Drug Class Review

Long-Acting Opioid Analgesics

Preliminary Scan Report 2

December 2013

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. 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.

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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 to assist with Participating Organizations' consideration of allocating resources. 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 rule in favor of a full update. The literature search for this report focuses only on new randomized controlled trials and comparative effectiveness reviews, and actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies, including observational studies, could exist.

Date of Last Update Report

Update #6, July 2011 (searches through January 2011)

Date of Last Preliminary Update Scan Report

Scan 1, April 2013 (searches through April 2013)

Scope and Key Questions

The scope of the review and key questions were originally developed and refined by the Pacific Northwest 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 the review:

1. What is the comparative effectiveness of different long-acting opioids in reducing pain and improving functional outcomes in adult patients being treated for chronic noncancer pain?

2. What is the comparative effectiveness of long-acting opioids compared with short-acting opioids in reducing pain and improving functional outcomes when used for treatment of adults with chronic noncancer pain?

3. What are the comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic noncancer pain?

4. What are the comparative harms of long-acting opioids compared with short-acting opioids in adult patients being treated for chronic noncancer pain?

5. Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status type of pain, or comorbidities) with chronic noncancer pain for which one long-acting opioid is more effective or associated with fewer harms?

6. Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status, type of pain, or comorbidities) with chronic noncancer pain for which long-acting opioids are more effective or associated with fewer harms than short-acting opioids?

Inclusion Criteria

Populations

The population included in the review was adult (18 years old or greater) patients with chronic noncancer pain. We defined chronic noncancer pain as continuous or recurring pain for at least 6 months. Cancer patients and patients with HIV were excluded from the review.

Interventions

Table 1. Included drugs

Drug	Trade name(s)	Forms	Recommended usual dosing frequency (times per day)
Buprenorphine	Butrans™	ER transdermal film	Every 7 days
Fentanyl	Duragesic®	ER transdermal film	Every 72 hours
Hydromorphone	Exalgo®	ER oral tablet	1
Levorphanol	Generic	Oral tablet	3-4
Methadone	Generic, Dolophine®	Oral tablet	2-3
Morphine	Generic Avinza® Kadian® MS Contin® Oramorph SR®[a]	ER oral capsule ER oral capsule ER oral capsule ER oral tablet ER oral tablet	1 1 1-2 1-3 2-3
Morphine sulfate and naltrexone hydrochloride	Embeda™	ER oral capsule	1-2
Oxycodone	OxyContin®	ER oral tablet	2
Oxymorphone	Opana ER®	ER oral tablet	2
Tapentadol	Nucynta ER®	ER oral tablet	2
Hydrocodone bitartrate	Zohydro™ER	ER oral capsule	2

Abbreviations: ER, extended release; MS, morphine sulfate; SR, sustained release.

Shading indicates drugs approved since the last update report.

[a]Discontinued

Study designs

Effectiveness:

- Controlled clinical trials

- Good quality systematic reviews

Harms:
- Controlled clinical trials
- Good quality systematic reviews
- Comparative observational studies

Comparators

- Another long-acting opioid
- Another drug
- Placebo

Effectiveness outcomes

- Pain intensity
- Pain relief
- Function

Harms outcomes

- Overall withdrawals
- Withdrawals due to adverse events
- Risk of abuse and addiction, including death and hospitalization
- Specific adverse events (nausea, vomiting, constipation, dizziness, somnolence, confusion)

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE from April 2013 to December 2013 using terms for included drugs. To identify trials of drugs not included in the last full report, we did not restrict the start date of the search. We also searched the FDA website (http://www.fda.gov/medwatch/safety.htm) for identification of new drugs, indications, and safety alerts. To identify comparative effectiveness reviews we searched the websites of the Agency for Healthcare Research and Quality (http://www.ahrq.gov/) and the Canadian Agency for Drugs and Technology in Health (http://www.cadth.ca/). All citations were imported into an electronic database (EndNote X3) 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

New Drugs

Identified in this Preliminary Update Scan

Hydrocodone bitartrate extended release oral capsule (Zohydro™ER): FDA approved for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate (10/25/2013).

Identified in previous Preliminary Update Scans

Tapentadol extended release oral tablet (Nucynta ER®): FDA approved for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time (8/25/2011).

New Indications

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans

None

New Black Box Warnings

Identified in this Preliminary Update Scan

None

Identified in previous Preliminary Update Scans

None

Comparative Effectiveness Reviews

Reviews identified in this Preliminary Update Scan

There were several comparative effectiveness reviews (CERs) that were either published or were in progress (Table 1). Although it is not clear that these reviews evaluate long-acting drugs in the same way they are in the DERP report, details are included in Appendix A,

Source	Author, year	Population
AHRQ/EHCEPC report in progress	2013	Chronic Pain
AHRQ/EHC EPC report in	2013	Low Back Pain

progress		
CADTH Rapid Response Report	6/2012	Chronic Non-Cancer Pain
CADTH Rapid Response Report	10/2011	Chronic Pain
CADTH	4/2012	Drug Diversion and Misuse
Cochrane	Chapparro, 2013	Chronic low-back pain
Cochrane	McNicol, 2013	Neuropathic Pain
Cochrane	Haroutiunian, 2012	Chronic non-cancer pain in adults

Reviews identified in previous Preliminary Update Scans
None.

Controlled Clinical Trials

Trials identified since the most recent Full Report
Cumulatively, we identified 5 head to head trials, 3 active-control trials and 7 placebo controlled trials that have been published since the last full update of this report. Medline searches for the most recent scan resulted in 243 citations. Of those, there were 5 potentially relevant new trials (see Table 2). Abstracts of these trials are attached in Appendix B. We identified 2 head-to-head trials on chronic noncancer pain and 3 placebo controlled trials in patients with low back pain or osteoarthritis. In the previous scan we identified 3 new head-to-head trials, all comparing tapentadol ER to oxycodone CR in patients with osteoarthritis or low back pain. Three trials compared a long-acting opioid to a short-acting opioid, and 4 trials compared an included drug to placebo.

Table 2. New potentially relevant trials

Author Year	Drug/Comparator	Focus
Head-to-Head Trials		
Afilalo 2010	Tapentadol ER vs oxycodone CR	Osteoarthritis
Buynak 2010	Tapentadol ER vs oxycodone CR	Low back pain
Wild 2010	Tapentadol ER vs oxycodone CR	Osteoarthritis or low back pain
Mitra, 2013	Transdermal buprenorphine vs transdermal fentanyl	Persistent noncancer pain
Richarz, 2013	OROS Hydromorphone ER vs oxycodone CR	Chronic noncancer pain
Active-control Trials		
Cruciani 2012	Hydromorphone ER vs hydromorphone IR	Not specified
Etropolski 2010	Tapentadol ER vs tapentadol IR	Low back pain
Steiner 2011a	Buprenorphine transdermal system vs oxycodone IR	Low back pain

Placebo Controlled Trials		
Chu 2012	Morphine SR	Low back pain
Rauck, 2013	OROS hydromorphone ER	Chronic osteoarthritis
Jamison, 2013 (secondary analysis)	Hydromorphone ER	Low back pain
Peniston 2012	Oxymorphone ER	Patients with low back pain taking SSRIs or SNRIs
Schwartz 2011	Tapentadol ER	Painful diabetic neuropathy
Steiner 2011b	Buprenorphine transdermal system	Opioid-naïve patients with low back pain
Yarlas, 2013	Buprenorphine transdermal system	Opioid-naïve patients with chronic low back pain

Summary and Recommendation

A streamlined report on this topic based on direct and indirect evidence would likely be a medium update based on head to head, active control (long acting versus short acting), and placebo controlled studies of included interventions. The EPC recommends limiting the report to head to head and active comparisons (i.e. long-acting versus short-acting formulations) resulting in a small size report. If work on a small report started in Feb 2014, the final report would be delivered in July 2014. Two states have currently scheduled to review this class before July 2014 (February and May); we have no other PDL meeting scheduling information for this class.

Appendix A. Comparative Effectiveness Reviews

Noninvasive Treatments for Low Back Pain (EPC report in progress)

Question 1 What are the comparative benefits and harms of different pharmacological therapies for acute or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis? (Including NSAIDs, acetaminophen, opioids, muscle relaxants, antiseizure medications, antidepressants, corticosteroids and topicals/patch-delivered medications)

Question 2 What are the comparative benefits and harms of different nonpharmacological, noninvasive therapies for acute or chronic nonradicular low back pain, radicular low back pain, or spinal stenosis? (Including but not limited to interdisciplinary rehabilitation, exercise (various types), physical modalities (ultrasound, Transcutaneous Electrical Nerve Stimulation (TENS), Electrical Muscle Stimulation (EMS), Interferential Therapy (IFT), heat (various forms), ice), traction tables/devices, back supports/bracing, spinal manipulation, various psychological therapies, acupuncture, massage therapy (various types), yoga, magnets and low level lasers)

The Effectiveness and Risks of Long-term Opioid Treatment of Chronic Pain (EPC Report in progress)

Effectiveness and comparative effectiveness

1. In patients with chronic pain, what is the effectiveness of long-term opioid therapy versus placebo or no opioid therapy for long-term (>1 year) outcomes related to pain, function, and quality of life?
2. How does effectiveness vary depending on: 1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); 2) patient demographics (e.g., age, race, ethnicity, gender); 3) patient comorbidities (including past or current alcohol or substance abuse and related disorders, mental health disorder and those at high risk for addiction and medical comorbidities)?
3. In patients with chronic pain, what is the comparative effectiveness of opioids versus non-opioid therapies (pharmacological or non-pharmacological) on outcomes related to pain, function, and quality of life?
4. In patients with chronic pain, what is the comparative effectiveness of opioids plus non-opioid interventions (pharmacological or non-pharmacological) versus opioids or non-opioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?

Evaluation of Opioid Use for Patients with Chronic Non-Cancer Pain: Clinical Evidence (CADTH)

RESEARCH QUESTION
What is the clinical evidence evaluating inappropriate use of opioids by patients with chronic non-cancer pain, using administrative databases?
KEY MESSAGE

Seven non-randomized studies using administrative databases to evaluate inappropriate use of opioids by patients with chronic non-cancer pain were identified.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated lists of major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2002 and May 29, 2012. Internet links were provided, where available.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies. Seven non-randomized studies using administrative databases to evaluate inappropriate use of opioids by patients with chronic non-cancer pain were identified. No relevant health technology assessments, systematic reviews, meta-analyses, or randomized controlled trials were identified.

Long-acting Opioids for Chronic Pain: Comparative Efficacy and Safety (CADTH)

RESEARCH QUESTIONS

1. What is the comparative efficacy of different long-acting opioids for adult patients with chronic non-cancer pain?

2. What is the comparative safety of different long-acting opioids for adult patients with chronic non-cancer pain?

KEY MESSAGE

Evidence suggests that the comparative efficacy and safety of different long-acting opioids for adult patients with chronic non-cancer pain is generally similar.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 10), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and abbreviated list of major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2001 and October 24, 2011. Internet links were provided, where available.

RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

Fifteen randomized controlled trials and 11 non-randomized studies were identified regarding the comparative efficacy and safety of different long-acting opioids for adult patients with chronic non-cancer pain. No health technology assessment reports, systematic reviews, or meta-analyses were identified. Additional studies of potential interest are provided in the appendix.

Opioid Management Practices for the Prevention of Drug Diversion and Misuse: A Review of the Clinical Evidence and Guidelines (CADTH)

CONTEXT AND POLICY ISSUES

Opioids are indicated as part of a comprehensive plan for the management of chronic pain in carefully selected and monitored patients.[1] A marked increase in the misuse, abuse, and diversion of prescription opioids, however, has become a societal and public health concern and has led to increased healthcare costs and alterations in treatment plans.[1] Non-medical use of prescription opioids is a public health concern because it has been linked to serious personal health consequences, including addiction, fatal opioid overdose, injection drug use and poly drug use.[2] Opioid diversion signifies any instance where drugs are re-routed from their lawful purpose at any point in the pharmaceutical manufacturing and distribution process.[3] For example, opioids can be diverted in the preclinical stages through theft at plants, in transit or at pharmacies. Opioids can also be diverted during the post-clinical phase by sharing, selling and misusing of prescribed medications or by stealing medications.[3] Opioid misuse can be defined as the use of opioids for a medical purpose, other than as directed or indicated, whether or not intentional and regardless of harm.[1] Substance abuse can be defined as the use of any substance when such use is unlawful, or when such use is detrimental to the user or others.[1] The distinctions between these terms are often blurred and within the literature there has been no consensus around the definitions of opioid diversion, opioid misuse and substance abuse. In Canada, the prescribing of opioids has increased dramatically in recent years.[4] For example, oxycodone prescriptions among Ontario Drug Benefit recipients rose from 1991 to 2007, from 23 prescriptions per 1000 individuals per year to 197 prescriptions per 1000 individuals per year.[4] These increases have been accompanied by increases in opioid-related harms such as addiction and overdose.[4] Of the 1095 people who died of opioid-related overdose in Ontario, during 1991 to 2007, 56% had been given opioid prescriptions within four weeks before death.[5] The purpose of this report is to review the clinical evidence regarding opioid management practices to reduce drug diversion and misuse; examine the evidence-based guidelines for opioid management practices to reduce opioid diversion and misuse; and examine the clinical evidence regarding opioid use or prescription patterns for the prediction of substance abuse.

Opioids compared to placebo or other treatments for chronic low-back pain.

Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC.

Abstract

BACKGROUND:

The use of opioids in the long-term management of chronic low-back pain (CLBP) has increased dramatically. Despite this trend, the benefits and risks of these medications remain unclear. This review is an update of a Cochrane review first published in 2007.

OBJECTIVES:

To determine the efficacy of opioids in adults with CLBP.

SEARCH METHODS:

We electronically searched the Cochrane Back Review Group's Specialized Register, CENTRAL, CINAHL and PsycINFO, MEDLINE, and EMBASE from January 2006 to October 2012. We checked the reference lists of these trials and other relevant systematic reviews for potential trials for inclusion.

SELECTION CRITERIA:

We included randomized controlled trials (RCTs) that assessed the use of opioids (as monotherapy or in combination with other therapies) in adults with CLBP that were at least four weeks in duration. We included trials that compared non-injectable opioids to placebo or other treatments. We excluded trials that compared different opioids only.

DATA COLLECTION AND ANALYSIS:

Two authors independently assessed the risk of bias and extracted data onto a pre-designed form. We pooled results using Review Manager (RevMan) 5.2. We reported on pain and function outcomes using standardized mean difference (SMD) or risk ratios with 95% confidence intervals (95% CI). We used absolute risk difference (RD) with 95% CI to report adverse effects.

MAIN RESULTS:

We included 15 trials (5540 participants). Tramadol was examined in five trials (1378 participants); it was found to be better than placebo for pain (SMD -0.55, 95% CI -0.66 to -0.44; low quality evidence) and function (SMD -0.18, 95% CI -0.29 to -0.07; moderate quality evidence). Transdermal buprenorphine (two trials, 653 participants) may make little difference for pain (SMD -2.47, 95%CI -2.69 to -2.25; very low quality evidence), but no difference compared to placebo for function (SMD -0.14, 95%CI -0.53 to 0.25; very low quality evidence). Strong opioids (morphine, hydromorphone, oxycodone, oxymorphone, and tapentadol), examined in six trials (1887 participants), were better than placebo for pain (SMD -0.43, 95%CI -0.52 to -0.33; moderate quality evidence) and function (SMD -0.26, 95% CI -0.37 to -0.15; moderate quality evidence). One trial (1583 participants) demonstrated that tramadol may make little difference compared to celecoxib (RR 0.82, 95% CI 0.76 to 0.90; very low quality evidence) for pain relief. Two trials (272 participants) found no difference between opioids and antidepressants for either pain (SMD 0.21, 95% CI -0.03 to 0.45; very low quality evidence), or function (SMD -0.11, 95% -0.63 to 0.42; very low quality evidence). The included trials in this review had high drop-out rates, were of short duration, and had limited interpretability of functional improvement. They did not report any serious adverse effects, risks (addiction or overdose), or complications (sleep apnea, opioid-induced hyperalgesia, hypogonadism). In general, the effect sizes were medium for pain and small for function.

AUTHORS' CONCLUSIONS:

There is some evidence (very low to moderate quality) for short-term efficacy (for both pain and function) of opioids to treat CLBP compared to placebo. The very few trials that compared opioids to non-steroidal anti-inflammatory drugs (NSAIDs) or antidepressants did not show any differences regarding pain and function. The initiation of a trial of opioids for long-term management should be done with extreme caution, especially after a comprehensive assessment of potential risks. There are no placebo-RCTs supporting the effectiveness and safety of long-term opioid therapy for treatment of CLBP.

Opioids for neuropathic pain.

McNicol ED, Midbari A, Eisenberg E.

Abstract

BACKGROUND:

This is an updated version of the original Cochrane review published in Issue 3, 2006, which included 23 trials. The use of opioids for neuropathic pain remains controversial. Studies have been small, have yielded equivocal results, and have not established the long-term profile of benefits and risks for people with neuropathic pain.

OBJECTIVES:

To reassess the efficacy and safety of opioid agonists for the treatment of neuropathic pain.

SEARCH METHODS:

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (to 24th October 2012), MEDLINE (1966 to 24th October 2012), and EMBASE (1980 to 24th October 2012) for articles in any language, and reference lists of reviews and retrieved articles.

SELECTION CRITERIA:

We included randomized controlled trials (RCTs) in which opioid agonists were given to treat central or peripheral neuropathic pain of any etiology. Pain was assessed using validated instruments, and adverse events were reported. We excluded studies in which drugs other than opioid agonists were combined with opioids or opioids were administered epidurally or intrathecally.

DATA COLLECTION AND ANALYSIS:

Two review authors independently extracted data and included demographic variables, diagnoses, interventions, efficacy, and adverse effects.

MAIN RESULTS:

Thirty-one trials met our inclusion criteria, studying 10 different opioids: 23 studies from the original 2006 review and eight additional studies from this updated review.Seventeen studies (392 participants with neuropathic pain, average 22 participants per study) provided efficacy data for acute exposure to opioids over less than 24 hours. Sixteen reported pain outcomes, with contradictory results; 8/16 reported less pain with opioids than placebo, 2/16 reported that some but not all participants benefited, 5/16 reported no difference, and 1/16 reported equivocal results. Six studies with about 170 participants indicated that mean pain scores with opioid were about 15/100 points less than placebo.Fourteen studies (845 participants, average 60 participants per study) were of intermediate duration lasting 12 weeks or less; most studies lasted less than six weeks. Most studies used imputation methods for participant withdrawal known to be associated with considerable bias; none used a method known not to be associated with bias. The evidence, therefore, derives from studies predominantly with features likely to overestimate treatment effects, i.e. small size, short duration, and potentially inadequate handling of dropouts. All demonstrated opioid efficacy for spontaneous neuropathic pain. Meta-analysis demonstrated at least 33% pain relief in 57% of participants receiving an opioid versus 34% of those receiving placebo. The overall point estimate of risk difference was 0.25 (95% confidence interval (CI) 0.13 to 0.37, $P < 0.0001$), translating to a number needed to treat for an additional beneficial

outcome (NNTB) of 4.0 (95% CI 2.7 to 7.7). When the number of participants achieving at least 50% pain relief was analyzed, the overall point estimate of risk difference between opioids (47%) and placebo (30%) was 0.17 (95% CI 0.02 to 0.33, P = 0.03), translating to an NNTB of 5.9 (3.0 to 50.0). In the updated review, opioids did not demonstrate improvement in many aspects of emotional or physical functioning, as measured by various validated questionnaires. Constipation was the most common adverse event (34% opioid versus 9% placebo: number needed to treat for an additional harmful outcome (NNTH) 4.0; 95% CI 3.0 to 5.6), followed by drowsiness (29% opioid versus 14% placebo: NNTH 7.1; 95% CI 4.0 to 33.3), nausea (27% opioid versus 9% placebo: NNTH 6.3; 95% CI 4.0 to 12.5), dizziness (22% opioid versus 8% placebo: NNTH 7.1; 95% CI 5.6 to 10.0), and vomiting (12% opioid versus 4% placebo: NNTH 12.5; 95% CI 6.7 to 100.0). More participants withdrew from opioid treatment due to adverse events (13%) than from placebo (4%) (NNTH 12.5; 95% CI 8.3 to 25.0). Conversely, more participants receiving placebo withdrew due to lack of efficacy (12%) versus (2%) receiving opioids (NNTH -11.1; 95% CI -20.0 to -8.3).

AUTHORS' CONCLUSIONS:

Since the last version of this review, new studies were found providing additional information. Data were reanalyzed but the results did not alter any of our previously published conclusions. Short-term studies provide only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo, but these results are likely to be subject to significant bias because of small size, short duration, and potentially inadequate handling of dropouts. Analgesic efficacy of opioids in chronic neuropathic pain is subject to considerable uncertainty. Reported adverse events of opioids were common but not life-threatening. Further randomized controlled trials are needed to establish unbiased estimates of long-term efficacy, safety (including addiction potential), and effects on quality of life.

Methadone for chronic non-cancer pain in adults.

Haroutiunian S, McNicol ED, Lipman AG.

Author information

Abstract

BACKGROUND:

Methadone belongs to a class of analgesics known as opioids, that are considered the cornerstone of therapy for moderate-to-severe pain due to life-threatening illnesses; however, their use in chronic non-cancer pain (CNCP) is controversial. Methadone has many characteristics that differentiate it from other opioids, which suggests that it may have a different efficacy and safety profile.

OBJECTIVES:

To assess the analgesic effectiveness and safety of methadone in the treatment of CNCP.

SEARCH METHODS:

We identified both randomized controlled trials (RCTs) and non-randomized studies of methadone use in chronic pain by searching the Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library 2011, issue 11, MEDLINE (1950 to November 2011),

and EMBASE (1980 to November 2011), together with reference lists of retrieved papers and reviews.

SELECTION CRITERIA:

We included RCTs with pain assessment as either the primary or secondary outcome. Quasi-randomized studies, cohorts and case-control trials were also considered for inclusion because we suspected that the beneficial and harmful effects of methadone in CNCP may not be adequately addressed in RCTs.

DATA COLLECTION AND ANALYSIS:

Two review authors independently extracted efficacy and adverse event data and assessed risk of bias.

MAIN RESULTS:

We included two RCTs and one non-randomized study, involving a total of 181 participants. Both RCTs were cross-over studies, one involving 19 participants with diverse neuropathic pain syndromes, the other involving 76 participants with postherpetic neuralgia. Study phases were 20 days and approximately eight weeks, respectively. The non-randomized study retrospectively evaluated 86 outpatients over an average of 8.8 ± 6.3 months.One RCT reported average pain intensity and pain relief, and found statistically significant improvements versus placebo for both outcomes, with 10 mg and 20 mg daily doses of methadone. The second RCT reported differences in pain reduction between methadone and morphine and found morphine to be statistically superior. The non-randomized study found that in patients initially prescribed methadone it was effective in fewer participants than in those initially prescribed other long-acting opioids (28% versus 42%, 33% and 50% for morphine, oxycodone and transdermal fentanyl, respectively).One RCT compared incidences for several individual adverse events, but found a difference between methadone and placebo for only one event, dizziness (P = 0.041).

AUTHORS' CONCLUSIONS:

The three studies provide very limited evidence of the efficacy of methadone for CNCP, and there were too few data for pooled analysis of efficacy or harm, or to have confidence in the results of the individual studies. No conclusions can be made regarding differences in efficacy or safety between methadone and placebo, other opioids, or other treatments.

Appendix B. Abstracts of potentially relevant new trials of long-acting opioids (Scan 2)

Head-to-head trials (N=2)

Mitra, F., S. Chowdhury, et al. (2013). "A feasibility study of transdermal buprenorphine versus transdermal fentanyl in the long-term management of persistent non-cancer pain." Pain Medicine 14(1): 75-83.

OBJECTIVE: Buprenorphine and fentanyl transdermal patches are used widely for the management of persistent malignant and nonmalignant pain. Buprenorphine and fentanyl transdermal patches, both potent opioids, are considered to be equally efficacious in managing persistent pain. Various retrospective studies comparing dosage changes of buprenorphine and fentanyl patches in persistent pain patients have been completed; however, no long-term prospective, randomized, clinical study has compared the effectiveness of these patches. The objective of the present study was to satisfy this need.

AIMS: This study aims to compare prospectively the long-term efficacy, acceptability, and side effects of both of these patches in patients with persistent pain. This study would examine the feasibility and lay the groundwork for a larger, multicenter study where such efficacy and safety outcomes of the two medications can be adequately assessed.

DESIGN: The participants were 46 adults (range 22-80 years.) with nonmalignant persistent pain (mean=11 years), predominantly with lower back pain. Data were obtained monthly for 12 months. Participants recruited were opioid-naive patients, having pain for the greater part of the day and night, and appropriate for treatment with transdermal patches. After initial assessment, participants were randomly allocated to either buprenorphine or fentanyl patch treatment. Participants were then titrated to optimal doses of medication. Patients with adverse effects or unsatisfactory pain relief were treated alternatively and discontinued from the study.

RESULTS: Nearly one-third of all patients, 41% (8 of 22) of the transdermal buprenorphine (TDB) group and 37.5% (8 of 24) of the transdermal fentanyl (TDF) group stopped treatment due to unacceptable side effects or inadequate pain relief. The remaining participants showed a similar trend in the improvement of pain intensity, physical activity, sleep, and mood throughout the study. Significant relief in the intensity of pain was achieved for the initial 6 months and the effects stabilized in the remainder of the study in both groups. There were no significant group differences over time. However, a higher equipotent dose of fentanyl was required for comparable pain relief. Compared with TDF group, the TDB group initially experienced relatively less side effects. However, a greater number of buprenorphine users suffered from local skin reactions. Buprenorphine users had significant improvement in mood. Thirty-one percent (5 of 16) of the buprenorphine group and 57% (8 of 14) of the fentanyl users needed additional pain relief medications by the end of 3 months. By the end of 12 months, a significant number 78% (7 of 9) of buprenorphine users but comparatively fewer 44% (4 of 9) of the fentanyl group used rescue medicines. Both had more doctor visits in the latter half of the study.

CONCLUSION: Thirty percent of the total number of patients discontinued treatment because of side effects or unsatisfactory pain relief. For those continuing treatment, clinical improvements were seen in the initial 6 months in both groups. Fifty percent of the TDB and 43% of TDF groups had significant relief in 3 months, which persisted up to 6

months. Only 11% and 13% of patients, respectively, had sustained relief after 6 months. Twenty percent more patients in the TDB group benefited significantly in symptoms of depression from TDB compared with the TDF group. Interestingly, switching of patches seemed to increase acceptability by preventing adverse effects and tolerance. Confirmation of these effects should be studied in future with a multicenter study and larger sample. Wiley Periodicals, Inc.

Richarz, U., S. Waechter, et al. (2013). "Sustained safety and efficacy of once-daily hydromorphone extended-release (OROS hydromorphone ER) compared with twice-daily oxycodone controlled-release over 52 weeks in patients with moderate to severe chronic noncancer pain." Pain Practice 13(1): 30-40.

Once-daily hydromorphone extended-release (OROS() hydromorphone ER) and oxycodone controlled-release (CR) are semisynthetic, ER opioid analgesics with established efficacy. An open-label, randomized, 24-week, parallel group, flexible-dose study demonstrated noninferiority of OROS hydromorphone ER vs. twice-daily oxycodone CR in patients with chronic noncancer pain. In total, 112 patients were enrolled in a 28-week, open-label extension study; 60 patients received OROS hydromorphone ER and 52 received oxycodone CR. The primary efficacy measure was the change from baseline to Weeks 38 and 52 in Brief Pain Inventory item "pain right now." Global assessments of efficacy, dosing convenience, and tolerability were secondary endpoints. Mean change in "pain right now" from baseline to Week 38 was -3.0 (OROS hydromorphone ER) vs. -2.8 (oxycodone CR), and from baseline to Week 52 was -2.9 vs. -2.8; these changes were similar to the changes in the core phase (-2.1 vs. -2.1). Similar improvements were demonstrated for secondary assessments, including pain, pain interference, and quality of life. At Week 52, global assessment of efficacy was rated as "very good" or "good" by the majority of patients (OROS hydromorphone ER, 91.7%; oxycodone CR, 86.5%). More patients in the OROS hydromorphone ER group (35.0% vs. 21.2%) assessed mode of drug intake as "very convenient." The majority of patients receiving OROS hydromorphone ER (88.3%) and oxycodone CR (88.5%) rated tolerability as "good" or "very good" at Week 52; few patients discontinued treatment because of an adverse event (1.6% vs. 0.4%, respectively). The effectiveness of OROS hydromorphone ER and oxycodone CR was maintained through 1 year. 2012 Janssen Global Services. Pain Practice 2012 World Institute of Pain.

Placebo controlled trials (N=3)

Jamison, R. N., R. R. Edwards, et al. (2013). "Relationship of negative affect and outcome of an opioid therapy trial among low back pain patients." Pain Practice 13(3): 173-181.

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.

Rauck, R., R. Rapoport, et al. (2013). "Results of a double-blind, placebo-controlled, fixed-dose assessment of once-daily OROS hydromorphone ER in patients with moderate to severe pain associated with chronic osteoarthritis." Pain Practice 13(1): 18-29.

OBJECTIVE: Opioids are recommended for patients with moderate to severe pain due to osteoarthritis (OA), who do not receive adequate analgesia from nonopioid treatment. The objective of this study was to evaluate the efficacy and safety of OROS hydromorphone extended-release (ER) compared with placebo in patients with moderate to severe pain associated with OA.

METHODS: This was a randomized, placebo-controlled, double-blind, fixed-dose study. Patients received placebo or fixed-dose OROS hydromorphone ER (8 or 16 mg). The primary efficacy measure was pain intensity score (11-point Numeric Rating Scale) at Maintenance Week 12, analyzed with baseline observation carried forward (BOCF) imputation for missing data.

RESULTS: This study did not meet the primary efficacy measure using the BOCF imputation. Study discontinuation was high (52%). When analyzed using last observation carried forward (LOCF) imputation, the prespecified alternate method, OROS hydromorphone ER 16 mg provided significantly better analgesia than placebo ($P = 0.0009$). Treatment was associated with significant improvements in patient global assessment ($P = 0.01$), the overall Western Ontario and McMaster Osteoarthritis Index (WOMAC) ($P = 0.0003$), and its subscales: pain ($P = 0.0001$), stiffness ($P = 0.0023$), and physical function ($P =$

0.0006). Gastrointestinal adverse events, such as constipation and nausea, were common among patients receiving OROS hydromorphone ER.

CONCLUSIONS: OROS hydromorphone ER failed to achieve statistical significance for the primary endpoint using the prespecified imputation method (BOCF), likely due to the high discontinuation rate associated with the fixed-dose design. When data were analyzed according to an alternate method of imputation (LOCF), OROS hydromorphone ER demonstrated statistically significant improvements in pain, stiffness, and physical function. 2012 The Authors. Pain Practice 2012 World Institute of Pain.

Yarlas, A., K. Miller, et al. (2013). "A randomized, placebo-controlled study of the impact of the 7-day buprenorphine transdermal system on health-related quality of life in opioid-naive patients with moderate-to-severe chronic low back pain." Journal of Pain 14(1): 14-23.

UNLABELLED: This study evaluated the impact of treatment with Buprenorphine Transdermal System (BTDS) on the health-related quality of life for patients with moderate-to-severe chronic low back pain (CLBP), and the correspondence between quality of life and pain. A multicenter, enriched, double-blind (DB), placebo-controlled, randomized trial evaluated BTDS 10 and 20 ug/hour for treatment of opioid-naive patients with moderate-to-severe CLBP. The SF-36v2 survey, which measures 8 domains of quality of life, was administered at screening and following an open-label run-in period with BTDS and at weeks 4, 8, and 12 of the DB phase. Post hoc analyses compared SF-36v2 scores between BTDS and placebo groups during the DB phase. Condition burden was examined through comparisons with a U.S. general population sample. Correlations examined the correspondence between quality of life and pain measures. BTDS produced larger improvements than placebo at 12 weeks in all quality-of-life domains (Ps < .05). Treatment group differences in both physical and mental quality of life emerged by 4 weeks. Patients' pretreatment quality of life was worse than that in the general population (Ps < .05); only BTDS treatment eliminated deficits in pain, social functioning, and role limitations due to emotional health. Improvements in quality of life were moderately associated with pain reduction. These data suggest that moderate-to-severe CLBP patients receiving BTDS exhibited better quality of life than patients receiving placebo.

PERSPECTIVE: This post hoc analysis suggests that patients with moderate-to-severe CLBP treated with BTDS exhibit better health-related quality of life than those using placebo within 4 weeks of treatment, and were more likely to exhibit clinically meaningful improvements in quality of life following 12 weeks of treatment. Copyright 2013 American Pain Society. Published by Elsevier Inc. All rights reserved.

Abstracts of potentially relevant new trials of long-acting opioids (Scan 1)

Head-to-head trials (N=3)

Afilalo, M., M. S. Etropolski, et al. (2010). "Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study." Clinical Drug Investigation **30**(8): 489-505.

BACKGROUND: Tapentadol is a novel, centrally acting analgesic with mu-opioid receptor agonist and norepinephrine reuptake inhibitor activity. OBJECTIVE: to evaluate the efficacy and safety of Tapentadol extended release (ER) compared with oxycodone controlled release (CR) for management of moderate to severe chronic osteoarthritis-related knee pain. METHODS: this was a randomized, double-blind, active- and placebo-controlled, parallel-arm, multicentre, phase III study during which patients received Tapentadol ER, oxycodone CR or placebo for a 3-week titration period followed by a 12-week maintenance period. The study was carried out at sites in Australia, Canada, New Zealand and the US. A total of 1030 patients with chronic osteoarthritis-related knee pain were randomized to receive Tapentadol ER 100-250 mg twice daily, oxycodone HCl CR 20-50 mg twice daily or placebo. Primary endpoints (as determined prior to initiation of the study) were the changes from baseline in average daily pain intensity (rated by patients on an 11-point numerical rating scale) over the last week of maintenance and over the entire 12-week maintenance period; last observation carried forward was used to impute missing values after early treatment discontinuation. RESULTS: efficacy and safety were evaluated for 1023 patients. Tapentadol ER significantly reduced average pain intensity from baseline to week 12 of the maintenance period versus placebo (least squares mean [LSM] difference [95% CI], -0.7 [-1.04, -0.33]), and throughout the maintenance period (-0.7 [-1.00, -0.33]). Oxycodone CR significantly reduced average pain intensity from baseline throughout the maintenance period versus placebo (LSM difference [95% CI], -0.3 [-0.67, -0.00]) but not at week 12 (-0.3 [-0.68, 0.02]). A significantly higher percentage of patients achieved > or =50% improvement in pain intensity in the Tapentadol ER group (32.0% [110/344]) compared with the placebo group (24.3% [82/337]; p = 0.027), indicating a clinically significant improvement in pain intensity, while a significantly lower percentage of patients achieved > or =50% improvement in pain intensity in the oxycodone CR group (17.3% [59/342]; p = 0.023 vs placebo). In the placebo, Tapentadol ER and oxycodone CR groups, respectively, 61.1% (206/337), 75.9% (261/344) and 87.4% (299/342) of patients reported at least one treatment-emergent adverse event (TEAE); incidences of gastrointestinal-related TEAEs were 26.1% (88/337), 43.0% (148/344) and 67.3% (230/342). CONCLUSION: treatment with Tapentadol ER 100-250 mg twice daily or oxycodone HCl CR 20-50 mg twice daily was effective for the management of moderate to severe chronic osteoarthritis-related knee pain, with substantially lower incidences of gastrointestinal-related TEAEs associated with treatment with Tapentadol ER than with oxycodone CR.

Buynak, R., D. Y. Shapiro, et al. (2010). "Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study.[Erratum appears in Expert Opin Pharmacother. 2010 Nov;11(16):2773]." Expert Opinion on Pharmacotherapy **11**(11): 1787-1804.

OBJECTIVE: To evaluate the efficacy and safety of tapentadol extended release (ER) for the management of moderate to severe chronic low back pain.

RESEARCH DESIGN: Patients (N = 981) were randomized 1:1:1 to receive tapentadol ER 100 - 250 mg b.i.d., oxycodone HCl controlled release (CR) 20 - 50 mg b.i.d., or placebo over 15 weeks (3-week titration period, 12-week maintenance period).

MAIN OUTCOME MEASURES: Efficacy was assessed as change from baseline in average pain intensity (11-point NRS) at week 12 of the maintenance period and

throughout the maintenance period; last observation carried forward was used to impute missing pain scores. Adverse events (AEs) were monitored throughout the study.
RESULTS: Tapentadol ER significantly reduced average pain intensity versus placebo at week 12 (least squares mean difference vs placebo [95% confidence interval], -0.8 [-1.22, -0.47]; $p < 0.001$) and throughout the maintenance period (-0.7 [-1.06,-0.35]; $p < 0.001$). Oxycodone CR significantly reduced average pain intensity versus placebo at week 12 (-0.9 [-1.24,-0.49]; $p < 0.001$) and throughout the maintenance period (-0.8 [-1.16,-0.46]; $p < 0.001$). Tapentadol ER was associated with a lower incidence of treatment-emergent AEs (TEAEs) than oxycodone CR. Gastrointestinal TEAEs, including constipation, nausea, and vomiting, were among the most commonly reported TEAEs (placebo, 26.3%; tapentadol ER, 43.7%; oxycodone CR, 61.9%). The odds of experiencing constipation or the composite of nausea and/or vomiting were significantly lower with tapentadol ER than with oxycodone CR (both $p < 0.001$).
CONCLUSIONS: Tapentadol ER (100 - 250 mg b.i.d.) effectively relieved moderate to severe chronic low back pain over 15 weeks and had better gastrointestinal tolerability than oxycodone HCl CR (20 - 50 mg b.i.d.).

Wild, J. E., S. Grond, et al. (2010). "Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain." Pain Practice **10**(5): 416-427.

BACKGROUND: Tapentadol is a novel, centrally acting analgesic with 2 mechanisms of action: -opioid receptor agonism and norepinephrine reuptake inhibition. This randomized, open-label phase 3 study (ClinicalTrials.gov Identifier: NCT00361504) assessed the long-term safety and tolerability of tapentadol extended release (ER) in patients with chronic knee or hip osteoarthritis pain or low back pain.
METHODS: Patients were randomized 4:1 to receive controlled, adjustable, oral, twice-daily doses of tapentadol ER (100 to 250 mg) or oxycodone HCl controlled release (CR; 20 to 50 mg) for up to 1 year. Efficacy evaluations included assessments at each study visit of average pain intensity (11-point numerical rating scale) over the preceding 24 hours. Treatment-emergent adverse events (TEAEs) and discontinuations were monitored throughout the study.
RESULTS: A total of 1,117 patients received at least 1 dose of study drug. Mean (standard error) pain intensity scores in the tapentadol ER and oxycodone CR groups, respectively, were 7.6 (0.05) and 7.6 (0.11) at baseline and decreased to 4.4 (0.09) and 4.5 (0.17) at endpoint. The overall incidence of TEAEs was 85.7% in the tapentadol ER group and 90.6% in the oxycodone CR group. In the tapentadol ER and oxycodone CR groups, respectively, TEAEs led to discontinuation in 22.1% and 36.8% of patients; gastrointestinal TEAEs led to discontinuation in 8.6% and 21.5% of patients.
CONCLUSION: Tapentadol ER (100 to 250 mg bid) was associated with better gastrointestinal tolerability than oxycodone HCl CR (20 to 50 mg bid) and provided sustainable relief of moderate to severe chronic knee or hip osteoarthritis or low back pain for up to 1 year. 2010 World Institute of Pain.

Active-control trials (N=3)

Cruciani, R. A., N. Katz, et al. (2012). "Dose equivalence of immediate-release hydromorphone and once-daily osmotic-controlled extended-release hydromorphone: a randomized, double-blind trial incorporating a measure of assay sensitivity." Journal of Pain **13**(4): 379-389.

Dose selection of a once-daily, osmotic-controlled extended-release (ER) hydromorphone assumes that this drug and immediate-release (IR) hydromorphone are dose equivalent. This trial evaluated dose equivalence using a measure of assay sensitivity. Patients were converted to open-label IR hydromorphone, underwent dose titration, and those on a satisfactory dose entered a randomized, double-blind phase receiving 7 days of: 1) hydromorphone IR 5 times/day at approximately this dose; 2) once-daily hydromorphone ER at this dose; or 3) once-daily hydromorphone ER at one-half this dose. Efficacy was measured using breakthrough medication use, pain, sleep, and global assessments. Of 148 patients, 113 (76%) were randomized. IR and full-dose ER groups produced comparable effects on all measures. Although the prespecified primary analysis of the difference in total daily dose of breakthrough medication between the full-dose ER and half-dose ER groups was not significant, more patients in the half-dose ER group required an increase in breakthrough medication (P = .026) and the half-dose ER group both increased the number of breakthrough doses (P = .026) and had greater percent change in the total daily dose of breakthrough medication (P = .037) than the full-dose group, suggesting that switching from IR to ER hydromorphone at the same daily dose provides equivalent analgesia. PERSPECTIVE: In a randomized, double-blind trial, the same total daily dose of immediate-release hydromorphone and once-daily osmotic-controlled extended-release hydromorphone had comparable effects. Detection of different effects between blinded dose levels was used as a measure of assay sensitivity. The measure of assay sensitivity can enhance the interpretation of dose equivalence or noninferiority trials. Copyright 2012 American Pain Society. Published by Elsevier Inc. All rights reserved.

Etropolski, M. S., A. Okamoto, et al. (2010). "Dose conversion between tapentadol immediate and extended release for low back pain." Pain Physician **13**(1): 61-70.

BACKGROUND: Tapentadol, a novel, centrally acting analgesic with 2 mechanisms of action (mu-opioid receptor agonism and norepinephrine reuptake inhibition), has been developed in an immediate-release (IR) and an extended-release (ER) formulation. Determination of the safety and equianalgesic ratios for conversion between formulations is important for physicians with patients taking tapentadol IR who may want to switch to tapentadol ER, or vice versa, for any reason.

OBJECTIVES: To test whether the total daily dose (TDD) of tapentadol IR may be directly converted into a comparable TDD of tapentadol ER, and vice versa, with equivalent efficacy and comparable safety.

STUDY DESIGN: Randomized, double-blind, 2-period (2 weeks each) crossover study.

SETTING: Study centers (N = 13) in the United States.

METHODS: Patients with moderate to severe chronic low back pain received tapentadol IR 50, 75, or 100 mg every 4 or 6 hours (maximum TDD, 500 mg) during the 3-week open-label period to identify an optimal, stable dose of tapentadol IR for each patient. Patients were then randomized in a 1:1 ratio to receive, during the first 2-week double-blind period, either the optimal dose of tapentadol IR identified during the open-label period or a TDD of tapentadol ER (100, 150, 200, or 250 mg bid) that was as close as possible to the TDD of tapentadol IR from the open-label period. During a subsequent, 2-

week double-blind period, patients received whichever formulation was not received during the first double-blind period. The primary endpoint was the mean average daily pain intensity (on an 11-point numerical rating scale) during the last 3 days of each double-blind treatment period. If the 95% confidence intervals (CIs) of the least squares mean difference between formulations were within the range of -2 to 2, the formulations were considered equivalent.
RESULTS: Of the 88 patients who were randomized, 72 completed both double-blind treatments, and 60 were included in the per-protocol analysis. The mean (standard deviation [SD]) pain intensity score decreased from 7.3 (1.19) pre-treatment to 4.2 (2.13) after 3 weeks of open-label treatment with tapentadol IR and remained constant throughout double-blind treatment (3.9 or 4.0 each week) for both formulations. The mean (SD) of the average pain intensity scores over the last 3 days of double-blind treatment was 3.9 (2.17) with tapentadol IR and 4.0 (2.29) with tapentadol ER, for an estimated difference of 0.1 (95% CI, -0.09 to 0.28). For both tapentadol IR and tapentadol ER, the median TDD administered was 300.0 mg, and acetaminophen was used by 39.5% and 45.2% of patients, respectively. The incidence of treatment-emergent adverse events during double-blind treatment was similar between the tapentadol IR and tapentadol ER groups.
LIMITATIONS: Use of rescue medication theoretically could have influenced pain measurements, but in practice, pain measurements did not differ between treatments.
CONCLUSIONS: Approximately equivalent TDDs of tapentadol IR and tapentadol ER provided equivalent analgesic efficacy for the relief of moderate to severe chronic low back pain and were similarly well tolerated, allowing for direct conversion between the 2 formulations. Clinical Trial Registration: NCT00594516.

Steiner, D., C. Munera, et al. (2011). "Efficacy and safety of buprenorphine transdermal system (BTDS) for chronic moderate to severe low back pain: a randomized, double-blind study." Journal of Pain **12**(11): 1163-1173.

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 oxycodone 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 oxycodone 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 oxycodone 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 was found to be efficacious and generally well tolerated. Copyright A 2011 American Pain Society. Published by Elsevier Inc. All rights reserved.

Placebo controlled trials (N=4)

Chu, L. F., N. D'Arcy, et al. (2012). "Analgesic tolerance without demonstrable opioid-induced hyperalgesia: a double-blinded, randomized, placebo-controlled trial of sustained-release morphine for treatment of chronic nonradicular low-back pain." Pain **153**(8): 1583-1592.

Although often successful in acute settings, long-term use of opioid pain medications may be accompanied by waning levels of analgesic response not readily attributable to advancing underlying disease, necessitating dose escalation to attain pain relief. Analgesic tolerance, and more recently opioid-induced hyperalgesia, have been invoked to explain such declines in opioid effectiveness over time. Because both phenomena result in inadequate analgesia, they are difficult to distinguish in a clinical setting. Patients with otherwise uncomplicated low-back pain were titrated to comfort or dose-limiting side effects in a prospective, randomized, double-blind, placebo-controlled clinical trial using sustained-release morphine or weight-matched placebo capsules for 1 month. A total of 103 patients completed the study, with an average end titration dose of 78 mg morphine/d. After 1 month, the morphine-treated patients developed tolerance to the analgesic effects of remifentanil, but did not develop opioid-induced hyperalgesia. On average, these patients experienced a 42% reduction in analgesic potency. The morphine-treated patients experienced clinically relevant improvements in pain relief, as shown by a 44% reduction in average visual analogue scale pain levels and a 31% improvement in functional ability. The differences in visual analogue scale pain levels (P = .003) and self-reported disability (P = .03) between both treatment groups were statistically significant. After 1 month of oral morphine therapy, patients with chronic low-back pain developed tolerance but not opioid-induced hyperalgesia. Improvements in pain and functional ability were observed. Copyright 2012 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Peniston, J. H., X. Hu, et al. (2012). "Tolerability of concomitant use of selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors and oxymorphone extended release." Postgraduate Medicine **124**(2): 114-122.

BACKGROUND: Opioids and antidepressants are frequently prescribed for chronic low back pain (cLBP). This post hoc analysis was conducted to assess the tolerability of oxymorphone extended release (ER) for cLBP in patients taking selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) compared with patients not taking SSRIs/SNRIs.

METHODS: Patients in 2 clinical trials (NCT00225797, November 22, 2004 to July 18, 2005; NCT00226421, October 13, 2004 to August 19, 2005) aged >= 18 years with moderate to severe cLBP were titrated to a stabilized dose of oxymorphone ER during an open-label titration phase and then randomized to treatment with this dose or placebo every 12 hours for 12 weeks. In a post hoc analysis, adverse events (AEs) were compared between patients taking versus not taking SSRIs/SNRIs. Treatment efficacy was assessed as change from baseline in average daily pain intensity on a 100-mm visual analog scale.

RESULTS: Of 575 patients enrolled, 45 of 89 (50.6%) taking SSRIs/SNRIs and 303 of 486 (62.3%) not taking SSRIs/SNRIs successfully titrated to oxymorphone ER. The frequency of any AE did not differ significantly between the 2 subpopulations. During the titration phase, serious AEs occurred more frequently in patients taking SSRIs/SNRIs (3/89; 3.4%) compared with those not taking SSRIs/SNRIs (4/486; 0.8%; P = 0.04); however, during the double-blind treatment phase, there was no significant difference in the frequency of serious AEs in patients treated with oxymorphone ER taking (1/29; 3.4%) versus those not taking (3/146; 2.0%) SSRIs/SNRIs. Visual analog scale scores were similar in patients taking versus those not taking SSRIs/SNRIs throughout the study.
CONCLUSION: The concomitant use of oxymorphone ER with SSRIs or SNRIs was well tolerated in patients with cLBP.

Schwartz, S., M. Etropolski, et al. (2011). "Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial." Current Medical Research & Opinion **27**(1): 151-162.

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.
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 (100-250mg 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 during double-blind treatment and may present a risk of unblinding because of changes in side effects from the open-label to the double-blind phase.

CONCLUSIONS: Compared with placebo, tapentadol ER 100-250mg bid provided a statistically significant difference in the maintenance of a clinically important improvement in pain 1 , 2 and was well-tolerated by patients with painful DPN.

Steiner, D. J., S. Sitar, 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." Journal of Pain & Symptom Management **42**(6): 903-917.

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.