The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.
OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations’ consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

April 2008 (searches through September 2007)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Oregon Evidence-based Practice Center with input from a statewide panel of experts (pharmacists, primary care clinicians, pain care specialists, and representatives of the public). Subsequently, the key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
   a. In head-to-head comparisons, have one or more long-acting opioid been shown to be superior to other long-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?
   b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is more effective than another?
   c. Have long-acting opioids been shown to be superior to short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic non-cancer pain?
2. What are the comparative incidence and nature of adverse effects (including addiction and abuse) of long-acting opioid medications in adult patients being treated for chronic non-cancer pain?

   a. In head-to-head comparisons, have one or more long-acting opioid been shown to be associated with fewer adverse events compared to other long-acting opioids when used for treatment of adults with chronic non-cancer pain?
   b. In trials comparing long-acting opioids to other types of drugs or to placebo, is there a pattern to suggest that one long-acting opioid is associated with fewer adverse events than another?
   c. Have long-acting opioids been shown to have fewer adverse events than short-acting opioids when used for treatment of adults with chronic non-cancer pain?

3. Are there subpopulations of patients (specifically by race, age, sex, or type of pain) with chronic non-cancer pain for which one long-acting opioid is more effective or associated with fewer adverse effects?

**Inclusion Criteria**

**Populations**
Adult (greater than 18 years old) patients with chronic non-cancer pain. We defined chronic non-cancer pain as continuous or recurring pain of at least 6 months’ duration. Cancer patients and patients with HIV were excluded from this review.

**Interventions**
We included oral or transdermal long-acting opioids. “Long-acting” was defined as opioids administered three times a day or less frequently. Long-acting opioids that we identified were transdermal fentanyl and oral oxycodone, morphine, methadone, levorphanol, codeine, dihydrocodeine, and oxymorphone.

**Outcomes**
The main efficacy measures were pain intensity, pain relief, and function. There is no single accepted standard regarding how to measure these outcomes.

**Study types**
We included controlled clinical trials to evaluate efficacy. To evaluate adverse event rates, we included clinical trials and observational cohort studies designed to assess adverse events between different long-acting opioids.
METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE (April 2007 to June 2009) using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (http://www.fda.gov/medwatch/safety.htm) and Health Canada (http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/2007/index_e.html) web sites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote XI) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.
RESULTS

Overview

Searches resulted in 389 citations. Of those, there are 6 new potentially relevant trials and 1 secondary analysis of an already published trial (see Appendix A). Table 1 below summarizes the trials.

Table 1.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Comparator</th>
<th>Conditions</th>
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<tbody>
<tr>
<td><strong>Head to head (secondary analysis of a trial)</strong></td>
<td></td>
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<tr>
<td>Kalso, 2007</td>
<td>Transdermal fentanyl vs. SR oral morphine</td>
<td>Low back pain</td>
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<tr>
<td><strong>Active control trials</strong></td>
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<tr>
<td>Gatti, 2009</td>
<td>CR Oxycodone vs. Pregabalin</td>
<td>Neurpathic pain</td>
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<tr>
<td>Hale, 2007</td>
<td>ER Oxycodone vs. OROS Hydromorphone</td>
<td>Osteoarthritis pain</td>
</tr>
<tr>
<td>Lowenstein, 2009</td>
<td>Oxycodone PR vs Oxycodone PR/Naloxone</td>
<td>Improvement in constipation in patients with chronic pain</td>
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<tr>
<td>Simpson, 2008</td>
<td>Oxycodone PR vs Oxycodone PR/Naloxone</td>
<td>Improvement in constipation in patients with noncancer pain</td>
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<tr>
<td><strong>Placebo-controlled trial</strong></td>
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<tr>
<td>Ma, 2008</td>
<td>CR Oxycodone vs placebo</td>
<td>Acute pain in chronic neck pain patients</td>
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<td><strong>One group trial</strong></td>
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<tr>
<td>Panjabi, 2008</td>
<td>ER Morphine</td>
<td>Chronic pain</td>
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</table>

New Drugs

Generic product Oxycodone hydrochloride ER oral 80 mg approved April 2009, manufacturer Impax Labs

Generic Product Oxycodone hydrochloride ER oral 10, 20, 40, 80 mg approved July 2008, manufacturer Mallinckrodt

Generic Product Fentanyl ER transdermal 25, 50, 75, 100 UGM/HR approved October, 2008, manufacturer Teva Pharms
New Indications

None at this time.

New Safety Alerts
There were a number of recalls issued since the last update both in U.S. and Canada. See below for details.

FDA

Morphine Sulfate extended release tablets 15 mg

[UPDATE 01/28/2009] ETHEX Corporation issued a nationwide voluntary recall of products at a wholesale or a retail level as a precautionary measure because they may have been manufactured under conditions that did not sufficiently comply with current Good Manufacturing Practices (cGMPs). Some of these products have had specific lots recalled earlier due to defects found, including oversized tablets delivering higher than labeled doses. These additional products are being removed to assure that no other defective products remain in the marketplace.

[Posted 11/10/2008] Ethex Corp and FDA notified healthcare professionals of a voluntary recall of five generic products (Propafenone HCl Tablets, Isosorbide Mononitrate Extended Release Tablets, Morphine Sulfate Extended Release Tablets, Morphine Sulfate Immediate Release Tablets, and Dextroamphetamine Sulfate Tablets). The products were recalled because they may contain oversized tablets. Oversized tablets may contain more than the intended levels of the active drug ingredient that could result in patients receiving as much as twice the expected dosage of these drugs, which could cause serious or life-threatening consequences. Overdoses can include arrhythmias and low blood pressure with Propafenone HCl; fainting and low blood pressure with Isosorbide Mononitrate; respiratory depression and low blood pressure with Morphine Sulfate; and rapid heart rate and high blood pressure with Dextroamphetamine Sulfate. Patients who experience any adverse reactions to these drugs should contact their healthcare professional immediately. See the manufacturer’s recall notice for specific lot numbers of the products affected by this recall.

Morphine Sulfate 60 mg, 30mg extended release tablets

[UPDATE 06/16/2008] Additional lots of morphine sulfate 60 mg extended release tablets, and specific lots of morphine sulfate 30 mg extended release tablets, were recalled due to the possible presence of oversized tablets. The recalled lots were distributed by ETHEX Corporation under an “ETHEX” label between June 2006 and May 2008.

[Posted 06/10/2008] ETHEX Corporation notified healthcare professionals of a voluntary recall of a single lot of morphine sulfate 60 mg extended release tablets (Lot No. 91762)
due to a report of a tablet with twice the appropriate thickness. Oversized tablets may contain as much as two times the labeled level of active morphine sulfate. The lot was distributed by ETHEX Corporation under an "ETHEX" label between April 16th and April 27th of 2008. Opioids such as morphine have life-threatening consequences if overdosed. Consequences can include respiratory depression (difficulty or lack of breathing), and low blood pressure. Many patients for whom this product is prescribed are likely to be highly debilitated with reduced strength or energy as a result of illness, and may be less likely to determine that a tablet is overweight or oversized than an unimpaired individual. If consumers have any questions about the recall, they should call their physician, pharmacist, or other health care provider.

**Fentanyl transdermal System CII Patches**

[UPDATED 08/12/2008] Watson Pharmaceuticals, Inc., issued a voluntary recall of one lot of 75mcg/hr Fentanyl Transdermal System patches (lot 92461850; Expiration Date: 8/31/2009) sold in the United States between January 30, 2008, and March 19, 2008. The product was recalled because a small number of the patches were leaking and may expose patients or caregivers directly to fentanyl gel.

**Safety labeling changes**

[June 2008] OxyContin (oxycodone HCl controlled-release) Tablets

Adverse reactions: The following adverse reactions occurred in less than 1% of patients involved in clinical trials or were reported in postmarketing experience. (The adverse reaction categories have been re-organized. The adverse events listed below include only the new reactions added.)

- Cardiac Disorders
  - Palpitations (in the context of withdrawal)
- Investigations
  - Increased hepatic enzymes

**Health Canada**

July 2008: ratiopharm inc., in consultation with Health Canada, is advising health care professionals of the immediate voluntary recall of a number of lots (see in attachment) of ratio-Morphine SR 15 mg, 30 mg and 60 mg tablets (DIN 02244790 - 02244791 - 02244792) due to the possibility that they may contain oversized tablets. The lots are being recalled as a precaution. The voluntary recall follows a report that tablets with as much as double the appropriate thickness were identified creating the possibility of taking double the dose prescribed.

If patients ingest oversized tablets they would be exposed to the potential risk of accidental overdose. The most important signs of overdose are respiratory depression, dizziness, confusion or extreme drowsiness. Serious overdosage may result in apnea, circulatory collapse, cardiac arrest and death.
APPENDIX A. Potentially Relevant New Trials

Oxycodone


Aims: The aim of our study was to compare the efficacy, safety, and quality of life of combination therapy with controlled-release (CR) oxycodone plus pregabalin versus monotherapy with either CR oxycodone or pregabalin in patients with neuropathic pain. Materials and Methods: Patients with moderate to severe neuropathic pain, despite the use of various pharmacologic treatments prior to study entry, were enrolled (n = 409) and treated with CR oxycodone plus pregabalin (n = 169), CR oxycodone (n = 106), and pregabalin (n = 134). Pain intensity was rated on an 11-point numerical rating scale (NRS). Results: The combination of CR oxycodone plus pregabalin and CR oxycodone monotherapy were both more effective for alleviating neuropathic pain than pregabalin monotherapy (reduction in NRS value: 80, 76, and 46%, respectively; p <= 0.003). Significantly greater improvements from baseline in quality of life were reported with combination therapy than with monotherapy (p = 0.0009). At the end of treatment, the majority (91.2%) of patients receiving CR oxycodone plus pregabalin found that the treatment had been 'effective' or 'very effective'. Combination therapy also allowed a dose reduction of both agents (22% for CR oxycodone and 51% for pregabalin) compared with the dosages of the respective monotherapies. Combination therapy had a superior safety profile compared with pregabalin monotherapy. Conclusions: The combination of CR oxycodone plus pregabalin may represent a valuable addition to the existing pharmacotherapy for neuropathic pain and warrants further investigation. Copyright (c) 2008 S. Karger AG, Basel.


OBJECTIVE: This study compared the efficacy and tolerability of a once-daily controlled-release formulation of hydromorphone (OROS) hydromorphone, Janssen-Cilag, Beerse, Belgium) and twice-daily extended-release (ER) oxycodone in patients with chronic, moderate to severe osteoarthritis (OA) pain. OROS hydromorphone is currently available only in Europe. METHODS: Adults who met American College of Rheumatology clinical criteria for OA of the knee or hip with moderate to severe mean daily pain intensity despite chronic use of stable doses of NSAIDs or other nonsteroidal, nonopioid therapies were eligible for participation in this randomized, open-label study. The study consisted of a 14-day...
dose-titration and stabilization phase and a 28-day maintenance phase. OROS hydromorphone and ER oxycodone were initiated at dosages of 8 mg QD and 10 mg BID, respectively. Patients maintained diaries in which they rated their pain (from 0 = none to 3 = severe) and pain relief (from 0 = no relief to 4 = complete relief). Other assessments completed every 14 days included patient and investigator global evaluations of treatment effectiveness (scale from 1 = poor to 5 = excellent), the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index, and the Medical Outcomes Study (MOS) Sleep Scale. Adverse events (whether observed by study personnel, identified in response to questioning, or spontaneously reported) and vital signs were monitored throughout the study. The primary efficacy measures were the mean pain relief score at end point and the time from initiation of treatment to the third day of moderate to complete pain relief, as reported in the patient diary. Noninferiority analyses were conducted on all primary and secondary efficacy variables. RESULTS: One hundred thirty-eight patients (71 OROS hydromorphone, 67 ER oxycodone) received treatment (safety population), and 83 (60.1%) completed the study. Data from 124 patients were included in the efficacy analyses; the majority of these patients were white (85.5%) and female (69.4%), with a mean age of 63.6 years. The most commonly affected joint was the knee (79.8%). At end point, the OROS hydromorphone group had a mean pain relief score of 2.3 (median, 2.0) and the ER oxycodone group had a mean pain relief score of 2.3 (median, 2.3) (95% CI, -0.30 to infinity). The mean time to the third day of moderate to complete pain relief was 6.2 days (median, 4.0) in the OROS hydromorphone group and 5.5 days (median, 5.0) in the ER oxycodone group (95% CI, -0.31 to infinity). Mean pain intensity decreased from baseline to end point by 0.6 point in the OROS hydromorphone group and by 0.4 point in the ER oxycodone group. Mean scores on the patient global evaluation improved by a respective 1.2 and 1.0 points (median, 1 in both groups). Approximately two thirds of patients in each group (67.2% and 66.7%) rated the overall effectiveness of treatment as good to excellent at end point. There were no statistically significant differences between groups in total WOMAC scores at end point, and similar improvements from baseline in the WOMAC physical function, stiffness, and pain scales were observed in both groups. Whereas MOS sleep outcomes scores improved from baseline in both groups, OROS hydromorphone was associated with a significantly greater improvement on the MOS Sleep Problems Index I compared with ER oxycodone (P < 0.045). Adverse events were comparable in both groups; the most frequently reported adverse events were nausea (35.2% and 29.9%), constipation (29.6% and 25.4%), somnolence (25.4% and 17.9%), vomiting (16.9% and 11.9%), and dizziness (14.1% and 22.4%). Adverse events led to study discontinuation in 35.2% (25/71) of patients in the OROS hydromorphone group and 32.8% (22/67) in the ER oxycodone group. Discontinuations due to adverse events during the titration phase were numerically greater in the OROS hydromorphone group (29.6% [21/71]) than in the ER oxycodone group (19.4% [13/67]). Only 1 serious adverse event (diarrhea in a patient receiving OROS hydromorphone)

**BACKGROUND:** This randomised, double-blind, double-dummy, parallel-group multicentre study assessed the impact of a total daily dose of 60-80 mg oral oxycodone prolonged-release (PR)/naloxone PR (OXN PR) as fixed-ratio combination for patients with opioid-induced constipation (OIC) having moderate-to-severe, non-malignant pain. **METHODS:** During pre-randomisation patients receiving opioids for moderate-to-severe non-malignant pain were converted to oxycodone PR (OXY PR) and titrated to an effective analgesic dose. During randomisation 265 patients on a stable OXY PR dose (60-80 mg/day) and with OIC were included in the full analysis population to receive OXN PR or OXY PR alone. Primary outcome was improvement in symptoms of constipation as measured by the Bowel Function Index (BFI). Secondary/exploratory outcomes examined analgesic efficacy and other bowel function parameters. **RESULTS:** After 4 weeks of treatment, patients receiving OXN PR showed a significant improvement in bowel function compared with those in the OXY PR group (-14.9; 95% CI: -17.9, -11.9; p<0.0001) as measured by BFI which was seen after only 1 week of treatment continuing to the end of the study. After 4 weeks of treatment, patients receiving OXN PR had a median number of 3.0 complete spontaneous bowel movements (CSBM) per week compared with only 1.0 for OXY PR alone. Laxative intake was lower in the OXN PR than the OXY PR group. Furthermore, improvements in bowel function were achieved without loss of analgesic efficacy; pain intensity scores were comparable between the groups and consistent for duration of the study. Most frequently reported adverse events were consistent with those reported for opioid analgesics; no new or unexpected adverse reactions attributable to OXN PR used in higher doses were observed. **CONCLUSION:** This study shows that the fixed-ratio combination of OXN PR is superior to OXY PR alone in terms of bowel function, while providing effective equivalent analgesia.


**OBJECTIVE:** Most treatments of acute pain associated with non-malignant chronic pains are not satisfactory. The aim of this study is to evaluate the efficacy and side effects of oxycodone controlled release (Oxy-CR) in managing chronic neck pain with acute pain episodes. **DESIGN:** Randomised, double-blind, stand controlled study. A total of 116 patients were evenly divided into an oxycodone group (Oxy-CR, 5-10 mg and q12 h/day) and a placebo group (placebo, q12 h/day). Patients were assessed for the frequency of pain flares, visual analgesia score (VAS), quality of life (QOL), quality of sleep (QOS) and adverse effects before the treatment and
on days 1, 3, 7, 14, 21 and 28 after the treatment. Withdrawal symptoms were monitored during the study, also on the completion of the entire study. The SF-36 was administered at the beginning and the end of the study for each patient.

RESULTS: Compared with the baselines of Oxy-CR and the placebo groups, the frequency of pain episodes and VAS were decreased significantly starting on day 3 of administration of Oxy-CR (p<0.05). Improvements in QOL and QOS were significant on day 3 after treatment with Oxy-CR (p<0.05). The patients who were treated with Oxy-CR reported significantly higher side effects than the patients in the placebo group (p<0.05). However, these side effects started to diminish after day 7 of the treatment. Withdrawal symptoms did not emerge in this study. Most domains of SF-36 were improved in the treated patients at the end of study (p<0.05). CONCLUSION: Oxycondon controlled release could be an important optional drug for the management of refractory and frequent acute episodes of chronic neck pain in patients who failed to respond to non-opioid conservative treatment.


OBJECTIVE: Opioid therapy is frequently associated with treatment-limiting constipation. Naloxone is an opioid antagonist with low oral systemic bioavailability. This Phase III clinical trial assessed the safety and efficacy of an oral fixed-ratio combination of oxycodone prolonged-release (PR) and naloxone PR compared with oxycodone PR in relieving opioid-induced constipation. STUDY DESIGN: This double-blind, multicenter trial was conducted in specialist and primary care centers in four European countries in an out-patients setting. The study included 322 adult patients with moderate-to-severe, noncancer pain requiring opioid therapy in a range of >or=20 mg/day and <or=50 mg/day oxycodone. Following a run-in phase patients were randomized to receive oxycodone PR/naloxone PR or oxycodone PR for 12 weeks. The primary outcome was improvement in constipation as measured using the Bowel Function Index (BFI). Secondary/exploratory assessments focused on pain intensity and additional bowel parameters. Trial registration: NCT00412152. RESULTS: A significant improvement in BFI scores occurred with oxycodone PR/naloxone PR compared with oxycodone PR after 4 weeks of double-blind treatment (-26.9 vs. -9.4, respectively; p < 0.0001), observed after only 1 week of treatment and continued until study end. A significant increase in the number of complete spontaneous bowel movements and decrease in laxative use were also reported. This improvement in bowel function was achieved without compromising the analgesic efficacy of the oxycodone component; pain intensity remained constant throughout the study. The incidence of adverse events was comparable in both groups and consistent with those expected of opioid analgesics. As the study was limited to a dose range of up to 50 mg oxycodone equivalent per day, further
research on higher doses would be recommended. CONCLUSION: The fixed-ratio combination of oxycodone PR/naloxone PR is superior to oxycodone PR alone, offering patients effective analgesia while significantly improving opioid-induced constipation.

Morphine


OBJECTIVE: To evaluate the impact of an extended-release, once-daily morphine sulfate formulation on depressive symptoms and neurocognition in patients with chronic nonmalignant pain. DESIGN: Prospective, open-label, one-group trial with a pretest-posttest design. SETTING: Outpatient pain management clinic. PATIENTS AND INTERVENTION: Chronic nonmalignant pain patients inadequately controlled with short-acting opioid analgesics and eligible for treatment with once-daily morphine sulfate were initiated on a dose at or near the morphine-equivalent dose of the short-acting regimen. OUTCOMES: The following assessments were made at baseline and 4 weeks after initiating intervention: pain intensity, pain unpleasantness, pain suffering, pain behaviors, Beck Depression Inventory, and cognitive function. RESULTS: Eighty-four patients provided usable data. Pain intensity, unpleasantness, and suffering scores were significantly reduced at follow-up (P = 0.001). The mean Beck Depression Inventory scores were significantly lower at follow-up (P = 0.001). Significant improvements were seen in scores at follow-up on the three validated neurocognitive tests: the digit span test, the digit symbol substitution test, and the paced auditory serial addition test (P = 0.001). CONCLUSIONS: Achieving adequate pain control with once-daily morphine was associated with a reduction in pain and improvements in depressive symptoms and cognitive functioning in the short term.

Morphine and Transdermal fentanyl


BACKGROUND: Some patients with long-standing low back pain will benefit from treatment with strong opioids. However, it would be helpful to predict which patients will have a good response. A fixed-term opioid trial has been recommended, but there is little evidence to suggest how long this trial should be. We assessed data from a large-scale randomized comparison of transdermal fentanyl (TDF) and sustained-release oral morphine (slow-release morphine; SRM) to determine characteristics of treatment responders. METHODS: This was a secondary analysis of a previously published 13-month randomized trial involving
680 patients with long-standing low back pain (median age 52 years, 61% women, median duration of back pain 87 months). Pain relief was recorded using visual analogue scales (VAS). Treatment response was defined as pain relief of at least 30% from baseline to any point during the trial. We used a step-wise logistic regression to identify variables that might predict response to treatment. Covariates included treatment group, sex, age, duration of pain, presence of neuropathic pain, baseline pain scores, educational/employment status, use of high doses of opioids, and social functioning (SF)-36 scores. RESULTS: Over half the patients in both groups (n = 370; 54% TDF, 55% SRM) were treatment responders. There were no differences between the TDF and SRM responders in terms of age, sex, type or duration of pain between responders and non-responders. The difference in response to treatment between responders and non-responders could be detected at 3 weeks. Lack of response after 1 month had a stronger negative predictive value (i.e., ability to detect non-responders) than the presence of response after 1 month. The most influential factors for predicting a response were employment status ($\chi^2 = 11.06$, $p = 0.0259$) and use of high doses of opioids ($\chi^2 = 3.04$, $p = 0.0811$). CONCLUSION: No clear pattern of baseline pain (type or severity) or patient characteristics emerged that could be used to predict responders before the start of opioid treatment. However, a 1-month trial period appears sufficient to determine response and tolerability in most cases.