withdrawals. **MAIN RESULTS:** We included six studies; five (1863 participants) in painful diabetic neuropathy (PDN) and one (159 participants) in fibromyalgia. All were placebo-controlled and titrated to a target dose of 200 mg, 400 mg or 600 mg lacosamide daily, given as a divided dose. Study reporting quality was generally good, although the imputation method of last observation carried forward used in analyses of the primary outcomes could overestimate treatment effect. Both doses of lacosamide provided moderate levels of pain relief to about 40% of those treated, compared to 30% with placebo, giving a number needed to treat of 8 to 10. Adverse events were common in both lacosamide (87%) and placebo (78%) groups, but serious adverse events (< 2%) did not differ between groups. Nausea and constipation were the most common events showing the greatest difference between groups (number needed to treat for an additional harmful outcome of 7 and 13 respectively, compared with placebo). Withdrawals for any reason were more common with lacosamide than placebo, and more common with 200 mg than 100 mg (NNH of 23 and 8.8 respectively, compared with placebo). This was largely driven by adverse event withdrawals, where the NNH compared with placebo was 14 for 100 mg, and 7.0 for 200 mg). Withdrawals due to lack of efficacy were more common with milnacipran than placebo but did not differ between doses (number needed to treat to prevent an additional unwanted outcome of 45 and 41 respectively). Authors’ conclusions: The evidence available indicates that milnacipran 100 mg or 200 mg is effective for a minority in the treatment of pain due to fibromyalgia, providing moderate levels of pain relief (at least 30%) to about 40% of participants, compared with about 30% with placebo. There were insufficient data to assess substantial levels of pain relief (at least 50%), and the use of last observation carried forward imputation may overestimate drug efficacy. Milnacipran is associated with increased adverse events and adverse event withdrawals, which were significantly greater for the higher dose. There were no data for the use of milnacipran for other chronic neuropathic pain conditions.

### Title

| Derry, Gill, Phillips and Moore (2012) | Background: Milnacipran is a serotonin?norepinephrine reuptake inhibitor (SNRI) that is sometimes used to treat chronic neuropathic pain and fibromyalgia. Objectives: To evaluate the analgesic efficacy and adverse effects of milnacipran in the management of chronic neuropathic pain or fibromyalgia. Search methods: We searched CENTRAL, MEDLINE, and EMBASE to 4th of January 2012, together with reference lists of retrieved papers and reviews. Selection criteria: We included randomised, double-blind studies of eight weeks duration or longer, comparing milnacipran with placebo or another active treatment in chronic neuropathic pain or fibromyalgia. Data collection and analysis: We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. Main results: Five studies (4138 participants) were included, all of which were placebo-controlled, involved participants with fibromyalgia, and used titration to a target dose of 100 mg or 200 mg milnacipran. There were no other active comparators or studies in other neuropathic pain conditions. Study quality was generally good, although the imputation method used in analyses of the primary outcomes could overestimate treatment effect. Both doses of milnacipran provided moderate levels of pain relief to about 40% of those treated, compared to 30% with placebo, giving a number needed to treat of 8 to 10. Adverse events were common in both milnacipran (87%) and placebo (78%) groups, but serious adverse events (< 2%) did not differ between groups. Nausea and constipation were the most common events showing the greatest difference between groups (number needed to treat for an additional harmful outcome of 7 and 13 respectively, compared with placebo). Withdrawals for any reason were more common with milnacipran than placebo, and more common with 200 mg than 100 mg (NNH of 23 and 8.8 respectively, compared with placebo). This was largely driven by adverse event withdrawals, where the NNH compared with placebo was 14 for 100 mg, and 7.0 for 200 mg). Withdrawals due to lack of efficacy were more common with milnacipran than placebo but did not differ between doses (number needed to treat to prevent an additional unwanted outcome of 45 and 41 respectively). Authors' conclusions: The evidence available indicates that milnacipran 100 mg or 200 mg is effective for a minority in the treatment of pain due to fibromyalgia, providing moderate levels of pain relief (at least 30%) to about 40% of participants, compared with about 30% with placebo. There were insufficient data to assess substantial levels of pain relief (at least 50%), and the use of last observation carried forward imputation may overestimate drug efficacy. Milnacipran is associated with increased adverse events and adverse event withdrawals, which were significantly greater for the higher dose. There were no data for the use of milnacipran for other chronic neuropathic pain conditions. |
| Hearn, Derry and Moore (2012) | Lacosamide for neuropathic pain and fibromyalgia in adults. | BACKGROUN D: Antiepileptic drugs have been used in pain management since the 1960s; some seem to be especially useful for neuropathic pain. Lacosamide is an antiepileptic drug that has recently been investigated for neuropathic pain relief, although it failed to get approval for painful diabetic peripheral neuropathy from either the Food and Drug Administration or the European Medicines Agency. **OBJECTIVES:** To evaluate the analgesic efficacy and adverse effects of lacosamide in the management of chronic neuropathic pain or fibromyalgia. **SEARCH METHODS:** We searched the Cochrane Neuromuscular Disease Group Specialized Register (2011, Issue 4), CENTRAL (2011, Issue 3), MEDLINE (January 2000 to August 2011) and EMBASE (2000 to August 2011) without language restriction, together with reference lists of retrieved papers and reviews. **SELECTION CRITERIA:** We included randomised, double-blind studies of eight weeks duration or longer, comparing lacosamide with placebo or another active treatment in chronic neuropathic pain or fibromyalgia. **DATA COLLECTION AND ANALYSIS:** Two review authors independently extracted data for efficacy and adverse events and examined issues of study quality, including risk of bias assessments. Where possible, we calculated numbers needed to treat to benefit from dichotomous data for effectiveness, adverse events and study withdrawals. **MAIN RESULTS:** We included six studies; five (1863 participants) in painful diabetic neuropathy (PDN) and one (159 participants) in fibromyalgia. All were placebo-controlled and titrated to a target dose of 200 mg, 400 mg or 600 mg lacosamide daily, given as a divided dose. Study reporting quality was generally good, although the imputation method of last observation carried forward used in analyses of the primary outcomes could overestimate treatment effect. Both doses of lacosamide provided moderate levels of pain relief to about 40% of those treated, compared to 30% with placebo, giving a number needed to treat of 8 to 10. Adverse events were common in both lacosamide (87%) and placebo (78%) groups, but serious adverse events (< 2%) did not differ between groups. Nausea and constipation were the most common events showing the greatest difference between groups (number needed to treat for an additional harmful outcome of 7 and 13 respectively, compared with placebo). Withdrawals for any reason were more common with milnacipran than placebo, and more common with 200 mg than 100 mg (NNH of 23 and 8.8 respectively, compared with placebo). This was largely driven by adverse event withdrawals, where the NNH compared with placebo was 14 for 100 mg, and 7.0 for 200 mg). Withdrawals due to lack of efficacy were more common with milnacipran than placebo but did not differ between doses (number needed to treat to prevent an additional unwanted outcome of 45 and 41 respectively). Authors’ conclusions: The evidence available indicates that milnacipran 100 mg or 200 mg is effective for a minority in the treatment of pain due to fibromyalgia, providing moderate levels of pain relief (at least 30%) to about 40% of participants, compared with about 30% with placebo. There were insufficient data to assess substantial levels of pain relief (at least 50%), and the use of last observation carried forward imputation may overestimate drug efficacy. Milnacipran is associated with increased adverse events and adverse event withdrawals, which were significantly greater for the higher dose. There were no data for the use of milnacipran for other chronic neuropathic pain conditions. |
outcomes is known to known to impart major bias where, as here, adverse event withdrawal rates were high. This, together with small numbers of patients and events for most outcomes at most doses meant that most results were of low quality, with moderate quality evidence available for some efficacy outcomes for 400 mg lacosamide. There were too few data for analysis of the 200 mg dose for painful diabetic neuropathy or any dose for fibromyalgia. In painful diabetic neuropathy, lacosamide 400 mg provided statistically increased rates of achievement of "moderate" and "substantial" benefit (at least 30% and at least 50% reduction from baseline in patient-reported pain respectively) and the patient global impression of change outcome of "much or very much improved". In each case the extra proportion benefitting above placebo was about 10%, yielding numbers needed to treat to benefit compared with placebo of 10 to 12. For lacosamide 600 mg there was no consistent benefit over placebo. There was no significant difference between any dose of lacosamide and placebo for participants experiencing any adverse event or a serious adverse event, but adverse event withdrawals showed a significant dose response. The number needed to treat to harm for adverse event withdrawal was 11 for lacosamide 400 mg and 4 for the 600 mg dose.

AUTHORS’ CONCLUSIONS: Lacosamide has limited efficacy in the treatment of peripheral diabetic neuropathy. Higher doses did not give consistently better efficacy, but were associated with significantly more adverse event withdrawals. Where adverse event withdrawals are high with active treatment compared with placebo and when last observation carried forward imputation is used, as in some of these studies, significant overestimation of treatment efficacy can result. It is likely, therefore, that lacosamide is without any useful benefit in treating neuropathic pain; any positive interpretation of the evidence should be made with caution if at all.


Background: Amitriptyline is a tricyclic antidepressant that is widely used to treat chronic neuropathic pain (pain due to nerve damage) and fibromyalgia, and is recommended in many guidelines. These types of pain can be treated with antidepressant drugs in doses below those at which the drugs act as antidepressants. Objectives: To assess the analgesic efficacy of amitriptyline for chronic neuropathic pain and fibromyalgia. To assess the adverse events associated with the clinical use of amitriptyline for chronic neuropathic pain and fibromyalgia. Search methods: We searched CENTRAL, MEDLINE, and EMBASE to September 2012, together with reference lists of retrieved papers, previous systematic reviews, and other reviews; we also used our own handsearched database for older studies. Selection criteria: We included randomised, double-blind studies of at least four weeks’ duration comparing amitriptyline with placebo or another active treatment in chronic neuropathic pain or fibromyalgia. Data collection and analysis: We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. We performed analysis using two tiers of evidence. The first tier used data meeting current best standards, where studies reported the outcome of at least 50% pain intensity reduction over baseline (or its equivalent), without the use of last observation carried forward (LOCF) or other imputation method for dropouts, reported an intention-to-treat (ITT) analysis, lasted 8 to 12 weeks or longer, had a parallel-group design, and where there were at least 200 participants in the comparison. The second tier used data that failed to meet this standard and were therefore subject to potential bias. Main results: Twenty-one studies (1437 participants) were included; they individually involved between 15 and 235 participants, only four involved over 100 participants, and the median study size was 44 participants. The median duration was six weeks. Ten studies had a cross-over design. Doses of amitriptyline were generally between 25 mg and 125 mg, and dose escalation was common. There was no top-tier evidence for amitriptyline in treating neuropathic pain or fibromyalgia. Second-tier evidence indicated no evidence of effect in cancer-related neuropathic pain or HIV-related neuropathic pain, but some evidence of effect in painful diabetic neuropathy (PDN), mixed neuropathic pain, and fibromyalgia. Combining the classic neuropathic pain conditions of PDN, postherpetic neuralgia (PHN) and post-stroke pain with fibromyalgia for second-tier evidence, in eight studies and 687 participants, there was a statistically significant benefit (risk ratio (RR) 2.3, 95% confidence interval (CI) 1.8 to 3.1) with a number needed to treat (NNT) of 4.6 (3.6 to 6.6). The analysis showed that even using this potentially biased data, only about 38% of participants benefited with amitriptyline and 16% with placebo; most participants did not get adequate pain relief. Potential benefits of amitriptyline were supported by a lower rate of lack of efficacy withdrawals; 8/153 (5%) withdrew because of lack of efficacy with
amitriptyline and 14/119 (12%) with placebo. More participants experienced at least one adverse event; 64% of participants taking amitriptyline and 40% taking placebo. The RR was 1.5 (95% CI 1.4 to 1.7) and the number needed to treat to harm was 4.1 (95% CI 3.2 to 5.7). Adverse event and all-cause withdrawals were not different. Authors’ conclusions: Amitriptyline has been a first-line treatment for neuropathic pain for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against decades of successful treatment in many patients with neuropathic pain or fibromyalgia. There is no good evidence of a lack of effect; rather our concern should be of overestimation of treatment effect. Amitriptyline should continue to be used as part of the treatment of neuropathic pain or fibromyalgia, but only a minority of patients will achieve satisfactory pain relief. Limited information suggests that failure with one antidepressant does not mean failure with all. It is unlikely that any large randomised trials of amitriptyline will be conducted in specific neuropathic pain conditions or in fibromyalgia to prove efficacy


BACKGROUND: Topiramate is an antiepileptic drug with multiple possible mechanisms of action. Antiepileptic drugs are widely used to treat chronic neuropathic pain (pain due to nerve damage) and fibromyalgia, and many guidelines recommend them. OBJECTIVES: To assess the analgesic efficacy and associated adverse events of topiramate for chronic neuropathic pain and fibromyalgia in adults (aged 18 years and above). SEARCH METHODS: On 8 May 2013, we searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL, MEDLINE, and EMBASE. We reviewed the bibliographies of all randomised trials identified and reviewed articles, and also searched two clinical trial databases, ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform, to identify additional published or unpublished data. SELECTION CRITERIA: We included randomised controlled trials (RCTs) with double-blind assessment of participant outcomes following two weeks of treatment or longer (though the emphasis of the review was on studies of eight weeks or longer) that used a placebo or active comparator. DATA COLLECTION AND ANALYSIS: We extracted efficacy and adverse event data, and two study authors examined issues of study quality independently. We performed analysis using two tiers of evidence. The first tier used data where studies reported the outcome of at least 50% pain reduction from baseline, lasted at least eight weeks, had a parallel group design, included 200 or more participants in the comparison, and reported an intention-to-treat analysis. The second tier used data that failed to meet this standard; second tier results were therefore subject to potential bias. MAIN RESULTS: We included four studies with 1684 participants. Three parallel-group placebo comparisons were in painful diabetic neuropathy (1643 participants), and one cross-over study with diphenhydramine as an active placebo (41 participants) was in lumbar radiculopathy. Doses of topiramate were titrated up to 200 mg/day or 400 mg/day. All studies had one or more sources of potential major bias, as they either used LOCF imputation or were of small size. No study provided first tier evidence for an efficacy outcome. There was no convincing evidence for efficacy of topiramate at 200 to 400 mg/day over placebo. Eighty-two per cent of participants taking topiramate 200 to 400 mg/day experienced at least one adverse event, as did 71% with placebo, and the number needed to treat for an additional harmful effect (NNTH) was 8.6 (95% confidence interval (CI) 4.9 to 35). There was no difference in serious adverse events recorded (6.6% versus 7.5%). Adverse event withdrawals with 400 mg daily were much more common with topiramate (27%) than with placebo (8%), with an NNTH of 5.4 (95% CI 4.3 to 7.1). Lack of efficacy withdrawal was less frequent with topiramate (12%) than placebo (18%). Weight loss was a common event in most studies. No deaths attributable to treatment were reported. AUTHORS’ CONCLUSIONS: Topiramate is without evidence of efficacy in diabetic neuropathic pain, the only neuropathic condition in which it has been adequately tested. The data we have includes the likelihood of major bias due to LOCF imputation, where adverse event withdrawals are much higher with active treatment than placebo control. Despite the strong potential for bias, no difference in efficacy between topiramate and placebo was apparent.
## SECTION D – PRIMARY RESEARCH

### 2.D.1: RCTs with enriched enrolment, randomised withdrawal design

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<th>Title</th>
<th>Abstract [The following text is verbatim]</th>
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<td>Allan, et al., (2001). Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain.</td>
<td>OBJECTIVES: To compare patients' preference for transdermal fentanyl or sustained release oral morphine, their level of pain control, and their quality of life after treatment. DESIGN: Randomised, multicentre, international, open label, crossover trial. SETTING: 35 centres in Belgium, Canada, Denmark, Finland, the United Kingdom, the Netherlands, and South Africa. PARTICIPANTS: 256 patients (aged 26-82 years) with chronic non-cancer pain who had been treated with opioids. MAIN OUTCOME MEASURES: Patients' preference for transdermal fentanyl or sustained release oral morphine, pain control, quality of life, and safety assessments. Results: Of 212 patients, 138 (65%) preferred transdermal fentanyl, whereas 59 (28%) preferred sustained release oral morphine and 15 (7%) expressed no preference. Better pain relief was the main reason for preference for fentanyl given by 35% of patients. More patients considered pain control as being &quot;good&quot; or &quot;very good&quot; with fentanyl than with morphine (35% v 23%, P=0.002). These results were reflected in both patients' and investigators' opinions on the global efficacy of transdermal fentanyl. Patients receiving fentanyl had on average higher quality of life scores than those receiving morphine. The incidence of adverse events was similar in both treatment groups; however, more patients experienced constipation with morphine than with fentanyl (48% v 29%, P&lt;0.001). Overall, 41% of patients experienced mild or moderate cutaneous problems associated with wearing the transdermal fentanyl patch, and more patients withdrew because of adverse events during treatment with fentanyl than with morphine (10% v 5%). However, within the subgroup of patients naive to both fentanyl and morphine, similar numbers of patients withdrew owing to adverse effects (11% v 10%, respectively). CONCLUSION: Transdermal fentanyl was preferred to sustained release oral morphine by patients with chronic non-cancer pain previously treated with opioids. The main reason for preference was better pain relief, achieved with less constipation and an enhanced quality of life.</td>
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<td>Baron, et al. (2010) The efficacy and safety of pregabalin in the treatment of neuropathic pain associated with chronic lumbosacral radiculopathy.</td>
<td>We evaluated the efficacy of pregabalin in patients with chronic lumbosacral radiculopathy. This randomized, controlled, withdrawal trial included five phases: screening (4-18 days); run-in (4-10 days) to screen out placebo responders; single-blind (28 days) to identify pregabalin responders; double-blind to randomize responders to pregabalin or placebo (35 days); and final study medication taper (7 days). The primary endpoint was time to loss of response (LOR) during the double-blind phase (1-point increase in pain, discontinuation, or rescue-medications use). In the single-blind phase, 58% of patients had 30% pain reduction. In the double-blind phase, pregabalin (n=110) and placebo (n=107) groups did not differ significantly in time to LOR. Adverse events caused the discontinuation of 9.9% and 5.6% of pregabalin-treated and placebo-treated patients, respectively. Most patients with chronic lumbosacral radiculopathy responded to pregabalin therapy; however, time to LOR did not significantly differ between pregabalin and placebo. Considering the results of all phases of the study, it is difficult to draw definitive conclusions from it, suggesting a need for further work to understand the clinical potential of pregabalin treatment for lumbosacral radiculopathy. Copyright (c) 2010 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.</td>
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<td>Binder, et al. (2009) Topical 5% lidocaine (lignocaine) medicated plaster treatment for post-herpetic neuralgia: results of a double-blind, placebo-controlled,</td>
<td>BACKGROUND AND OBJECTIVE: Post-herpetic neuralgia (PHN) is a distressing neuropathic pain condition mainly affecting elderly patients. Neuropathic pain symptoms can be of a burning, shooting and stabbing nature, and may continue for prolonged periods and are often poorly controlled by polymedication. The aim of this study was to evaluate the analgesic efficacy and safety of topical analgesic treatment (5% lidocaine [lignocaine] medicated plaster) compared with placebo plaster in patients with PHN. METHODS: This was a double-blind, placebo plaster-controlled, parallel-group, multicentre study employing enriched enrolment with randomized withdrawal methodology. After an initial 8-week open-label, active run-in phase, responders entered a 2-week randomized, double-blind, placebo-controlled phase. The study was conducted at 33 outpatient investigational centres in 12 European</td>
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multinational efficacy and safety trial. Patients with PHN were selected who were aged ≥50 years, had experienced neuropathic pain persisting for ≥3 months after rash healing, and had a mean pain intensity of ≥4 on an 11-point numerical rating scale. A total of 265 patients entered the open-label phase and subsequently a pre-defined number of 71 patients entered the randomized phase. Patients applied up to three 5% lidocaine medicated plasters for up to 12 hours per day. The primary endpoint of the study was time-to-exit due to a ≥2-point reduction in pain relief on two consecutive days of plaster application using a 6-point verbal rating scale. RESULTS: Of the 265 patients entering the run-in phase, 51.7% achieved at least moderate pain relief. In the double-blind phase (full analysis set, n = 71), median times-to-exit were 13.5 (range 2-14) and 9.0 (range 1-14) days for lidocaine and placebo plaster groups, respectively (p = 0.151). For per-protocol patients (n = 34), median time-to-exit was 14.0 (range 3-14) and 6.0 (range 1-14) days for lidocaine and placebo plaster groups, respectively (p = 0.0398). Drug-related adverse events occurred in 13.6% of patients. Treatment with 5% lidocaine medicated plaster was associated with improvements in pain, allodynia, quality of life and sleep measures. CONCLUSIONS: This study adds to a growing body of evidence that the 5% lidocaine medicated plaster can be considered a valuable treatment option for patients with PHN, providing beneficial effects on pain, allodynia, quality of life and sleep, with minimal adverse effects.

Bohme and Likar (2003) Efficacy and tolerability of a new opioid analgesic formulation, buprenorphine transdermal therapeutic system (TDS), in the treatment of patients with chronic pain. A randomised, double-blind, placebo-controlled study. This randomised, double-blind, placebo-controlled study evaluated the efficacy and tolerability of buprenorphine TDS, a new transdermal formulation of the opioid analgesic buprenorphine. Patients (151) with severe to very severe chronic pain of malignant or non-malignant origin who maintained at least satisfactory pain relief with sublingual buprenorphine 0.8-1.2 mg/day during an open-label 5-day run-in phase, were randomly allocated to buprenorphine TDS in one of three dose strengths: 35 [mu]g/h, 52.5 [mu]g/h or 70 [mu]g/h, or placebo, receiving two patches consecutively, each applied for 72 hours. Rescue analgesic medication comprised sublingual buprenorphine tablets (0.2 mg). Responders were patients reporting at least satisfactory pain relief and taking no more than 0.2 mg/day rescue analgesic. The proportion of respondents in each treatment group increased dose-dependently (34%, 37% and 50% for the 35 [mu]g/h, 52.5 [mu]g/h and 70 [mu]g/h groups, respectively). However, because of a high response rate in the placebo group (31%), these response rates failed to reach statistical significance (p = 0.374). Twenty percent less patients in the placebo group reported good to complete pain relief while the proportion reporting moderate to very severe pain increased by 14%. In contrast, relative numbers of patients in the active treatment groups reporting good to complete pain relief increased by 5-13%, while the proportion reporting moderate to very severe pain fell by 3-14%. The duration of sleep uninterrupted by pain was shorter in the placebo than in the active treatment groups. The incidence of adverse events was 23%. Most local adverse events were mild to moderate erythema or pruritus.

Burch, et al. (2007) A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis. One thousand twenty-eight (1,028) patients with pain due to osteoarthritis (OA) of the knee were enrolled in this multicenter, randomized, double-blind, parallel study designed to assess the analgesic efficacy of Tramadol Contramid OAD compared to placebo. An open-label phase was followed by a double-blind phase, in which a total of 646 patients were randomized to double-blind treatment with placebo or Tramadol Contramid OAD. Patients were titrated to their optimal dose (200mg or 300 mg), which was maintained for 12 weeks. An absolute mean reduction of 3.0+-2.1 on a Pain Intensity Numerical Rating Scale (PI-NRS) was noted in the Tramadol Contramid OAD treatment group. The difference between active and placebo groups regarding this absolute mean reduction was statistically significant (P<0.001) throughout the study. The responder analysis demonstrated that a significantly greater percentage of patients in the active treatment arm achieved a reduction of ≥1 and ≥2 points on the PI-NRS score by the end of the study (P=0.035). A significantly greater percentage of respondents in the Tramadol Contramid OAD group indicated improvement on both the Patient and Physician Global Impressions of Change (P=0.0002). Both the 200mg and 300 mg doses contributed to the overall superiority of Tramadol Contramid OAD. The most frequent adverse events were consistent with the known side effects of tramadol and were generally mild to moderate in intensity. These results confirm that Tramadol Contramid OAD given...
Because a variety of mechanisms may generate pain in neuropathic pain syndromes, conventional clinical trial methods may fail to identify some potentially useful drugs; a drug affecting just a single mechanism may work in too few patients to yield a statistically significant result for the trial. To test a previous clinical observation that approximately one-quarter of patients with painful diabetic neuropathy appear responsive to clonidine, we conducted a formal clinical trial of transdermal clonidine in painful diabetic neuropathy patients using a 2-stage enriched enrollment design. In the first stage (study I), 41 patients with painful diabetic neuropathy completed a randomized, 3-period crossover comparison of transdermal clonidine (titrated from 0.1 to 0.3 mg/day) to placebo patches. Twelve apparent responders from study I were entered into the ‘enriched enrollment’ second stage (study II), consisting of an additional 4 double-blind, randomized, 1-week treatment periods with transdermal clonidine and placebo. Study I showed that in the overall group of 41 patients, pain intensity differed little during clonidine and placebo treatment. In study II, however, the 12 apparent responders from study I had 20% less pain with clonidine than placebo (95% confidence interval (CI): 4-35% pain reduction; P = 0.015), confirming that their pain was responsive to clonidine. None of the 3 consistent clonidine responders who were tested with the alpha-adrenergic blocker phentolamine had relief of pain, suggesting that clonidine’s pain relief is not mediated by a decrease in sympathetic outflow. A post-hoc analysis of many variables suggested that patients who described their pain as sharp and shooting may have a greater likelihood of responding to clonidine. (ABSTRACT TRUNCATED AT 250 WORDS)

OBJECTIVE: To compare the efficacy and safety of controlled release oxycodone given every 12 h around the clock with immediate release oxycodone-acetaminophen (APAP) given 4 times daily for osteoarthritis (OA) pain. METHODS: Adults (n=167) with moderate to severe OA pain despite regular use of nonsteroidal antiinflammatory drugs (NSAID) entered open label titration for 30 days with immediate release oxycodone qid; 107 qualified for randomization to double blind, parallel group treatment for 30 days with placebo, controlled release oxycodone, or immediate release oxycodone-APAP. RESULTS: Following titration with immediate release oxycodone, mean (SE) pain intensity (0, none to 3, severe) decreased from 2.44 (0.04) to 1.38 (0.05) (p=0.0001), and quality of sleep (1, very poor; 5, excellent) improved from 2.58 (0.08) to 3.57 (0.07) (p=0.0001). Mean dose was about 40 mg/day. Pain intensity and quality of sleep were significantly improved in both active groups compared with the placebo group (p< or =0.05) during the double blind trial. Pain intensity and sleep scores were comparable in both active groups during double blind treatment. Nausea (p=0.03) and dry mouth (p=0.09) were less common with controlled release oxycodone than immediate release oxycodone-APAP. CONCLUSION: Controlled release oxycodone q12h and immediate release oxycodone-APAP qid, added to NSAID, were superior to placebo for reducing OA pain and improving quality of sleep. The active treatments provided comparable pain control and sleep quality. Controlled release oxycodone was associated with a lower incidence of some side effects.

OBJECTIVE: Low-dose transdermal opioids offer a new therapeutic option for osteoarthritis (OA). This study compared symptom relief obtained with buprenorphine patches plus oral paracetamol with that obtained with an oral codeine-paracetamol combination tablet (co-codamol) in older adults with OA. METHOD: Two hundred and twenty people (aged >=60 years) with OA hip and/or knee pain were randomised to treatment with 7-day buprenorphine patches plus oral paracetamol (5-25 ug/h buprenorphine patches plus 1000 mg oral paracetamol q.i.d. (4 times daily); n=110) or co-codamol tablets (two 8/500-two 30/500 mg tablets q.i.d.; n=110). They entered a titration period of up to 10 weeks, during which their dose of study medication was adjusted until they reached optimum pain control. Patients who achieved optimum pain control entered a 12-week assessment period. The primary outcome was average daily pain scores recorded using the box scale-11 (BS-11) pain scale. RESULTS: Both treatments significantly reduced patient pain scores. The estimated treatment difference [95% confidence interval (CI)] was -0.02 (-0.64, 0.60) for the per protocol (PP) population. The results were similar for the full analysis population. Patients receiving 7-day buprenorphine patches plus oral paracetamol needed

This double-blind clinical trial compares droxicam, a new non-steroidal anti-inflammatory agent and the reference compound diclofenac sodium. After a 7 day placebo run-in period, 80 patients with gonarthrosis and coxarthrosis were randomized to receive 20mg/day of droxicam and 150mg/day of diclofenac for 6 weeks. Evaluations were carried out at weeks 0 (placebo run-in), 2, 3, and 6. Both drugs showed statistically significant improvements in all clinical measurements (index of severity, pain intensity, morning stiffness, maximal forced flexion and extension of the knee) after 6 weeks of treatment. Investigator's and patient's opinions were consistent with these results. The consumption of paracetamol was significantly lower amongst patients treated with droxicam. Withdrawals due to lack of therapeutic efficacy did not occur. A lower incidence of side effects, mostly upper gastrointestinal symptoms, was noticed amongst droxicam-treated patients. However, two patients in the droxicam group were withdrawn at week 3 and two days after week 6 because of epigastric pain and nausea, and cutaneous rash, respectively. Both study drugs are of benefit in reducing pain and improving joint motion and function in patients with coxarthrosis and gonarthrosis.


OBJECTIVE: Fibromyalgia syndrome (FMS) is characterized by widespread musculoskeletal pain and lowered pain threshold. Other prominent symptoms include disordered sleep and fatigue. FMS affects an estimated 2% of the population, predominantly women. This trial was designed to evaluate the efficacy and safety of pregabalin, a novel alpha(2)-delta ligand, for treatment of symptoms associated with FMS. METHODS: This multicenter, double-blind, 8-week, randomized clinical trial compared the effects of placebo with those of 150, 300, and 450 mg/day pregabalin on pain, sleep, fatigue, and health-related quality of life in 529 patients with FMS. The primary outcome variable was the comparison of end point mean pain scores, derived from daily diary ratings of pain intensity, between each of the pregabalin treatment groups and the placebo group. RESULTS: Pregabalin at 450 mg/day significantly reduced the average severity of pain in the primary analysis compared with placebo (-0.93 on a 0-10 scale) (P = 0.001), and significantly more patients in this group had >50% improvement in pain at the end point (29%, versus 13% in the placebo group; P = 0.003). Pregabalin at 300 and 450 mg/day was associated with significant improvements in sleep quality, fatigue, and global measures of change. Pregabalin at 450 mg/day improved several domains of health-related quality of life. Dizziness and somnolence were the most frequent adverse events. Rates of discontinuation due to adverse events were similar across all 4 treatment groups. CONCLUSION: Pregabalin at 450 mg/day was efficacious for the treatment of FMS, reducing symptoms of pain, disturbed sleep, and fatigue compared with placebo. Pregabalin was well tolerated and improved global measures and health-related quality of life.


OBJECTIVE: To evaluate the efficacy and safety of pregabalin in the treatment of postherpetic neuralgia (PHN). METHODS: The authors conducted a multicenter, parallel-group, double-blind, placebo-controlled, 8-week, randomized clinical trial in PHN, defined as pain for 3 or more months following herpes zoster rash healing. Patients (n = 173) were randomized to treatment with pregabalin or placebo. Patients randomized to pregabalin received either 600 mg/day (creatinine clearance > 60

1 Identified as a ‘partial enriched enrolment’ trial by Struabe, Derry, McQuay and Moore (2008)
2 Identified as a ‘partial enriched enrolment’ trial by Struabe, Derry, McQuay and Moore (2008)
| Friedman, Klutzaritz and Webster (2011) | OBJECTIVE: To evaluate the efficacy and safety of an encapsulated, highly viscous formulation of extended-release oxycodone designed to resist common physical manipulation and chemical challenges (Remoxy; King Pharmaceuticals, Inc., Bristol, TV, which was acquired by Pfizer Inc. in March 2011). DESIGN: An enriched enrollment randomized withdrawal trial design was used whereby patients entered a double-blind, multicenter, placebo-controlled trial after completing an open-label titration phase. SETTING: Sixty-one US clinics. PATIENTS: All patients (40-75 years) had experienced moderate to severe chronic osteoarthritic pain in the hip or knee for > or = 3 months. INTERVENTIONS: During 2 weeks of open-label treatment (N = 558), patients were titrated from Remoxy 5 mg twice daily (bid) to 20 mg bid. Patients who tolerated the drug were randomly assigned to Remoxy or placebo bid for 12 weeks. Dose titration was permitted during weeks 1-4 (range, 10-80 mg/d) and fixed thereafter. MAIN OUTCOME MEASURES: The area under the curve (AUC) for change in pain intensity (PI) scores from prerandomization to the end of the 12-week period was the primary endpoint. Patient assessment of quality of analgesia, global assessment of study medication, quality of life, and safety were also evaluated. RESULTS: The mean AUC for change in PI score was significantly greater for Remoxy than for placebo (p = 0.007). Patients receiving Remoxy reported significantly better scores on quality of analgesia (p = 0.004) and global assessment of study medication (p = 0.007) when compared with patients receiving placebo. Remoxy had a safety profile consistent with other opioids. CONCLUSIONS: Remoxy significantly improved analgesia among patients with moderate to severe chronic osteoarthritic pain with an adverse event profile similar to other opioids. |

| Galer, Rowbotham, Perander and Friedman (1999). | This study compared the efficacy of topical lidocaine patches versus vehicle (placebo) patches applied directly to the painful skin of subjects with postherpetic neuralgia (PHN) utilizing an 'enriched enrollment' study design. All subjects had been successfully treated with topical lidocaine patches on a regular basis for at least 1 month prior to study enrollment. Subjects were enrolled in a randomized, two-treatment period, vehicle-controlled, cross-over study. The primary efficacy variable was 'time to exit'; subjects were allowed to exit either treatment period if their pain relief score decreased by 2 or more categories on a 6-item Pain Relief Scale for any 2 consecutive days. The median time to exit with the lidocaine patch phase was greater than 14 days, whereas the vehicle patch exit time was 3.8 days (P < 0.001). At study completion, 25/32 (78.1%) of subjects preferred the lidocaine patch treatment phase as compared with 3/32 (9.4%) the placebo patch phase (P < 0.001). No statistical difference was noted between the active and placebo treatments with regards to side effects. Thus, topical lidocaine patch provides significantly more pain relief for PHN than does a vehicle patch. Topical lidocaine patch is a novel therapy for PHN that is effective, does not cause systemic side effects, and is simple to use. |

<p>| Gammaitoni, et al. (2013) Predicting response to | OBJECTIVE: The aim of this study is to assess the Pain Quality Assessment Scale (PQAS) in predicting pregabalin in peripheral neuropathic pain (NP). STUDY DESIGN: Post hoc analysis of a double-blind, placebo-controlled, enriched |</p>
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<td>OBJECTIVES: To date, published neuropathic pain randomized controlled trials of pregabalin have involved primarily diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (PHN). This multicenter trial evaluated pregabalin in a broader range of neuropathic pain etiologies. METHODS: In this enriched enrollment randomized withdrawal trial, 256 patients received single blind, flexible dose pregabalin for 4 weeks; stable concomitant analgesics were allowed. One hundred sixty-five (65%) had a &gt;=30% pain improvement and 157 were randomized and treated, double blind, to either continue pregabalin (n=80) or to receive placebo (n=77) for 5 weeks. RESULTS: Of the single blind responders randomized, 81% on placebo and 86% on pregabalin completed the double-blind phase. At the double-blind endpoint, mean (SD) pain scores were 2.9 (1.9) in the pregabalin group and 3.5 (1.7) in the placebo group (P=0.002). These modest yet significant pregabalin-placebo differences were observed within each of the subgroups of patients with a diagnosis of either DPN or PHN (P=0.03), and with other diagnoses (P=0.02). Significant differences were also observed in sleep interference, Hospital Anxiety and Depression Scale Anxiety and Depression subscales, and other secondary measures. In total, 28 out of 80 (35.0%) in the pregabalin group and 28 out of 77 (36.4%) in the placebo group had either a meaningful increase in pain or discontinued the double-blind phase. Adverse events were consistent with the known tolerability profile of pregabalin and led to discontinuation of 9 during the single-blind phase, and 5 and 2 patients from the placebo and pregabalin groups, respectively. DISCUSSION: These results support previous evidence of pregabalin efficacy but further demonstrate efficacy and tolerability in a broader range of peripheral neuropathic pain conditions beyond just DPN and PHN.</td>
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| Grach, Massalha, Pud, Adler and Eisenberg (2004)                      | Can co-administration of oxycodone and morphine produce analgesic synergy in humans? An experimental cold pain study. Aims: The coadministration of subantinociceptive doses of oxycodone with morphine has recently been shown to result in a synergistic antinociceptive effect in rats. The present study was aimed to investigate the possibility that coadministration of morphine and oxycodone can produce a similar synergistic effect in humans exposed to an experimental model of cold pressor test (CPT). Methods: The enriched enrolment design was used to exclude 'stoic' and 'placebo responders' in a single-blind fashion. 'Nonstoic', placebo 'nonresponder' female volunteers (n = 30) were randomly assigned to receive 0.5 mg kg<sup>-1</sup> oral morphine sulphate, 0.5 mg kg<sup>-1</sup> oral oxycodone hydrochloride, and the combination of 0.25 mg kg<sup>-1</sup> morphine sulphate with 0.25 mg kg<sup>-1</sup> oxycodone hydrochloride, 1 week apart from each other, in a double-blind crossover design. Latency to pain onset (threshold), pain intensity (VAS), and pain tolerance (time until removal of the hand from the water) were measured six times over a 3-h period, subsequent to the administration of each medication, and were used to assess their antinociceptive effect. Results: The combination produced a significantly higher effect on latency to pain onset than that of morphine alone [difference in mean postbaseline value 2.2; 95% confidence interval (CI) 0.48, 3.9; P = 0.01] but the effect was...
nonsignificantly smaller that that of oxycodone alone. Similarly, the effect of the combination on pain tolerance was significantly larger than that of morphine alone (combination difference 8.4; 95% CI 2.5, 14.3; P = 0.007), whereas oxycodone alone caused a nonsignificantly larger effect than that of the combination treatment. Comparisons of pain magnitude failed to show any significant differences between the three treatments. Conclusions: These results indicate that at the doses tested, morphine and oxycodone do not produce synergistic antinociceptive effects in healthy humans exposed to the CPT.

Hale, Khan, Kutch and Li (2010) Once-daily OROS hydromorphone ER compared with placebo in opioid-tolerant patients with chronic low back pain. OBJECTIVE: This multicenter, double-blind, placebo-controlled study using a randomized withdrawal design evaluated the efficacy and safety of once-daily OROS hydromorphone ER in the treatment of opioid-tolerant patients with chronic moderate-to-severe low back pain (LBP). MAIN OUTCOME MEASURES: The primary efficacy assessment was mean change in pain intensity based on patient diary Numeric Rating Scale (NRS) scores from baseline to final visit of the 12-week double-blind phase. Secondary endpoints included mean change from baseline to each visit in patient diary NRS scores; and office NRS scores; time to treatment failure; Patient Global Assessment; rescue medication use; and Roland Morris Disability Questionnaire total scores. CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov NCT00549042. RESULTS: For the primary outcome measure, hydromorphone ER significantly reduced pain intensity compared to placebo (p < 0.001). Median diary [corrected] hydromorphone ER (0.2 units) compared to placebo (1.6 units). A significantly higher proportion of hydromorphone ER (60.6%) vs. placebo (42.9%) patients had at least a 30% reduction in diary NRS pain score from screening to endpoint (p < 0.01). Hydromorphone ER was well-tolerated, although 60 (13%) discontinued during the enrichment phase for adverse events and more active (9, 6.7%) than placebo (4, 3.0%) patients discontinued treatment for adverse events during the randomized phase. CONCLUSIONS: These results provide evidence for the efficacy and safety of hydromorphone ER in opioid-tolerant patients with chronic moderate-to-severe LBP. Potential limitations include the shortened dose-conversion/titration phase, limiting the daily allowable dose of hydromorphone ER to 64 mg, and the allowance of limited rescue medication throughout the entire double-blind phase. Other trial design elements such as the use of an enrichment phase and the inclusion of only opioid tolerant patients may limit the generalizability of these results.

Hale, Ahdieh, Ma and Rauck (2007) Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. Opioid-experienced (N = 250) patients with chronic, moderate to severe low back pain (LBP) were converted from their prestudy opioid(s) to an approximately equianalgesic dose of OPANA ER (oxymorphone extended release). Patients continued slow titration, with 56% stabilized within 1 month to a dose of OPANA ER that reduced average pain to <40 mm on a visual analog scale with good tolerability. Stabilized patients (n = 143) were randomized to placebo or their stabilized dose of OPANA ER every 12 hours for a 12-week double-blind period. Pain intensity increased significantly more for patients randomized to placebo than for patients who continued their stabilized dose of OPANA ER; the increase from baseline (at randomization) to final visit was 31.6 mm for placebo versus 8.7 mm with OPANA ER (P < .0001). During double-blind treatment, placebo patients were approximately 8-fold more likely than OPANA ER patients to discontinue because of lack of efficacy (P < .001). Discontinuations as a result of adverse events were similar between groups, 10% with placebo and 11% with OPANA ER. Opioid-related adverse events included constipation (6%), somnolence (3%), and nausea (3%). Fifty-seven percent of opioid-experienced patients with chronic, moderate to severe LBP achieved a stable dose of OPANA ER that was efficacious and generally well-tolerated for up to 12 weeks. PERSPECTIVE: In a 12-week, double-blind, randomized, placebo-controlled trial in opioid-experienced patients with chronic, moderate to severe LBP, OPANA ER provided efficacious, long-term analgesia and was generally well-tolerated. OPANA ER may provide clinicians with a new treatment option for patients experiencing suboptimal analgesic responses or poor tolerability with other opioids.

Hale, Dvergsten and Gimbel (2005). Efficacy This multicenter, randomized, double-blind, placebo- and active-controlled trial was conducted to compare the analgesic efficacy and safety of oxymorphone extended release (ER) with placebo and oxycodone controlled release (CR) in ambulatory...
and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study.

P PURPOSE: To describe the efficacy and safety of hydromorphone extended-release tablets (OROS hydromorphone ER) during dose conversion and titration.

PATIENTS AND METHODS: A total of 459 opioid-tolerant adults with chronic moderate to severe low back pain participated in an open-label, 2- to 4-week conversion/titration phase of a double-blind, placebo-controlled, randomized withdrawal trial, conducted at 70 centers in the United States. Patients were converted to one-daily OROS hydromorphone ER at 75% of the equianalgesic dose of their prior total daily opioid dose (5:1 conversion ratio), and titrated as frequently as every 3 days to a maximum dose of 64 mg/day. The primary outcome measure was change in pain intensity numeric rating scale; additional assessments included the Patient Global Assessment and the Roland-Morris Disability Questionnaire scores. Safety assessments were performed at each visit and consisted of recording and monitoring all adverse events (AEs) and serious AEs. RESULTS: Mean (standard deviation) final daily dose of OROS hydromorphone ER was 37.5 (17.8) mg. Mean (standard error of the mean [SEM]) numeric rating scale scores decreased from 6.6 (0.1) at screening to 4.3 (0.1) at the final titration visit (mean [SEM] change, -2.3 [0.1], representing a 34.8% reduction). Mean (SEM) change in Patient Global Assessment was -0.6 (0.1), and mean change (SEM) in the Roland-Morris Disability Questionnaire was -2.8 (0.3). Patients achieving a stable dose showed greater improvement than patients who discontinued during titration for each of these measures (P < 0.001). Almost 80% of patients achieving a stable dose (213/268) had a >=30% reduction in pain. Commonly reported AEs were constipation (15.4%), nausea (11.9%), somnolence (8.7%), headache (7.8%), and vomiting (6.5%); 13.0% discontinued from the study due to AEs. CONCLUSION: The majority of opioid-tolerant patients with chronic low back pain were successfully converted to effective doses of OROS hydromorphone ER within 2 to 4 weeks.


The objective of this study was to evaluate how enrichment for responders increases assay sensitivity in an enriched enrollment randomized withdrawal (EERW) proof-of-concept (POC) study in neuropathic pain. Adults with moderate to severe peripheral neuropathic pain entered a 3- to 4-day screening period, followed by a 12-day titration to the highest tolerated dose that provided pain control (pregabalin 50-200mg t.i.d.), and then a 9-day maintenance period. Subjects were stratified as primary responders (30%), secondary responders (10% to <30%), or nonresponders (<10%) based on decrease in pain intensity and were randomized to placebo or pregabalin during the randomized withdrawal period. The primary endpoint was mean of average 24-h pain intensity during the last 3days of treatment period relative to the 3days before randomization. Time-to-efficacy-failure was the key secondary endpoint. Other features included not requiring discontinuation of current analgesic therapies and blinding investigators to study design elements that could contribute to non-treatment-related responses. Effect size (ES) (mean treatment difference/SD) was used to measure assay sensitivity. Pregabalin-treated subjects (n=52) had significantly less pain than those receiving placebo (n=51) (P.003). Effect size of the primary endpoint
was 0.72 for primary responders and decreased if secondary and nonresponders were included in the analysis. The highest ES (1.68) was demonstrated for the endpoint time-to-efficacy-failure seen in primary responders with painful diabetic neuropathy. The EERW trial design using time-to-efficacy-failure may provide a sensitive and efficient method to conduct POC studies of novel therapies in patients with neuropathic pain. Enriching a study population with patients who have achieved a 30% decrease in pain with an investigational therapy, and using time-to-efficacy-failure during the randomized withdrawal phase as the primary endpoint, can be used for a proof-of-concept study to optimize assay sensitivity and efficiently determine the analgesic potential of a new treatment for neuropathic pain. Copyright 2010 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

**Ho, et al. (2009) Efficient assessment of neuropathic pain drugs in patients with small fiber sensory neuropathies.** We sought to develop an enrichment crossover study design that would allow us to efficiently evaluate and compare promising candidate neuropathic pain drugs. We evaluated the efficacy of gabapentin or tramadol vs. active placebo (diphenhydramine) in subjects with biopsy-proven painful idiopathic small fiber neuropathy (SFN) who were self-reported gabapentin responders. Eligible subjects entered two single blind run-in phases. In the first phase (Period A), subjects were treated with single blinded gabapentin at their prestudy dose followed by a second run-in phase (Period B) in which they were treated with diphenhydramine active placebo. Subjects with >or=3 pain and a >or=30% increase in pain intensity in Period B compared to Period A were then randomized to a double-blind three period cross over trial of gabapentin at pre study dosage, tramadol 50mg QID and diphenhydramine 50mgqs. Of the 59 subjects enrolled, 41 subjects were excluded: Twenty-three had an insufficient rise in pain intensity in Period B; eight had skin biopsies that did not confirm SFN. Eighteen subjects were randomized into the double-blind, crossover phase. There was a significant treatment effect of gabapentin vs. diphenhydramine (p=0.001) and tramadol vs. diphenhydramine (p=0.018) by the before-bed daily pain score averaged over the final 7 days of each treatment period. We conclude that gabapentin and tramadol were effective in the treatment of painful SFN and that this experimental enrichment paradigm is attractive to screen potential neuropathic pain compounds for efficacy in proof-of-concept studies.

**Ho, et al. (2012) Efficacy and tolerability of rizatriptan in pediatric migraineurs: Results from a randomized, double-blind, placebo-controlled trial using a novel adaptive enrichment design.** Background: Treatment options for children and adolescents with migraine are limited. This study evaluated rizatriptan for the acute treatment of migraine in children and adolescents. Methods: Randomized, double-blind, placebo-controlled, parallel-group trial in migraineurs 6-17 years old with unsatisfactory response to nonsteroidal anti-inflammatory drugs or acetaminophen/paracetamol. The trial included a double-blind run-in with weight-based rizatriptan dosing (5 mg for <40 kg, 10 mg for >40 kg). In the Stage 1 run-in, patients were randomized in a ratio of 20:1 placebo:rizatriptan and were instructed to treat within 30 minutes of a moderate/severe migraine. Patients with mild/no pain after 15 minutes of treatment (responders) took no further study medication, whereas patients with moderate/severe pain (non-responders) proceeded to take study medication in Stage 2. Non-responders who received placebo in Stage 1 were randomized 1:1 to rizatriptan:placebo, whereas non-responders who received rizatriptan in Stage 1 were allocated to placebo in Stage 2. The primary efficacy endpoint was pain freedom at 2 hours after Stage 2 dose in 12-17-year-olds. Results: A higher proportion of 12-17-year-olds on rizatriptan had pain freedom at 2 hours compared with those on placebo: 87/284 (30.6%) versus 63/286 (22.0%), odds ratio = 1.55 [95% CI: 1.06 to 2.26], p = 0.025. Adverse events within 14 days of dose in 12-17-year-olds were similar for rizatriptan and placebo. The pattern of findings was similar in 6-17-year-olds. Conclusion: Rizatriptan demonstrated a statistically significant improvement over placebo in eliminating pain and was generally well tolerated in migraineurs aged 12-17 and 6-17 years. 2012 International Headache Society.

**Irving, et al. (2009) Efficacy and tolerability of gastric-retentive gabapentin for the treatment of**

OBJECTIVE: To determine the efficacy and safety of a gastric-retentive, extended-release gabapentin (gabapentin ER) taken once or twice daily for treatment of postherpetic neuralgia. METHODS: Using an enrichment design, a randomized, double-blind, placebo-controlled study was conducted in 158 patients who had experienced pain for at least 3 months after healing of acute herpes zoster skin rash and who had a baseline average daily pain (ADP) score of > or =4 on a 0 to 10.
postherpetic neuralgia: results of a double-blind, randomized, placebo-controlled clinical trial.

Numerical Rating Scale. Patients received gabapentin ER either once daily (1800 mg PM) or twice daily (600 mg AM, 1200 mg PM) or placebo for 4 weeks. Efficacy measures included changes from baseline to end point in ADP score and average daily sleep interference score. RESULTS: Mean (SEM) changes for ADP score were -1.93 (0.28), -2.24 (0.29), and -1.29 (0.29) in the gabapentin ER once daily, twice daily, and placebo groups, respectively (P=0.089 and 0.014 for gabapentin ER once daily and twice daily, respectively, vs. placebo), with 25.5%, 28.8%, and 11.8% of patients, respectively, reporting > or =50% decrease from baseline in ADP score. Mean (SEM) changes in sleep interference scores were -1.94 (0.30), -2.28 (0.30), and -1.16 (0.30), respectively (P=0.048 and 0.006 for gabapentin ER once daily and twice daily, respectively, vs. placebo). Common adverse events in the gabapentin ER once daily, twice daily, and placebo groups, respectively, were dizziness (22.2%, 11.3%, and 9.8%) and somnolence (9.3%, 7.5%, and 7.8%). CONCLUSIONS: Gabapentin ER administered twice daily is effective and safe for the treatment of pain associated with postherpetic neuralgia.

Jamison, et al. (2013) Relationship of negative affect and outcome of an opioid therapy trial among low back pain patients.

OBJECTIVES: Patients with chronic noncancer pain frequently report symptoms of depression and anxiety (negative affect), which are associated with higher ratings of pain intensity and a greater likelihood of being prescribed chronic opioid therapy. The purpose of this secondary analysis was to test the hypothesis that initial levels of negative affect can predict treatment-related outcomes in a double-blind, placebo-controlled study of extended-release (ER) hydromorphone among opioid-tolerant patients with chronic low back pain. METHODS: Four hundred fifty-nine (N = 459) patients participated in the titration/conversion phase of a multicenter study, of which 268 were randomized to receive once-daily hydromorphone or placebo. All patients completed the Hospital Anxiety and Depression Scale (HADS) at baseline and were divided evenly into Low (N = 157), Moderate (N = 155), and High (N = 147) negative affect groups based on their scores. Group differences in numerical pain intensity measures at home and in the clinic, Roland-Morris Disability ratings, and measures of symptoms from the Subjective Opiate Withdrawal Scale (SOWS) throughout the trial were analyzed. RESULTS: Two hundred sixty-eight of the initial 459 subjects who entered the 2 to 4-week titration/conversion phase (pretreatment) were successfully randomized to either placebo or ER hydromorphone; a total of 110 patients then completed this double-blind phase of the study. Those in the Moderate and High negative affect groups tended to drop out more often during the titration/conversion phase because of the adverse effects or lack of efficacy of their prescribed opioid than those in the Low negative mood group (P < 0.05). Overall, those patients in the Moderate and High groups reported significantly higher pain intensity scores in at-home and in-clinic pain intensity ratings (P < 0.05), greater disability on the Roland-Morris Scale (P < 0.01), and more withdrawal symptoms on the SOWS (P < 0.05) than those in the Low group. Higher negative affect scores also predicted less favorable ratings of the study drug during the titration phase (P < 0.05). Interestingly, the High negative affect group showed the most improvement in pain in the placebo condition (P < 0.05). CONCLUSIONS: Negative affect is associated with diminished benefit during a trial of opioid therapy and is predictive of dropout in a controlled clinical trial. 2012 The Authors. Pain Practice 2012 World Institute of Pain.


OBJECTIVE: To identify and describe the response profile of pregabalin on the quality of pain associated with peripheral neuropathy. METHODS: A post hoc analysis to examine the effects of pregabalin on pain quality in patients with moderate-to-severe peripheral neuropathic pain was performed using data from an enriched enrollment randomized withdrawal proof-of-concept study. Patients rated the quality of their pain experience using the Pain Quality Assessment Scale (PQAS) at baseline, after a 12-day titration period, after a 9-day maintenance period, and after a 19-day randomized withdrawal period. Pretitration to posttitration and prewithdrawal to postwithdrawal changes in PQAS paroxysmal, surface, and deep pain scale scores were examined. RESULTS: PQAS data were available for 99 of the 104 participants who entered all phases of the study. There were significant (P<0.006, Bonferroni adjusted for multiple tests) improvements pretitration to posttitration in all 3 PQAS subscales, with a greater effect on paroxysmal and deep pain than on surface pain. During the withdrawal phase, pregabalin was significantly (P<0.006) more effective than placebo for improvements in paroxysmal and surface pain only, although the pregabalin group continued to show numerical improvement in deep pain relative to
Landau, et al. (2007) Buprenorphine transdermal delivery system in adults with noncancer-related pain who required opioid analgesics. METHODS: This was a multicenter, double-blind, parallel-group study in adult subjects (age >/=18 years) with at least a 2-month history of noncancer-related pain for which they received oral opioid combination agents. The study employed a maintenance-of-analgesia, or

Katz, et al. (2007) A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naïve patients with chronic low back pain. OBJECTIVE: To assess the efficacy and tolerability of oxymorphone extended release (OPANA ER) in opioid-naïve patients with moderate to severe chronic low back pain (CLBP). DESIGN AND METHODS: Patients >/=18 years of age were titrated with oxymorphone ER (5- to 10-mg increments every 12 h, every 3-7 days) to a well-tolerated, stabilized dose. Patients were then randomized to continue their oxymorphone ER dose or receive placebo every 12 h for 12 weeks. Oxymorphone immediate release was available every 4-6 h, as needed, for the first 4 days and twice daily thereafter. RESULTS: Sixty-three percent of patients (205/325) were titrated to a stabilized dose of oxymorphone ER, most (203/205) within 1 month. During titration, 18% discontinued from adverse events (AEs) and 1% from lack of efficacy. For patients completing titration, average pain intensity decreased from 69.4 mm at screening to 22.7 mm (p < 0.0001). After randomization, 68% of oxymorphone ER and 47% of placebo patients completed 12 weeks of double-blind treatment. Approximately 8% of patients in each group discontinued because of AEs. Placebo patients discontinued significantly sooner from lack of efficacy than those receiving oxymorphone ER (p < 0.0001). Pain intensity increased significantly more in the placebo group (least squares [LS] mean change 26.9 +/- 2.4 [median 28.0]) than in the oxymorphone ER group (LS mean change 10.0 +/- 2.4 [median 2.0]; p < 0.0001). Oxymorphone ER was generally well tolerated without unexpected AEs. Although limitations of a randomized withdrawal study include the potential for unblinding and opioid withdrawal in placebo patients, opioid withdrawal was limited to two patients in the placebo group and one in the oxymorphone ER group. CONCLUSIONS: Stabilized doses of oxymorphone ER were generally safe and effective over a 12-week double-blind treatment period in opioid-naïve patients with CLBP.

Katz, Hale, Morris and Stauffer (2010) Morphine sulfate and naltrexone hydrochloride extended release capsules (EMBEDA; MS-sNT), which contain morphine sulfate pellets with a sequestered naltrexone core, in treating patients with chronic, moderate-to-severe osteoarthritis (hip or knee) pain. PATIENTS AND METHODS: This phase 3 study had an enriched-enrollment, randomized-withdrawal, double-blind, multicenter design. Patients (N = 547) were titrated to an effective dose of MS-sNT (20-160 mg/day). Responders (n = 344) were randomized to 12 weeks maintenance with an effective MS-sNT dose or were tapered to placebo over 2 weeks. The primary efficacy measure was the change from baseline (CFB) in diary average-pain scores (0-10 scale, Brief Pain Inventory [BPI]) from randomization to the last 7 days of the maintenance period. Secondary efficacy measures included the remaining BPI scores and Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index. Opioid withdrawal symptoms were assessed by the Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS). The study ran from January 10, 2007 through November 8, 2007. RESULTS: MS-sNT maintained pain control better than placebo (mean CFB, diary average-pain score, - 0.2 +/- 1.9 vs +/-.03 +/- 2.1; P = 0.045). Change from baseline for MS-sNT pain-diary score (worst, least, average, current) was superior during the maintenance period visits, weeks 2 to 12 (P < 0.05). WOMAC composite score CFB was superior at most visits. MS-sNT was generally well tolerated, with a typical morphine safety profile. No patient taking MS-sNT as directed experienced withdrawal symptoms. CONCLUSION: MS-sNT provided effective analgesia in patients with chronic, moderate-to-severe osteoarthritis pain, with a safety profile typical of morphine-containing products. Naltrexone sequestered in MS-sNT had no clinically relevant effect when MS-sNT was taken as directed.

Katz, Hale, Morris and Stauffer (2007) Pain in adults with transdermal Buprenorphine (2007) efficacy of assessing the placebo. DISCUSSION: Pregabalin had a greater effect on PQAS-assessed paroxysmal pain than on surface or deep pain in patients with peripheral neuropathy. The findings corroborate previous research demonstrating differential effects of analgesic drugs across pain qualities, further emphasizing the need to assess individual pain qualities in addition to overall pain intensity.
Central neuropathic pain (CNP) occurs in many multiple sclerosis (MS) patients. The provision of adequate pain relief to these patients can be very difficult. Here we report the first phase III placebo-controlled study of the efficacy of the endocannabinoid system modulator delta-9-tetrahydrocannabinol (THC)/cannabinoid (CBD) oromucosal spray (USAN name, nabiximols; Sativex, GW Pharmaceuticals, Salisbury, Wiltshire, UK), to alleviate CNP. Patients who had failed to gain adequate analgesia from existing medication were treated with THC/CBD spray or placebo as an add-on treatment, in a double-blind manner, for 14 weeks to investigate the efficacy of the medication in MS-induced neuropathic pain. This parallel-group phase of the study was then followed by an 18-week randomized-withdrawal study (14-week open-label treatment period plus a double-blind 4-week randomized-withdrawal phase) to investigate time to treatment failure and show maintenance of efficacy. A total of 339 patients were randomized to phase A (167 received THC/CBD spray and 172 received placebo). Of those who completed phase A, 58 entered the randomized-withdrawal phase. The primary endpoint of responder analysis at the 30% level at week 14 of phase A of the study was not met, with 50% of patients on THC/CBD spray classed as responders at the 30% level compared to 45% of patients on placebo (p = 0.234). However, an interim analysis at week 10 showed a statistically significant treatment difference in favor of THC/CBD spray at this time point (p = 0.046). During the randomized-withdrawal phase, the primary endpoint of time to treatment failure was statistically significant in favor of THC/CBD spray, with 57% of
patients receiving placebo failing treatment versus 24% of patients from the THC/CBD spray group (p = 0.04). The mean change from baseline in Pain Numerical Rating Scale (NRS) (p = 0.028) and sleep quality NRS (p = 0.015) scores, both secondary endpoints in phase B, were also statistically significant compared to placebo, with estimated treatment differences of -0.79 and 0.99 points, respectively, in favor of THC/CBD spray treatment. The results of the current investigation were equivocal, with conflicting findings in the two phases of the study. While there were a large proportion of responders to THC/CBD spray treatment during the phase A double-blind period, the primary endpoint was not met due to a similarly large number of placebo responders. In contrast, there was a marked effect in phase B of the study, with an increased time to treatment failure in the THC/CBD spray group compared to placebo. These findings suggest that further studies are required to explore the full potential of THC/CBD spray in these patients.

**Lynch, Clark and Poole (2004).**

Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial.

OBJECTIVE: Pregabalin, an alpha2-delta ligand with analgesic, anxiolytic, and anticonvulsant activity, has been evaluated for treatment of neuropathic pain. The authors assessed the efficacy and tolerability of pregabalin (75, 300, 600 mg/day) vs placebo in patients with diabetic peripheral neuropathy (DPN). METHODS: Patients with a 1- to 5-year history of DPN and average weekly pain score of > or = 4 on an 11-point numeric pain-rating scale were enrolled in a 5-week, double-blind, multicenter, placebo-controlled study. Patients (n = 338) were randomized to receive one of three doses of pregabalin or placebo TID. Pregabalin 600 mg/day was titrated over 6 days; lower doses were initiated on day 1. RESULTS: Patients in the 300- and 600-mg/day pregabalin groups showed improvements in endpoint mean pain score (primary efficacy measure) vs placebo (p = 0.0001). Improvements were also seen in weekly pain score, sleep interference score, patient global impression of change, clinical global impression of change, SF-McGill Pain Questionnaire, and multiple domains of the SF-36 Health Survey. Improvements in pain and sleep were seen as early as week 1 and were sustained throughout the 5 weeks. Responders (patients with > or =50% reduction in pain compared to baseline) were 46% (300 mg/day), 48% (600 mg/day), and 18% (placebo). Pregabalin was well tolerated with a low discontinuation rate. The most common adverse events were dizziness and somnolence. CONCLUSIONS: In patients with diabetic peripheral neuropathy, pregabalin demonstrated early and sustained improvement in pain and a beneficial effect on sleep, which were confirmed by positive patient global impression. Pregabalin was well tolerated at all doses.

**Lesser, Sharma, LaMoreaux and Poole (2004).**

Adenosine analogs produce analgesic actions in nociceptive paradigms and alleviate manifestations of neuropathic pain in nerve injury models in rodents. In humans, previous work indicates an analgesic effect for adenosine administered intravenously in postoperative and neuropathic pain. In this double blind placebo controlled crossover trial, we used an enriched enrolment design to determine the effects of intravenous adenosine (50 microg/kg/min over 60min) on neuropathic pain. In Phase 1 of the trial, adenosine was administered in an open label manner, while in Phase 2 adenosine was administered in a double blind placebo controlled manner to 23 adenosine responders who had experienced a 30% or greater response in the open trial. Outcome measures included the McGill pain questionnaire (MPQ), which generates a pain rating index (PRI), and contains a visual analog scale (VAS) of pain intensity, the neuropathy pain scale (NPS), and a VAS for pain relief. Subjects also graded the degree of allodynia and hyperalgesia using a VAS. Adenosine led to a significant reduction in spontaneous pain according to the MPQ-PRI, the MPQ-VAS and the VAS for pain relief. The NPS showed a pattern similar to the MPQ-PRI, with statistically significant reductions in scales 1 (intensity), 3 (hot), 6 (sensitive), 7 (itchy) and 9 (unpleasant). Adenosine also led to a significant reduction in pinprick hyperalgesia, but not in allodynia. Three patients from Phase 1 of the trial experienced long term resolution of their pain following intravenous adenosine (5,16,25 months). The results of this study support previous reports that indicate intravenous adenosine alleviates neuropathic pain and hyperalgesia.

**Matsumoto, et al. (2002).**

OBJECTIVE: To evaluate the efficacy and tolerability of the highly selective cyclooxygenase-2 (COX-2) inhibitor etoricoxib for the treatment of rheumatoid arthritis.

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3 Identified as a ‘partial enriched enrolment’ trial by Struabe, Derry, McQuay and Moore (2008)
randomized, controlled, clinical trial of etoricoxib in the treatment of rheumatoid arthritis.


**OBJECTIVE:** To evaluate the influence of age, sex, and previous opioid experience on the likelihood of successfully titrating opioid-naïve and experienced patients with chronic low back pain (CLBP) to an effective and well-tolerated dose of oxymorph extended release (ER).  

**METHODS:** Post hoc analysis of open-label titration phases for opioid-naïve and experienced patients with CLBP who completed titration were randomly assigned to a 12-week double-blind study period with oxymorph ER or placebo. Oxymorph immediate release 5 mg was permitted q4-6h, as needed for rescue medication or withdrawal symptoms, for 4 days after randomization and restricted to 10 mg/d thereafter. Pain intensity (100-mm visual analog scale [VAS]; 0 = no pain to 100 = worst pain imaginable) and time to study discontinuation due to lack of efficacy were compared with stratification by age (<65 vs > or =65 years), sex, and prior opioid use. Adverse events were categorized by severity and relation to study medication. RESULTS: Of 575 patients, 348 completed titration and 347 entered the double-blind study phase. There were no significant between-group differences in demographic variables, except that the mean age in the oxymorph ER group was significantly higher (P = 0.04), and the proportion of men was significantly lower (P = 0.01). There was no significant age difference between the oxymorph ER and placebo groups stratified by age (<65 vs > or =65 years). Fewer patients aged > or =65 years versus <65 years completed titration (45.0% [36/80] vs 63.0% [312/495]; P = 0.002). The least-squares mean (SEM) differences in VAS pain scores between the oxymorph ER (n = 174) and placebo (n = 169) groups were significant at each postbaseline assessment (P < 0.001) and at study completion (12.3 [2.8] mm; P < 0.001) and was not significantly affected by age, sex, or prior opioid use. Age and sex had no significant influence on adverse events or discontinuations due to lack of efficacy. More discontinuations due to lack of efficacy occurred among patients in the placebo group (hazard ratio, 5.01; P < 0.001) and among opioid-experienced patients. The latter effect was limited to opioid-experienced patients who received placebo. The rates of discontinuation due to lack of efficacy were similar between oxymorph ER-treated opioid-naïve and opioid-experienced patients (11.4% vs 11.6%). The proportion of patients who experienced opioid-related adverse events was significantly greater in the oxymorph ER group compared with the placebo group (25.7% vs 16.3%; P = 0.03). The most frequent treatment-emergent adverse events in the oxymorph ER group were nausea (8.0%), constipation (6.3%), vomiting (4.6%), and diarrhea (4.0%); in the placebo group were nausea (5.8%), diarrhea (4.7%), and increased sweating (2.3%).  

**CONCLUSION:** In the enriched population of patients who successfully titrated to oxymorph ER, oxymorph ER was effective and generally well tolerated, independent of patients’ age, sex, or previous opioid use.


**OBJECTIVE:** This study assessed the potential effects of age, sex, and prior opioid use on the response to oxymorph extended release (ER) in patients with moderate to severe chronic low back pain. METHODS: Combined data from 2 placebo-controlled clinical trials with an enriched-enrollment, randomized-withdrawal design were analyzed. In patients aged > or =18 years with chronic low back pain, the dose of oxymorph ER was titrated to a stable, tolerable, effective dose. Patients who completed titration were randomly assigned to a 12-week double-blind study period with oxymorph ER or placebo. Oxymorph immediate release 5 mg was permitted q4-6h, as needed for rescue medication or withdrawal symptoms, for 4 days after randomization and restricted to 10 mg/d thereafter. Pain intensity (100-mm visual analog scale [VAS]; 0 = no pain to 100 = worst pain imaginable) and time to study discontinuation due to lack of efficacy were compared with stratification by age (<65 vs > or =65 years), sex, and prior opioid use. Adverse events were categorized by severity and relation to study medication. RESULTS: Of 575 patients, 348 completed titration and 347 entered the double-blind study phase. There were no significant between-group differences in demographic variables, except that the mean age in the oxymorph ER group was significantly higher (P = 0.04), and the proportion of men was significantly lower (P = 0.01). There was no significant age difference between the oxymorph ER and placebo groups stratified by age (<65 vs > or =65 years). Fewer patients aged > or =65 years versus <65 years completed titration (45.0% [36/80] vs 63.0% [312/495]; P = 0.002). The least-squares mean (SEM) differences in VAS pain scores between the oxymorph ER (n = 174) and placebo (n = 169) groups were significant at each postbaseline assessment (P < 0.001) and at study completion (12.3 [2.8] mm; P < 0.001) and was not significantly affected by age, sex, or prior opioid use. Age and sex had no significant influence on adverse events or discontinuations due to lack of efficacy. More discontinuations due to lack of efficacy occurred among patients in the placebo group (hazard ratio, 5.01; P < 0.001) and among opioid-experienced patients. The latter effect was limited to opioid-experienced patients who received placebo. The rates of discontinuation due to lack of efficacy were similar between oxymorph ER-treated opioid-naïve and opioid-experienced patients (11.4% vs 11.6%). The proportion of patients who experienced opioid-related adverse events was significantly greater in the oxymorph ER group compared with the placebo group (25.7% vs 16.3%; P = 0.03). The most frequent treatment-emergent adverse events in the oxymorph ER group were nausea (8.0%), constipation (6.3%), vomiting (4.6%), and diarrhea (4.0%); in the placebo group were nausea (5.8%), diarrhea (4.7%), and increased sweating (2.3%).  

**CONCLUSION:** In the enriched population of patients who successfully titrated to oxymorph ER, oxymorph ER was effective and generally well tolerated, independent of patients’ age, sex, or previous opioid use.
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| **acceptability of titrated oxymorphone extended release in chronic low back pain - an individual patient analysis.** | of two enriched-enrollment randomized-withdrawal phase III trials in 575 adults with moderate-to-severe CLBP. Opioid-naive patients (n = 325) initiated oxymorphone ER at 10 mg/day (5 mg q12 h). Opioid-experienced patients (n = 250) initiated at a dose equianalgesic to their previous opioid and were allowed doses of 5 mg oxymorphone immediate-release rescue medication every 4-6 h, as needed. Oxymorphone ER was gradually titrated to a dose that reduced pain to <or=40 mm on a 100 mm visual analog scale. Clinical trial registration: nct00225797, nct00226421. MAIN OUTCOME MEASURES: Number of patients reaching stabilized oxymorphone ER dose, reasons for treatment discontinuation in patients not reaching stabilized dose. RESULTS: Open-label titration was successful in 61% (348/575) of patients, and similar proportions of men (63%) and women (59%) and opioid-naive (63%) and experienced (57%) patients. Patients aged >or=65 years were less likely than patients aged <65 years to complete titration (45 vs. 63%; p = 0.002; 95% CI, -0.30 to -0.06) and more likely to discontinue owing to adverse events (40 vs. 15%; p < 0.001; 95% CI, 0.14-0.36). Oxycodone-experienced patients were less likely than hydrocodone-experienced patients to complete titration (46 vs. 62%, p = 0.03; 95% CI, -0.30 to -0.02). Among successfully titrated patients, pain decreased regardless of prior opioid therapy, sex, or age. CONCLUSIONS: Most patients with CLBP were titrated to an effective, generally well-tolerated oxymorphone ER dose. Older patients and those converted from oxycodone may require more gradual titration. A study limitation is that patients initiated oxymorphone ER to comply with protocol, whereas treatment failure typically motivates opioid initiation or switching in clinical practice. 

**BACKGROUND:** Short-acting opioids are commonly used to treat breakthrough pain (BTP) and rapid-onset formulations are being developed to improve the effectiveness of this approach. Fentanyl buccal tablet (FBT) is a new formulation of fentanyl that enhances transbuccal drug delivery via an effervescent reaction and may provide relatively rapid-onset analgesia. FBT was evaluated for BTP in opioid-treated patients with chronic low back pain—the first such study in a population with chronic noncancer pain. DESIGN: Randomized, double-blind, placebo-controlled. Patients and setting: Patients with chronic low back pain receiving long-term opioid therapy at 16 pain treatment centers in the United States. PROCEDURES: Following open-label titration to identify an effective FBT dose, patients were randomly assigned to one of three double-blind dose sequences (six doses of FBT, three placebo) to treat nine BTP episodes. Pain intensity (PI), measured on an 11-point scale (0 = no pain; 10 = worst pain), and other outcomes were assessed for 2 h after dosing. DATA ANALYSIS: The primary efficacy measure was the sum of pain intensity differences (PIDs) for the first 60 min (SPID60); secondary efficacy measures included PIDs at other time points, pain relief (PR), meaningful PR, time to meaningful PR, use of supplementary BTP medication, and self/investigator-reported adverse events. RESULTS: Of the 124 patients screened, 105 patients were enrolled, 84 identified an effective FBT dose, and 77 entered the double-blind phase. SPID60 significantly favored FBT (p < 0.0001). All secondary measures also favored FBT, with PIDs and PR showing significant differences versus placebo as early as 10 and 15 min, respectively. An improvement in PI score of > or = 33% occurred in a significantly larger proportion of FBT-treated episodes versus placebo from 15 min (20% vs. 11%, p < 0.01) through 2 h (65% vs. 28%, p < 0.0001). Patients were approximately four times more likely to require supplemental opioids for BTP episodes following administration of placebo compared with episodes treated with FBT. AEs were typical for opioids, and were mostly reported during dose titration. Limitations of this study may be related to its open-label dose-titration phase (which has the potential to compromise blinding) and the recruitment of patients from pain clinics, which could potentially yield a study population that is not representative of the general population with BTP. CONCLUSIONS: FBT was efficacious and well tolerated in the treatment of BTP in opioid-treated patients with chronic low back pain.

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4 Rice, Maton and Posterheretic Neuralgia Study Group (2001). A multicentre double blind, randomised, placebo controlled 7-week study evaluated the efficacy and safety of gabapentin 1800 or 2400 mg/day in treating posterheretic neuralgia. Three hundred and thirty-four men and women aged at least 18 years (mean 73) received gabapentin 1800 or 2400 mg daily or placebo in three divided

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4 Identified as a ‘partial enriched enrolment’ trial by Struabe, Derry, McQuay and Moore (2008)
Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study.

A randomized, double-blind, placebo-controlled, parallel-group, multicenter, 8-week trial (with subsequent open-label phase) evaluated the effectiveness of pregabalin in alleviating pain associated with diabetic peripheral neuropathy (DPN). For enrollment, patients must have had at baseline: 1- to 5-year history of DPN pain; pain score >=40 mm (Short-Form McGill Pain Questionnaire [SF-MPQ] visual analogue scale); average daily pain score of >=4 (11-point numerical pain rating scale [0=no pain, 10=worst possible pain]). One hundred forty-six (146) patients were randomized to receive placebo (n=70) or pregabalin 300 mg/day (n=76). Primary efficacy measure was endpoint mean pain score from daily patient diaries (11-point numerical pain rating scale). Secondary measures included SF-MPQ scores; sleep interference scores; Patient and Clinical Global Impression of Change (PGIC and CGIC); Short Form-36 (SF-36) Health Survey scores; and Profile of Mood States (POMS) scores. Safety assessment included incidence and intensity of adverse events, physical and neurological examinations, and laboratory evaluations. Pregabalin produced significant improvements versus placebo for mean pain scores (P<0.0001); mean sleep interference scores (P<0.0001); total SF-MPQ score (P<0.01); SF-36 Bodily Pain subscale (P<0.03); PGIC (P=0.001); and Total Mood Disturbance and Tension Anxiety components of POMS (P<0.03). Pain relief and improved sleep began during week 1 and remained significant throughout the study (P<0.01). Pregabalin was well tolerated despite a greater incidence of dizziness and somnolence than placebo. Most adverse events were mild to moderate and did not result in withdrawal. Pregabalin was safe and effective in decreasing pain associated with DPN, and also improved mood, sleep disturbance, and quality of life. 2004 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.


OBJECTIVE: To evaluate the efficacy of tramadol as adjunctive therapy in patients with musculoskeletal pain attributed to osteoarthritis (OA) who experienced breakthrough pain while taking a nonsteroidal antiinflammatory drug (NSAID).

METHODS: This single center, parallel, placebo controlled, 2 phase study was conducted in adults who experienced breakthrough OA pain while undergoing stable NSAID therapy. In a 24 h open label phase, patients took 100 mg of tramadol followed by 50 mg every 6 h (total 250 mg) in addition to their daily NSAID regimen. Supplemental analgesics were prohibited. Patients who met entry criteria and were willing to continue therapy were randomized to a 13 day double blind phase of adjunctive therapy with tramadol (50-100 mg every 4-6 h as needed for pain) or placebo; NSAID therapy was continued. The primary efficacy endpoint was the time to exit from the study because of therapeutic failure (i.e., insufficient pain relief or an inability to perform activities of daily living). RESULTS: The time to exit from the study because of insufficient pain relief tended to be longer in the tramadol group (250 mg/day) compared with the placebo group (p = 0.066). At the end of the double blind phase, pain at rest was significantly less severe in tramadol treated patients (p =

5 Identified as a ‘partial enriched enrolment’ trial by Struabe, Derry, McQuay and Moore (2008)
Russell, et al. (2000) Efficacy of tramadol in treatment of pain in fibromyalgia. An outpatient, randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate the efficacy and safety of tramadol in the treatment of the pain of fibromyalgia syndrome. One hundred patients with fibromyalgia syndrome, 1990 American College of Rheumatology criteria, were enrolled into an open-label phase and treated with tramadol 50-400 mg/day. Patients who tolerated tramadol and perceived benefit were randomized to treatment with tramadol or placebo in the double-blind phase. The primary efficacy outcome measurement was the time (days) to exit from the double-blind phase because of inadequate pain relief, which was reported as the cumulative probability of discontinuing treatment because of inadequate pain relief. One hundred patients entered the open-label phase; 69% tolerated and achieved benefit with tramadol. These patients were then randomized to continue tramadol (n = 35) or convert to a placebo (n = 34) during a 6-week, double-blind treatment period. The Kaplan-Meier estimate of cumulative probability of discontinuing the double-blind period because of inadequate pain relief was significantly lower in the tramadol group compared with the placebo group (p = 0.001). Twenty (57.1%) patients in the tramadol group successfully completed the entire double-blind phase compared with nine (27%) in the placebo group (p = .015). These results support the efficacy of tramadol over a period of 6 weeks in a double-blind study for the treatment of the pain of fibromyalgia in a group of patients who had been determined to tolerate it and perceive a benefit.

Sabatowski, et al. (2004). Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. The study was designed to assess the efficacy and safety of pregabalin—a novel alpha(2)-delta ligand with analgesic, anxiolytic, and anticonvulsant activity—for treating neuropathic pain in patients with post-herpetic neuralgia (PHN). Two hundred and thirty-eight patients were randomised into this multicentre, double-blind, placebo-controlled trial to receive 150 (n=81), 300 mg/day (n=76) pregabalin, or placebo (n=81) for 8 weeks. Among the exclusion criteria was failure to respond to previous treatment for PHN with gabapentin at doses > or =1200 mg/day. Endpoint mean pain scores were significantly reduced in patients receiving 150 or 300 mg/day pregabalin compared with placebo. Efficacy was observed as early as week 1 and was maintained throughout the study. Significantly more patients in both pregabalin groups (150 mg, 26%; 300 mg, 28%) were responders (> or =50% decrease in mean pain score from baseline to endpoint) than in the placebo group (10%). Additionally, by week 1 and for the study’s duration, 150 and 300 mg/day pregabalin significantly reduced weekly mean sleep interference scores. More pregabalin-treated patients than placebo-treated patients reported that they were ‘much improved’ or ‘very much improved’. Health-related quality-of-life (HRQoL) measurements using the SF-36 Health Survey demonstrated improvement in the mental health domain for both pregabalin dosages, and bodily pain and vitality domains were improved in the 300 mg/day group. The most frequent adverse events were dizziness, somnolence, peripheral oedema, headache, and dry mouth. Pregabalin efficaciously treated the neuropathic pain of PHN. Additionally, pregabalin was associated with decreased sleep interference and significant improvements in HRQoL measures.

OBJECTIVE: To evaluate the efficacy and safety of tramadol in the treatment of chronic low back pain. METHODS: A 3 phase trial: (1) a washout/screening phase; (2) a 3 week, open label, run-in phase; and (3) a 4 week, randomized, placebo controlled, double blind treatment phase. Three hundred eighty outpatients between 21 and 79 years with chronic low back pain with no or a distant history of back surgery enrolled in the open label phase and were treated with tramadol up to 400 mg/day. At the end of the open label phase, patients who tolerated tramadol and perceived benefit from it were randomized to continue treatment with tramadol or to convert to placebo in the double blind phase. Reasons for discontinuing from the

6 Identified as a ‘partial enriched enrolment’ trial by Struabe, Derry, McQuay and Moore (2008)
OBJECTIVE: To demonstrate that in patients receiving naproxen for the pain of osteoarthritis (OA), the addition of tramadol will allow a reduction in the naproxen dosage without compromising pain relief. METHODS: This trial consisted of a 5-week open-label run-in and an 8-week double-blind phase. Patients with at least moderate pain (> or =40 mm on a 100-mm visual analog scale) of OA of the knee after a 1-week medication washout were treated with naproxen 500 mg/day for 1 week. Patients whose pain scores were reduced to <20 mm were discontinued. The remaining patients received naproxen 1,000 mg/day for 3 weeks. Tramadol 200 mg/day was added during the third week. Patients were then randomized in a double-blind manner to continue tramadol 200 mg/day or to begin placebo in addition to naproxen. Randomization was stratified based on response to naproxen 1,000 mg/day. During the double-blind phase, the naproxen dose was reduced by 250 mg every 2 weeks. The primary efficacy end point was the minimum effective naproxen dosage (MEND). The MEND was defined as 250 mg above the naproxen daily dosage at which pain relief was no longer adequate. Patients discontinuing the double-blind phase of the study for reasons other than lack of efficacy were assigned a MEND equal to the last naproxen dose received. If the effect of treatment between the responder and nonresponder groups was statistically different, the difference in the MEND was assessed separately within the groups. RESULTS: Of 236 patients randomized (mean age 61 years; 147 females), 90 were stratified as naproxen responders and 146 as naproxen nonresponders. There was a significant difference (P = 0.040) in the treatment effect between the naproxen responders and nonresponders, thus demonstrating a difference in the way responders and nonresponders react to a decrease in naproxen dosage after the addition of tramadol. Among naproxen responders, the MEND was significantly lower in patients receiving tramadol (n = 36) than in patients receiving placebo (n = 54), 221 mg versus 407 mg, respectively (P = 0.021). For the naproxen nonresponders, the mean MEND was 419 mg in the tramadol group and 396 mg in the placebo group (P = 0.706). CONCLUSION: In patients with painful OA of the knee responding to naproxen 1,000 mg/day, the addition of tramadol 200 mg/day allows a significant reduction in the dosage of naproxen without compromising pain relief.

Schnitzer, Kivitz, Lipetz, Sanders and Hee (2005) Comparison of the COX-inhibiting nitric oxide donator AZD3582 and rofecoxib in treating the signs and symptoms of Osteoarthritis of the knee

OBJECTIVE: To compare the efficacy, safety, and tolerability of AZD3582 with that of rofecoxib, naproxen, and placebo in patients with osteoarthritis (OA) of the knee, and to define the dosage of AZD3582 (125 mg, 375 mg, and 750 mg twice a day) that is noninferior in efficacy to rofecoxib. METHODS: A double-blind study of 672 patients with OA of the knee was conducted. Patients who experienced increased pain on withdrawal of analgesia were randomized to receive AZD3582 125 mg, 375 mg, or 750 mg twice a day; rofecoxib 25 mg once a day; naproxen 500 mg twice a day; or placebo for 6 weeks. Efficacy, tolerability, and safety were monitored throughout the study. The primary variable was the change in Western Ontario and McMaster Universities Osteoarthritis Index pain subscale from baseline to the mean of weeks 4 and 6, comparing AZD3582 with placebo for superiority and with rofecoxib for noninferiority using a predefined margin of 10 mm. RESULTS: For the primary outcome measure in the double-blind phase, the difference in the change from baseline to the week 6 to the week 4 mean of the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale between AZD3582 and rofecoxib was 2.49 mm (P = 0.003) and 2.44 mm (P = 0.003) for AZD3582 125 mg and 375 mg, respectively. However, the change in the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale from baseline to the week 6 to the week 4 mean of the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale between AZD3582 750 mg and rofecoxib was not significant (P = 0.21). CONCLUSION: In patients with painful OA of the knee, AZD3582 125 mg and 375 mg are inferior to rofecoxib 25 mg in efficacy but are similar to rofecoxib in safety and tolerability. AZD3582 750 mg twice a day is not noninferior to rofecoxib 25 mg in efficacy, safety, and tolerability.

Study Group Neuropathic Pain placebo withdrawal, randomized. Results of a neuropathy: peripheral painful diabetic patients with tapentadol ER in and efficacy of neuropathy (ER) for relieving painful DPN. Research design and methods: Patients (n=588) with at least a 3-month history of opioid and/or non-opioid analgesic use for DPN, dissatisfaction with current treatment, and an average pain intensity score of at least 5 on an 11-point numerical rating scale (NRS; 0='no pain,' 10='pain as bad as you can imagine') were titrated to an optimal dose of tapentadol ER (100–250 mg bid) during a 3-week open-label phase. Subsequently, patients (n=395) with at least a 1-point reduction in pain intensity were randomized 1:1 to receive placebo or the optimal fixed dose of tapentadol ER determined during the open-label phase for a 12-week double-blind phase. Clinical trial registration: NCT00455520. Main outcome measures: The primary efficacy outcome was the change in average pain intensity from randomization, determined by twice-daily NRS measurements. Safety was assessed throughout the study. Results: The least-squares mean difference between groups in the change in average pain intensity from the start of double-blind treatment to week 12 was -1.3 (95% confidence interval, -1.70 to -0.92; p<0.001, tapentadol ER vs. placebo). A total of 60.5 (356/588) of patients reported at least a 30 improvement in pain intensity from the start to the end of the open-label titration phase; of the patients who were randomized to tapentadol ER, 53.6 (105/196) reported at least a 30 improvement from pre-titration to week 12 of the double-blind phase. The most common treatment-emergent adverse events that occurred during double-blind treatment with tapentadol ER included nausea, anxiety, diarrhea, and dizziness. Potential limitations of this study are related to the enriched enrollment randomized-withdrawal trial design, which may result in a more homogeneous patient population.

Objective: Painful diabetic peripheral neuropathy (DPN) may not be adequately managed with available therapeutic options. This phase III, randomized-withdrawal, placebo-controlled trial evaluated the safety and efficacy of tapentadol extended release (ER) for relieving painful DPN.

A double-blind, randomised, placebo-controlled 8-week study was conducted to evaluate the efficacy and safety of gabapentin in the treatment of neuropathic pain, using doses up to 2400 mg/day. The study used a novel design that was symptom-rather than syndrome-based; an approach that aimed to reflect the realities of clinical practice. Participants had a wide range of neuropathic pain syndromes, with at least two of the following symptoms: allodynia, burning pain, shooting pain, or hyperalgesia. Patients were randomised to gabapentin (n=153) or placebo (n=152).

Gabapentin was given in three divided doses, initially titrated to 900 mg/day over 3 days, followed by two further increases, to a maximum of 2400 mg/day if required by the end of week 5. The primary outcome measure was changed in average daily pain diary score (baseline versus final week). Over the 8 week study, this score decreased (i.e. improved) by 1.5 (21%) in gabapentin treated patients and by 1.0 (14%) in placebo treated patients (P=0.048, rank-based analysis of covariance). Significant differences were shown in favour of gabapentin (P<0.05) for the Clinician and Patient Global Impression of Change, and some domains of the Short Form-McGill Pain Questionnaire. Improvements were also shown in patient-reported outcomes in quality of life, as seen by significant differences in favour of gabapentin in several domains of the Short-Form-36 Health Survey. Gabapentin was well tolerated and the majority of patients completed the study (79 versus 73% for placebo). The most common adverse events were mild to moderate dizziness and somnolence, most of them self-limiting.


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7 Identified as a ‘partial enriched enrolment’ trial by Struabe, Derry, McQuay and Moore (2008)
which were transient and occurred during the titration phase. This study shows that gabapentin reduces pain and improves some quality-of-life measures in patients with a wide range of neuropathic pain syndromes.

| Simpson, Messina, Xie and Hale (2007) | BACKGROUND: Patients with chronic noncancer pain, including neuropathic pain, may have transitory exacerbations of pain (median duration, 60 minutes), termed breakthrough pain (BTP), that may reach peak intensity within minutes. Typical short-acting oral opioids may not provide sufficiently rapid relief (30- to 60-minute onset of analgesia). The fentanyl buccal tablet (FBT) provides a rapid onset of analgesia (10-15 minutes) by enhancing fentanyl absorption across the buccal mucosa. OBJECTIVE: This study evaluated the efficacy and tolerability of FBT in opioid-tolerant patients with BTP associated with chronic noncancer neuropathic pain. METHODS: This was a multicenter, randomized, double-blind, placebo-controlled study in men and women aged 18 to 80 years who were opioid tolerant; had a >/= 3-month history of chronic persistent neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome; and reported having episodes of BTP. After an open-label titration period to identify an effective FBT dose (the dose at which the patient reported receiving adequate pain relief within 30 minutes after administration of a single tablet of that dose during at least 2 of 3 BTP episodes), patients were randomly assigned to treat 9 consecutive episodes of BTP over the next 21 days with 1 of 3 double-blind dose sequences of FBT and placebo tablets. Pain intensity (PI) (rated on an 11-point pain scale, from 0 = no pain to 10 = worst pain) and other outcomes were assessed before dosing and for 2 hours after dosing. The primary efficacy measure was the sum of PI differences (PIDs) for the first 60 minutes (SPID(60)). Secondary efficacy measures included the proportion of BTP episodes with >/= 33% and >/= 50% improvement in PI from baseline; PID at other time points (5, 10, 15, 30, 45, 60, 90, and 120 minutes after dosing); pain relief (PR) at the same time points (rated on a 5-point Likert scale from 0 = none to 4 = complete); proportion of BTP episodes with meaningful PR; time to meaningful PR; and proportion of BTP episodes in which supplemental medication was required after administration of study drug. Adverse events (AEs) spontaneously reported by the patient or elicited by the investigator were recorded throughout the study. RESULTS: Of 102 patients in the open-label titration period, 80 identified an effective dose of FBT and 79 entered the double-blind phase. Of these 79 patients, 77 (97%) completed the study and 75 (95%) were evaluable for efficacy. Of the 79 patients who entered the double-blind phase, 63% were women and 92% were white; their mean (SD) age was 48.3 (10.42) years, and their mean weight was 96.8 (33.42) kg. Baseline demographic and pain characteristics were similar between the overall population and the double-blind population. SPID(60) was significantly greater for BTP episodes treated with FBT compared with those in which placebo was administered (mean [SE], 9.63 [0.75] vs 5.73 [0.72], respectively; P < 0.001). Significant differences between FBT and placebo were seen beginning at 10 minutes for PID (mean, 0.740 [0.149] vs 0.427 [0.081]; P < 0.047) and PR (mean, 0.561 [0.087] vs 0.324 [0.056]; P < 0.001). A >/= 33% improvement in PI from baseline was seen in a greater proportion of BTP episodes treated with FBT compared with placebo from 10 minutes (9% vs 3%; P = 0.008) through 2 hours (66% vs 37%; P < 0.001). Patients were almost 4 times less likely to require supplemental opioids when BTP episodes were treated with FBT compared with placebo (odds ratio = 0.28; 95% CI, 0.18-0.42). AEs were reported by 64 (63%) of 102 patients. The most commonly reported AEs were those typical of opioids (nausea [13%], dizziness [13%], somnolence [10%], and vomiting [5%]) and occurred more often during the dose-titration phase (55/102 [54%]) than during the double-blind phase (22/79 [28%]). CONCLUSION: In these opioid-tolerant patients with chronic neuropathic pain who identified an effective FBT dose, FBT had a rapid onset of action and was effective and well tolerated in the treatment of BTP. |

| Sorge and Sittl (2004), Transdermal buprenorphine in the treatment of chronic pain: results of a multicenter, randomized, double-blind, placebo-controlled study. | BACKGROUND: Buprenorphine, a potent opioid analgesic, has been available in parenteral and oral or sublingual(SL) formulations for >25 years. In 2001, the buprenorphine transdermal delivery system (TES) was introduced at 3 release rates (35, 52.5, and 70 microg/h) for the treatment of chronic cancer and noncancer pain. OBJECTIVE: This study compared the analgesic efficacy and tolerability of buprenorphine TES at a release rate of 35 microg/h with those of buprenorphine SL and placebo in patients with severe or very severe chronic cancer or noncancer pain. |
Efficacy and tolerability to buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study.

In this enriched design study, 1,160 opioid-experienced patients with chronic, moderate to severe low back pain entered an open-label run-in period; 660 demonstrated analgesic benefit from and tolerability to buprenorphine transdermal system 20 mcg/hour (BTDS 20) treatment and were randomized to receive either BTDS 20, BTDS 5 mcg/hour (BTDS 5), or the active control (immediate release oxycodeone 40 mg/day) during an 84-day double-blind phase. The primary endpoint, "average pain in the last 24 hours" during double-blind weeks 4, 8, and 12, was significantly lower for patients receiving BTDS 20 compared with patients receiving BTDS 5 (P < .001, treatment difference of -.67). A treatment difference of -.75 in favor of oxycodeone 40 mg/day versus BTDS 5 (P < .001) indicated the assay sensitivity of the study. Four sensitivity analyses, secondary, and exploratory analyses supported the results of the primary analysis. Incidences of treatment-emergent adverse events were 56% during the open-label period, and 59, 77, and 73% for the BTDS 5, BTDS 20, and oxycodeone 40 mg/day treatment groups, respectively, during the double-blind phase. One death considered unrelated to study treatment occurred in a patient receiving BTDS 10 during the run-in period. BTDS 20 treatment was demonstrated to be efficacious and generally well tolerated. PERSPECTIVE: This article presents results of a pivotal Phase 3 study that assesses a new treatment for the management of chronic low back pain: a transdermal patch containing the opioid buprenorphine (BTDS). In this active controlled, superiority study with an enriched design, BTDS 20
Steiner, et al. (2011) Efficacy and safety of the seven-day buprenorphine transdermal system in opioid-naive patients with moderate to severe chronic low back pain: an enriched, randomized, double-blind, placebo-controlled study.

CONTEXT: This article presents the results of a pivotal Phase 3 study that assesses a new treatment for the management of chronic low back pain: a transdermal patch containing the opioid buprenorphine. In this randomized, placebo-controlled study with an enriched enrollment design, the buprenorphine transdermal system (BTDS) was found to be efficacious and generally well tolerated. OBJECTIVES: This enriched, multicenter, randomized, double-blind study evaluated the efficacy, tolerability, and safety of BTDS in opioid-naive patients who had moderate to severe chronic low back pain. METHODS: Patients who tolerated and responded to BTDS (10 or 20 mcg/hour) during an open-label run-in period were randomized to continue BTDS 10 or 20 mcg/hour or receive matching placebo. The primary outcome was “average pain over the last 24 hours” at the end of the 12-week double-blind phase, collected on an 11-point scale (0=no pain, 10=pain as bad as you can imagine). Sleep disturbance (Medical Outcomes Study subscale) and total number of supplemental analgesic tablets used were secondary efficacy variables. RESULTS: Fifty-three percent of patients receiving open-label BTDS (541 of 1024) were randomized to receive BTDS (n=257) or placebo (n=284). Patients receiving BTDS reported statistically significantly lower pain scores at Week 12 compared with placebo (least square mean treatment difference: -0.58, P=0.010). Sensitivity analyses of the primary efficacy variable and results of the analysis of secondary efficacy variables supported the efficacy of BTDS relative to placebo. During the double-blind phase, the incidence of treatment-emergent adverse events was 55% for the BTDS treatment group and 52% for the placebo treatment group. Laboratory, vital sign, and electrocardiogram evaluations did not reveal unanticipated safety findings. CONCLUSION: BTDS was efficacious in the treatment of opioid-naive patients with moderate to severe chronic low back pain. Most treatment-emergent adverse events observed were consistent with those associated with the use of opioid agonists and transdermal patches. Copyright 2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.


Cannabinoids are emerging as potential options for neuropathic pain treatment. This study evaluated an oral cannabinoid, nabilone, in the treatment of refractory human diabetic peripheral neuropathic pain (DPN). We performed a single-center, randomized, double-blind, placebo-controlled, flexible-dose study with an enriched enrollment randomized withdrawal design. DPN subjects with a pain score >= 4 (0-10 scale) continued regular pain medications and were administered single-blindly adjuvant nabilone for 4 weeks. Subjects achieving >= 30% pain relief (26/37) were then randomized and treated with either flexible-dose nabilone 1-4 mg/day (n=13) or placebo (n=13) in a further 5-week double-blind treatment period, with 30% (11/37) of subjects deemed run-in-phase nabilone nonresponders. For nabilone run-in-phase responders, there was an improvement in the change in mean end-point neuropathic pain vs placebo (mean treatment reduction of 1.27; 95% confidence interval 2.29-0.25, P=0.02), with an average nabilone dose at end point of 2.9 +/- 1.1mg/day, and improvements from baseline for the anxiety subscale of the Hospital Anxiety and Depression Scale, the Medical Outcomes Study sleep scale problems index, and the European Quality of Life-5-Domains index score (each P<0.05). Nabilone run-in-phase responders reported greater global end-point improvement with nabilone than with placebo (100% vs 31%; P<0.05). Medication-related confusion led to discontinuation in 2/37 subjects during single-blind nabilone treatment. Potential unmasking occurred in 62% of both groups. Flexible-dose nabilone 1-4 mcg/day was effective in relieving DPN symptoms, improving disturbed sleep, quality of life, and overall patient status. Nabilone was well tolerated and successful as adjuvant in patients with DPN. Copyright 2012 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Vorsanger, Xiang, Gana, Pascual and Fleming (2008) Extended-release tramadol. BACKGROUND: This study evaluated the safety and efficacy of tramadol ER 300 mg and 200 mg versus placebo once daily in the treatment of chronic low back pain, using an open-label run-in followed by, without washout, a randomized controlled study design. METHODS: Adults with scores > or = 40 on a pain intensity visual analog scale (VAS; 0 = no pain; 100 = extreme pain) received open-label tramadol ER, initiated at 100 mg once daily and titrated to 300 mg once daily during a three-
**OBJECTIVES:** The aims of this multicenter, randomized, placebo-controlled, double-blind trial were to confirm the efficacy of lacosamide at a daily dose of 400 mg/d and to explore the efficacy, safety, and tolerability of lacosamide 200 mg/d and 600 mg/d in the treatment of painful diabetic neuropathy.

**METHODS:** The trial consisted of a 2-week run-in period, a 6-week titration phase, and a 12-week maintenance phase, during which patients received placebo or fixed doses of lacosamide 200, 400, or 600 mg/d. No back titration was allowed during the trial. The primary efficacy criterion was the change in Likert pain score from baseline to the average over the last 4 weeks of the maintenance phase in the intent-to-treat population.

**RESULTS:** The lacosamide 200 mg/d group demonstrated statistically significant improvement in Likert pain score over placebo for the primary efficacy measure. At the end of treatment, 58% of patients in the lacosamide 400 mg/d treatment group achieved at least a 2-point or 30% reduction in Likert pain score, compared with 46% of placebo-treated patients. The lacosamide 200 mg/d group separated from placebo, but failed to show statistical significance for any of the primary or secondary outcome measures. The lacosamide 600 mg/d group was significantly more efficacious than placebo in the observed cases but not in the intent-to-treat population. This was probably secondary to a relatively high-premature withdrawal rate due to adverse events that occurred during the titration phase in that group. Overall lacosamide at daily doses of 200 to 400 mg was well tolerated, with 8% of patients discontinuing due to an adverse event from the 200 mg/d group and 23% from the 400 mg/d group compared with 9% in the placebo group. Discontinuations due to adverse events were highest in the 600 mg/d group.
2.D.2: RCTs which may have an enriched enrolment, randomised withdrawal design

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<td>Bin, Wu, Zeng, Moore and Frank (2007) Efficacy of lumiracoxib in relieving pain associated with knee osteoarthritis: A 6-week, randomized, double-blind, parallel-group study.</td>
<td>Aim: The aim of the current study was to assess the efficacy, safety, and tolerability of lumiracoxib 200 mg once daily (o.d.) in relieving osteoarthritis (OA) knee pain in patients in China, Taiwan, and South Korea. Methods: Patients of either sex (aged [greater-than or equal to] 18 years) with symptomatic, primary OA of the knee for [greater-than or equal to] 3 months were eligible for inclusion if they had OA pain intensity of [greater-than or equal to] 40 mm (100 mm visual analogue scale [VAS]) in the target knee joint during the previous 24 h. Patients were required to undergo regular non-steroidal anti-inflammatory drug therapy for [greater-than or equal to] 6 weeks. After 3-7 days of screening, patients were randomized (1 : 1) to receive either lumiracoxib 200 mg o.d. or celecoxib 200 mg o.d. The primary efficacy comparison between the study groups was overall OA pain intensity (VAS) in the target knee after 6 weeks of treatment. Results: The mean overall OA pain intensity (VAS) in the target knee after 6 weeks decreased from 60.6 mm to 35.7 mm and 60.5 mm to 36.1 mm in the lumiracoxib and celecoxib groups, respectively. Both study groups showed similar results in terms of improvement in both patient's and physician's global assessment of disease activity and functional health status. The percentage of adverse events (AEs) in the lumiracoxib and celecoxib groups (40.3% and 37.9%, respectively) was similar, as was the proportion of treatment-related AEs (21.0% and 18.2%, respectively). Conclusions: Lumiracoxib 200 mg o.d. provided effective and well-tolerated pain relief similar to that achieved with celecoxib 200 mg o.d. in knee OA patients. copyright 2007 Asia Pacific League of Associations for Rheumatology. Copyright © 2011 Elsevier B. V., Amsterdam. All Rights Reserved.</td>
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<td>Cowan, et al. (2005) A randomized, double-blind,</td>
<td>OBJECTIVES: The long-term use of strong opioid analgesics among chronic noncancer pain (CNCP) patients remains controversial because of concerns over problematic drug use. However, previous surveys suggest that this is not necessarily the case. Therefore, we designed a controlled study to generate evidence in support of</td>
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<td>Placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine.</td>
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<td>Table 1: this study. RESULTS: Following cessation and abstinence, there were no indications of psychological dependence or drug craving, but there was evidence of the detrimental effects of pain intensity on activity, mood, relationships, sleep, and enjoyment of life. Three patients (30%) reported opioid drug withdrawal symptoms. Pharmacokinetic data demonstrated compliance with abstinence by all patients. CONCLUSION: The results suggest the existence of a group of CNCP patients whose long-term opioid consumption can be beneficial and remain moderate without them suffering from the consequences of problematic opioid drug use.</td>
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<td>Table 2: OBJECTIVE: Although common treatments for osteoarthritis (OA) pain, such as nonsteroidal antiinflammatory drugs (NSAIDs), simple analgesics, and weak opioids, provide relief in some cases, they fail to control pain or are poorly tolerated in many cases. Strong opioids have been used to successfully treat several types of noncancer pain but have rarely been tested in controlled studies. Therefore, we tested the effects of transdermal fentanyl (TDF) in patients with moderate-to-severe OA pain, in a placebo-controlled study. METHODS: The cohort comprised patients with radiologically confirmed OA of the hip or knee (meeting the American College of Rheumatology criteria) requiring joint replacement and with moderate-to-severe pain that had been inadequately controlled by weak opioids. The patients were randomized to receive TDF or placebo for 6 weeks after a 1-week pretreatment run-in phase. During study treatment, previously prescribed NSAIDs and simple analgesics were continued, but weak opioids were discontinued. All patients had access to paracetamol and metoclopramide. Pain was recorded on a visual analog scale (VAS), and function was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). RESULTS: Data were available for 399 patients (202 receiving TDF, 197 receiving placebo), of whom 199 (50%) completed the study. TDF provided significantly better pain relief than placebo, as demonstrated by the primary outcome measure (area under the curve for VAS scores -20 in the TDF group versus -14.6 in the placebo group; P = 0.007). TDF was also associated with significantly better overall WOMAC scores and pain scores. The most common adverse events were nausea, vomiting, and somnolence, and these occurred more often in the TDF group. CONCLUSION: TDF can reduce pain and improve function in patients with knee or hip OA.</td>
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<td>Table 3: OBJECTIVES: To assess the influence of vitamins B1, B6 and B12 on the analgesia success achieved by diclofenac in subjects with acute lumbago. RESEARCH DESIGN AND METHODS: A randomised, double blind controlled clinical study in parallel groups, in which subjects received twice-daily oral administration of either the combination therapy, Group DB (50 mg diclofenac plus 50 mg thiamine, 50 mg pyridoxine and 1 mg cyanocobalamin) or diclofenac monotherapy, Group D (50mg diclofenac). The study period lasted a maximum of 7 days. If sufficient pain reduction was achieved (defined as Visual Analogue Scale &lt;20 mm and patient's satisfaction), subjects could withdraw from the treatment after 3 or 5 days. All subjects gave written informed consent to participate in the study. Main outcome measures: The primary confirmatory study objective was to determine the number of patients with sufficient pain reduction after 3 days of treatment. RESULTS: Three hundred and seventy-five subjects were allocated at random to either treatment group: Group DB - 187 subjects and Group D - 185 subjects. After 3 days of treatment, a statistically significant higher proportion of subjects in Group DB (n = 87; 46.5%) than in Group D (n = 55; 29%) terminated the study due to treatment success (chi2(2): 12.06; p = 0.0005). Furthermore, the combination therapy yielded superior results in pain reduction, improvement of mobility and functionality. Drug safety monitoring profile throughout the study was within the expected range.</td>
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the trial was within the expected safety profile of diclofenac. CONCLUSIONS: The combination of diclofenac with B vitamins was superior to diclofenac monotherapy in lumbago relief after 3 days of treatment. As a study drawback, daily VAS measurements were only recorded until subject withdrawal from treatment, whether after 3, 5, or 7 days. There were no differences in safety profile between the two study groups.


This double-blind randomized controlled trial compares the efficacy of d Roxicam (20mg/day) and that of Indomethacin (100mg/day) administered to 20 patients (7 men, 13 women; aged 54.7 +/- 13.2 years) with active classical or definite rheumatoid arthritis during 9 weeks, after a 7-day single-blind run-in paracetamol (1,500mg/day) period. Evaluations were carried out at weeks 0 (washout), 1, 2, 4, 6 and 9. After 9 weeks of treatment, both drugs showed a statistically significant improvement of joint pain intensity, articular index (number of swollen or painful joints and degree of involvement), duration of morning stiffness, functional capacity, and level of fatigue. Inter-treatment differences at all study intervals were not observed. Grip strength improved only in Indomethacin-treated patients. Withdrawals due to lack of therapeutic efficacy did not occur. Side effects occurred in four patients from each group. One patient in the Indomethacin group withdrew at the week 1 due to epigastric pain and heartburn. In conclusion, d Roxicam (20mg/day) seems to be as effective as Indomethacin (100mg/day) in the alleviation of symptoms in patients with rheumatoid arthritis.

Shukla, Nag and Ahuja (1996) Alprazolam in chronic tension type headache.

Alprazolam was evaluated in the treatment of 62 patients of chronic tension type headache using a double blind cross over design with random allocation to drug or placebo. The duration of the trial was 4 months with a 2 week run in period and 2 week washout period separating two treatment periods of 4 weeks each. The patients were followed up for 4 weeks at the completion of the trial. 48 patients completed the trial. There was no significant difference in the overall response rate based in terms of percentage reduction in headache frequency per week, however a significant decrease in headache index was observed during treatment with alprazolam as compared to placebo (P < 0.05). The mean analgesic intake per week was also significantly lower during treatment with alprazolam as compared to the run in period. Side effects were seen in 16.67% patients. In none of the patients was it significant enough to require withdrawal from the study.


A randomized double-blind trial was carried out in 20 patients with osteoarthrosis of the hip or knee to compare the efficacy and tolerance of treatment with difflunisal or naproxen. During the first 4 weeks, patients received either 250 mg difflunisal or 250 mg naproxen twice daily and this was increased by 250 mg daily in 5 patients on difflunisal and in 3 on naproxen for the second 4 weeks of the trial. The results of subjective assessments made before and at the end of Week 8 showed a trend in favour of difflunisal for improvement of symptoms, except for weight-bearing pain which was improved in only 1 patient in each group. More of the patients receiving difflunisal than naproxen considered treatment to have been satisfactory, and rated their response as equally as good as or better than previous medication. Difflunisal produced significantly high incidence of gastro-intestinal upsets, leading to the withdrawal of 2 patients at Week 4.
APPENDIX 3

Clinical trials – conference abstracts


Pain, 10 (4 SUPPL. 1): S48. [Conference: 28th Annual Scientific Meeting of the American Pain Society, APS San Diego, CA United States. 07.05.2009 to 09.05.2009].


Of possible interest


