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Abbreviated Class Update: Long-Acting Opioids (LAOs)

Month/Year of Review: July 2013
New drug(s): morphine/naltrexone (Embeda™) August 2009
hydromorphone (Exalgo™) March 1, 2010
buprenorphine (Butrans™) June 30, 2010
tapentadol (Nucynta ER™) August 25, 2011
oxymorphone (Opana ER) *new formulation* December 9, 2011

End date of literature search: May 2013
Manufacturer: Alpharma King
Mallinckrodt, Inc.
Purdue Pharma LP
Janssen
Endo Pharms

Oregon PDL status	Drug	Trade name(s)	Forms evaluated in review	Recommended usual dosing frequency (times per day)
N	buprenorphine	Butrans™	ER transdermal film	Every 7 days
Y	fentanyl	Duragesic™	ER transdermal film	Every 72 hours
N	hydromorphone	Exalgo™	ER oral tablet	1
N	levorphanol	Generic	Oral tablet	3-4
Y	methadone	Generic, Dolophine™	Oral tablet	2-3
N	morphine sulfate	Generic	ER oral capsule	1
N		Avinza™	ER oral capsule	1
N		Kadian™	ER oral capsule	1-2
N		Generic	ER oral capsule	1-2
Y		Generic	ER oral tablet	2-3
Y		MS Contin™	ER oral tablet	2-3
Y		Oramorph SR™ [a]	ER oral tablet	2-3
N	morphine sulfate and naltrexone hydrochloride	Embeda™	ER oral capsule	1-2
N	oxycodone	OxyContin™	ER oral tablet	2
N	oxymorphone	Opana ER™	ER oral tablet	2
N	tapentadol	Nucynta ER™	ER oral tablet	2

Abbreviations: ER, extended release; MS, morphine sulfate; SR, sustained release.
[a]Discontinued

Additionally, there is a maximum dose prior authorization (PA) required for doses greater than 100 morphine equivalent doses (MED) on all LAOs. Duplication of LAOs is not allowed except for cross-titration. Methadone carries an additional PA for initial doses above 20mg per day when prescribed for pain. Methadone for addiction treatment is also covered via professional claims.

Research Questions:

- Is there any new evidence about comparative effectiveness of different long-acting opioids, in reducing pain and improving functional outcomes in adult patients being treated for chronic non-cancer pain?
- Is there any new evidence about comparative harms (including addiction and abuse) of different long-acting opioids in adult patients being treated for chronic non-cancer pain?
- Are there subpopulations of patients (specifically by race, age, sex, socioeconomic status type of pain, or comorbidities) with chronic non-cancer pain for which one long-acting opioid is more effective or associated with less harm?

Conclusions:

- There continues to be insufficient comparative evidence to establish differences in effectiveness among the LAOs. Morphine and fentanyl have the most evidence of efficacy against placebo per DynaMed. Treatment guidelines consistently recommend morphine as first-line with fentanyl patches recommended for patients who cannot tolerate oral medications.
- There continues to be insufficient comparative evidence to establish differences in safety among the LAOs. All LAOs carry FDA Black Box warnings for increased risk of death and risk of abuse and misuse. However, methadone alone carries the warning of accumulation and was associated with more than 30% of opioid related deaths in Oregon.
- There is insufficient comparative evidence in subpopulations to differentiate drugs.

Recommendations:

- Remove methadone from preferred status due to safety concerns.
- A form of morphine ER should remain a preferred option and relative cost of the different formulations evaluated in executive session to determine preference.
- All other drugs should be evaluated in executive session for relative cost.

Reason for Review: Oregon has not reviewed the literature in this class since 2006. Since then, the Drug Effectiveness Review Project (DERP) completed Update #6 (July 2011 with searches through January 2011)[1] and a recent literature scan for new information (searches through April 2013).[2] Additionally, the FDA published the Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS)[3] in response to a CDC report[4] of increasing deaths associated with all prescription opioids. Finally, Oregon Health Authority executives requested the committee specifically evaluate the safety of methadone in light of the 2012 Oregon Medical Examiner report.[5]

Previous HRC Conclusions (2006):

- There is insufficient evidence to draw any conclusions about the comparative efficacy of long-acting opioids.
- There is insufficient evidence to draw conclusions about incidence and nature of adverse effects, including discontinuation rates and addiction and abuse of long-acting opioids
- There is insufficient evidence to support differences in efficacy or adverse effects in sub-populations by race and ethnicity, age, gender, or type of pain in this class of drugs.
- Even though evidence does not demonstrate a difference between long-acting opioids or between long-acting opioids when compared to other drugs, limitations of studies currently available for review preclude a confident conclusion that no differences exist. It is possible that better controlled studies may yet demonstrate such differences.

Background: Long-acting opioids are indicated for moderate to severe chronic (at least 3 to 6 months) pain, which impairs function or quality of life, where the benefits outweigh risks and no alternative has a better risk/benefit profile. Opioids have been endorsed by the American Pain Society/American Academy of Pain Medicine,[6] the Canadian Pain Society[7,8] and others,[9,10,11] as appropriate treatment for refractory chronic non-cancer pain, in the general population and in older patients, when used judiciously and according to guidelines. The World Health Organization's (WHO) "analgesic ladder, "[12] originally published in the mid-1980s, outlines an approach to pain control that has widely influenced cancer pain management and subsequently many of the strategies used in nonmalignant pain.[13]

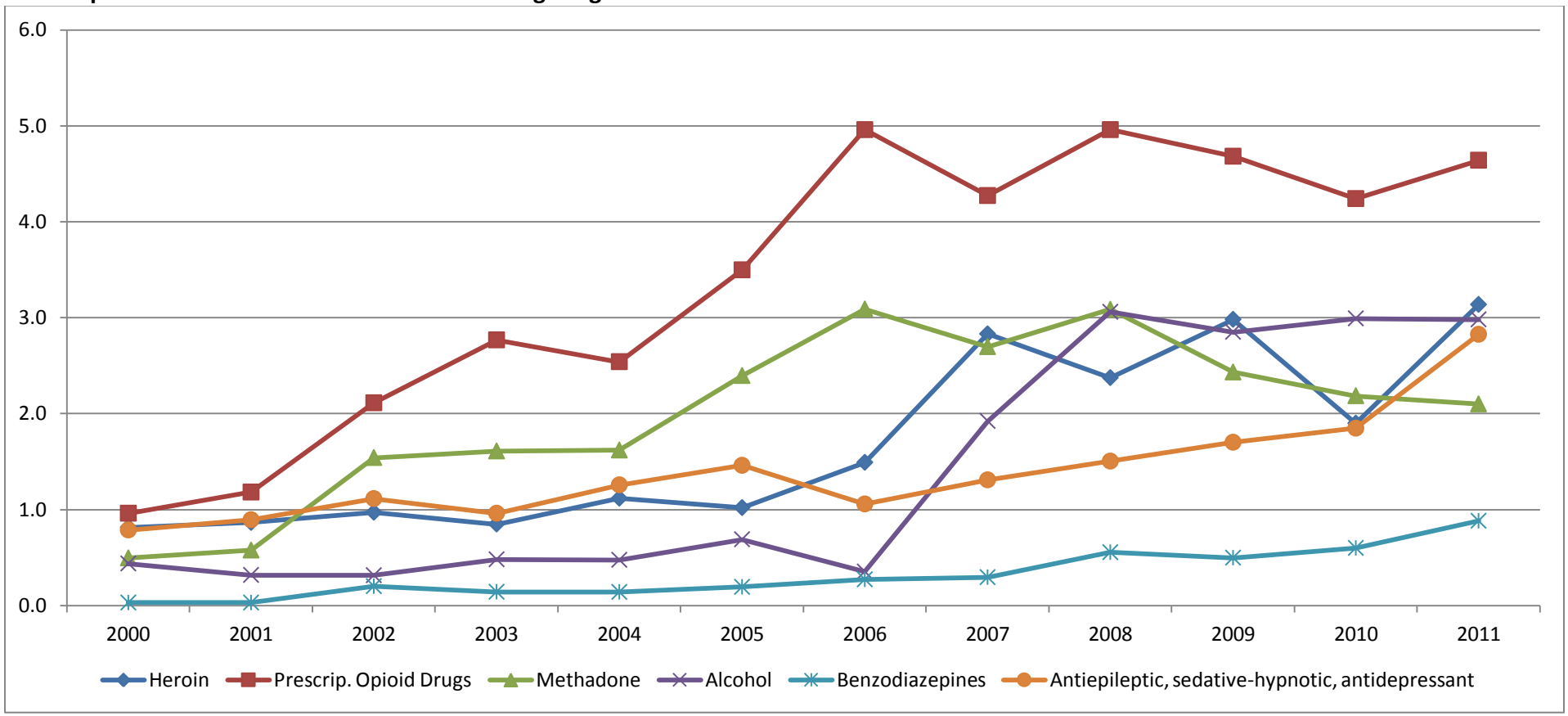
Previous DERP reports[14,15] have established there was insufficient evidence to distinguish differences in effectiveness or harms between LAOs when used to treat adult nonmalignant pain. In the absence of sufficient evidence, Oregon Health Plan preference has been established with cost. Several new drugs have been approved [i.e. morphine/naltrexone (Embeda™), hydromorphone (Exalgo™),buprenorphine (Butrans™) , tapentadol (Nucynta ER™) and a new formulation of oxymorphone (Opana ER)].

In July 2012, the Centers for Disease Control published a report[4] of the Drug Abuse Warning Network 2011 data[16] indicating, that despite a reduction since 2007, methadone used for pain relief was associated with 31.4% of opioid pain reliever deaths and almost 40% of single-drug

opioid pain reliever deaths in 2010. The overdose death rate for methadone was significantly higher than any other opioid. CDC recommended, "*For chronic non-cancer pain, methadone should not be considered a drug of first choice by prescribers or insurers.*"[4] This report and its recommendation have been widely reported in the lay press.[17,18,19] Unintentional drug poisonings were the fourth highest cause of death (9.4 per 100,000) in Oregon in 2007 (motor vehicle deaths were second at 12.1 per 100,000).[20] Prescription opioids represented 53% of all deaths due to poisoning by drugs in 2008 and methadone led all opioids.[20] The most recent Oregon Medical Examiner's Report[5] confirms a recent downward trend from a peak in 2007 for methadone deaths, decreasing 20% from 100 in 2011 to 78 in 2012. This decrease was attributed to the implementation of the 2010 Prescription Drug Monitoring Program (PDMP) in Oregon.[5] Despite the PDMP, oxycodone-related deaths rose from 56 in 2011 to 66 in 2012. The PDMP data in Figure 1 was presented at the National Governor's Association (NGA) Prescription Drug Misuse and Abuse Workgroup meeting in December 2012.[21] Methadone was linked to 30% of drug overdose deaths in Oregon and Medicaid was over-represented in the data generally.[21] However, the issue appears complex: 30% of patients did not have an opioid prescription; misuse or abuse contributed to 77% of deaths and 52% of patients had a history of mental illness.[21]

The FDA responded to the CDC report by publishing their efforts to "Address the Misuse and Abuse of Opioids."[22] It is a multi-pronged approach ranging from the encouragement of abuse-deterrent formulations (e.g. OxyContin[23]) to implementing a REMS[3] program for ***all*** LAOs (notably not singling out methadone). The REMS program requires all manufacturers of LAOs to ensure that training is made available to prescribers of LAOs and that patient medication guides are dispensed with all prescriptions. All of the LAOs carry at least one FDA Black Box warning of high potency and risk of respiratory depression, risk of misuse and abuse, cautions about appropriate patient selection, cautions against crushing or mixing with alcohol or accumulation.

Figure 1: Overdose death rate by drug type per 100,000 in Oregon 2000-2011[21]
Note: a person can have more than 1 contributing drug related to their death



Methods:
A Medline literature search ending May 2013 for new systematic reviews and randomized controlled trials (RCT's) that compared long-acting opioids in head to head trials was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, three recent systematic reviews[1,24,25] comparing opioid treatments, three updated chronic pain treatment guidelines[7,8,9,10] and three RCTs comparing tapentadol ER to oxycodone ER were included in this review.

Systematic Reviews:
The 2011 DERP Report[1] identified 10 head-to-head trials comparing two or more LAOs but still concluded the evidence was insufficient to determine if there are differences in effectiveness or harms among the drugs. Eight trials found no significant difference in pain relief or function. The two that found a significant difference were rate poor quality. The authors noted the included studies were relatively small, short and had important methodological flaws. Tapentadol ER was not included in the literature searches.

The DynaMed[24] review notes that not only is the comparative evidence lacking for this class but, that evidence of efficacy of the individual opioids is weak overall, with the best evidence for morphine ER tablets and transdermal fentanyl. It cites Level 2 (moderate) evidence that morphine ER (Avinza™) may be more effective than oxycodone ER (OxyContin™) in enabling patients with low back pain to return to work (n=266).[24] No comparative evidence of harms is presented outside the FDA labeling for each drug. However, three citations that associate the risk of death to increased opioid doses and that were previously reviewed by the Oregon DUR Board when considering the current LAO high dose limits are provided.[26,27,28]

Cochrane evaluated the use of methadone for chronic non-malignant pain and concluded that three studies (n=181) provided very limited evidence of efficacy.[25] No conclusions could be drawn on the differences in efficacy or safety between methadone and placebo or other opioids (i.e. morphine, oxycodone or transdermal fentanyl).[25]

New Guidelines:
The National Institute of Clinical Excellence published guidance on the use of strong opioids for pain in palliative care in 2012.[10] Morphine ER is recommended first-line unless the oral route is not viable, then fentanyl patches are recommended. The recommendations are based upon low-quality evidence from RCTs and expert opinion. The guideline does not cover all aspects of pain management, including second-line approaches.

The Canadian guidelines[7,8] for chronic nonmalignant pain were updated and published in 2011. The guidelines include recommendations on opioid indications, selection, titration, precautions and monitoring. Only selection recommendations are reported here. After a failed trial of either codeine or tramadol, morphine is recommended for patients without renal impairment. Oxycodone or hydromorphone are not recommended for patients at higher risk of opioid misuse or addiction. Methadone is only available to prescribers with a written Health Canada exemption because it is considered hazardous due to its bioaccumulation. Fentanyl is recommended only for patients already stabilized on 60-90 mg of MED for two weeks. Doses about 200mg MED of any opioid are not recommend.

The United States Veterans Administration and Department of Defense published guidelines on opioid therapy for chronic pain in 2010.[9] Drug selection recommendations are reported from this very comprehensive document. The authors report there is no evidence to recommend any specific opioid but recommend to base drug selection in a shared-decision making model to match the individual's needs and specific medical conditions. However, both fentanyl (not in opioid naïve patients) and methadone (arrhythmia risk) receive cautionary statements. Morphine ER is recommended as first-line, oxycodone ER is recommended second-line. The guidelines include a summary table of the evidence for opioids in special populations which is reproduced in Appendix 1.

Randomized Controlled Trials: Three trials[29,30,31] evaluating tapentadol ER were identified. Two were 12-week non-inferiority trials versus oxycodone ER in osteoarthritis[29] and low back pain[30] and the third was safety and tolerability study for up to one year. [31] However, only 52% took a study medication for 6 months. Evidence from these trials is insufficient to indicate tapentadol is more effective or safer than other LAOs. A summary is in Table 1 below and the abstracts are in Appendix 2.

Table 1: Potentially relevant comparative trials

Study	Comparison	Population	Primary Outcome	Results
Afilalo 2010 RCT DB	tapentadol ER 100-250mg BID vs. oxycodone ER 20-50mg BID vs. placebo	Osteoarthritis	Change from baseline on average daily pain intensity on 11-pt numerical scale at 12-weeks or last observation carried forward.	n=1023 (loss to f/u n=7) T vs. P least square means = -0.7[-1.04, -0.33] O vs. P least square means = -0.3 [-0.68, 0.02]

Buynak 2010 RCT 1:1:1	tapentadol ER 100-250mg BID vs. oxycodone ER 20-50mg BID vs. placebo	Low back pain	Change from baseline on average daily pain intensity on 11-pt numerical scale at 12-weeks or last observation carried forward.	n=981 T vs. P least square means = -0.8[-1.22, -0.47] O vs. P least square means = -0.9 [-1.24, -0.49]
Wild 2010 RCT 4:1	tapentadol ER 100-250mg BID vs. oxycodone ER 20-50mg BID vs. placebo	Osteoarthritis or low back pain	Safety and tolerability assessments for up to 1 year.	N=1121 (loss to f/up n=4) Withdrawal for ADE: T: 203 (22.7%) O: 82 (36.8%)

New Safety Alerts, Indications:

July 2012: FDA approved a risk evaluation and mitigation strategy (REMS)[3] for extended-release and long-acting opioid medications. The REMS consists of a Medication Guide, elements to assure safe use, and a timetable for submission of assessments of the REMS. This REMS will use a single, shared system for the elements to ensure safe use and the REMS assessments. This single shared system is known as the ER/LA Opioid REMS.

The updated labels include information on ER/LA prescription opioid analgesics abuse potential, the risk of life-threatening respiratory depression, and consumer-friendly information on the safe use and disposal of ER/LA opioid analgesics.

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Appendix 1:[9]

Table 3: Use of Opioids for Chronic Pain in Special Populations

Medication	Swallowing difficulty	GI mal-absorption	Pregnancy Risk Category (a)	Lactation (a)	Hepatic dysfunction	Renal dysfunction	Renal Dialysis	Prolonged QTc	Seizures	Elderly or debilitated	Decreased CYP-2D6 activity
Codeine (b)			C*‡	◆*	✖	◆ and ↓	✖			◆ and ↓	Less effective
Fentanyl transdermal	✚	✚	C†‡	UC (c)	◆ and ↓		◆				
Hydrocodone			C†‡	PC			◆				? less effective
Hydromorphone	✚ (OS, RS)	✚ (RS)	B†‡	PC	◆ and ↓		◆(RBD)				
Methadone (e)	✚ (OS)		B†‡	PC	◆ and ↓		◆	◆			
Morphine	✚ (OS, RS)	✚ (RS)	C†‡	PC		↓ or ✖	◆ or ✖(RBD)				
Morphine SR/CR (8-12h); ER (24h)											
Oxycodone	✚ (OS)		B†‡	PC		◆ and ↓	✖(ND)				? less effective
Oxycodone CR (12h)											
Oxymorphone			B†‡	PC	✖	◆ and ↓	◆(RBD)				
Oxymorphone ER (12h)											
Propoxyphene			C†‡	PC	✖	✖	✖		◆	✖	
Tapentadol			C†	✖(f)	◆	↓ or ✖	✖(ND)		◆		
Tramadol			C†	PC	◆ and ↓	◆ and ↓	✖ (RBD)		✖	◆ and ↓	? less effective
Tramadol ER (24h)											

(a) Estimates of risk of opioid therapy in pregnancy and while breastfeeding may be based on expectations of intermittent or short-term use; use of chronic opioid therapy during pregnancy or while breastfeeding should be approached with caution.
(b) Codeine is metabolized to morphine by CYP 2D6; both pass into breast milk in small amounts usually considered clinically insignificant; however, caution in known or suspected ultra rapid metabolizers of CYP 2D6 substrates; 2006 case report of death in a nursing infant of CYP 2D6 ultra rapid metabolizer mother associated with high morphine levels in breast milk (Koren et al., 2006).
(c) Manufacturer does not recommend use while breast-feeding; classified as compatible by the American Academy of Pediatrics
(d) Fentanyl citrate available as transmucosal lozenges, buccal tablets
(e) Methadone is the only long-acting opioid available as an oral solution. See Appendix E, Tables E1 and E2 and Appendix F Methadone Dosing Recommendations for Treatment of Chronic Pain for further details and references.
(f) Per product information.

CR = Controlled release
OS = Oral solution
RS = Rectal suppository
SR = Sustained release
TDS = Transdermal system
RBD = Removed by dialysis
ND = No data

✚ = Recommended
✹ = Use with caution
⇩ = Reduce dose
✖ = Not recommended
? less effective = conversion to the active metabolite may be decreased. Impact on analgesic efficacy unknown.

Pregnancy Risk Categories
A = controlled studies show no risk
B = no evidence of risk in humans
C = Risk cannot be ruled out, but potential benefits may justify potential risk
D = Positive evidence of risk; however, potential benefits may outweigh potential risk
X = Contraindicated in pregnancy.
*human data suggest risk (Briggs et al., 2008
† human data suggest risk in 3rd trimester (Briggs et al., 2008
‡Risk category D if prolonged periods or high doses at term (Briggs et al., 2008)

Use while breast-feeding
UC = usually compatible; either not excreted into human breast milk in clinically significant amounts or not expected to cause toxicity in infant
PC = probably compatible; no or limited human data
✹ = potential toxicity; no or limited human data
✖ = not recommended due to potential toxicity; no or limited human data
CI = contraindicated; potential for severe toxicity based on animal and/or human data

Appendix 2: Abstracts of potentially relevant randomized controlled trials and/or systematic reviews

Authors : Afilalo M. Etropolski MS. Kuperwasser B. Kelly K. Okamoto A. Van Hove I. Steup A. Lange B. Rauschkolb C. Haeussler J.
Title: 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.
Source: Clinical Drug Investigation. 30(8):489-505, 2010.

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.

Authors: Buynak R. Shapiro DY. Okamoto A. Van Hove I. Rauschkolb C. Steup A. Lange B. Lange C. Etropolski M.
Title: 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]
Source: Expert Opinion on Pharmacotherapy. 11(11):1787-804, 2010 Aug.

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.).

Authors: Wild JE. Grond S. Kuperwasser B. Gilbert J. McCann B. Lange B. Steup A. Haufel T. Etropolski MS. Rauschkolb C. Lange R.
Title: Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain.
Source: Pain Practice. 10(5):416-27, 2010 Sep-Oct.
Abstract: 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.