CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Tapentadol Hydrochloride Extended-Release Tablet
(Nucynta Extended-Release)

(Paladin Labs Inc.)

Indication: Management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. Tapentadol extended-release tablet is not indicated as an as-needed (prn) analgesic.

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Abbreviations

AAPS	Action Atlantic Pain Society
ACE	Arthritis Consumer Experts
AE	adverse event
ARCI-WOWS	Addiction Research Centre Inventory – Weak Opiate Withdrawal Scale
AUC	under the curve
BOCF	baseline observation carried forward
BPI	Brief Pain Inventory
CAPA	Canadian Arthritis Patient Alliance
CDR	CADTH Common Drug Review
CI	confidence interval
CINA	Clinical Institute Narcotic Assessment
CMH	Cochran–Mantel–Haenszel
COWS	Clinical Opiate Withdrawal Scale
CPAC	Chronic Pain Association of Canada
CPSG	Chronic Pain Support Group
CR	controlled release
DB	double blind
EQ-5D	EuroQol 5-Dimensions questionnaire
EQ-5D-3L	EuroQol 5-Dimensions 3-Levels questionnaire
ER	extended release
FAS	full analysis set
HADS	Hospital Anxiety and Depression Scale
HHCPSG	Halton/Hamilton Chronic Pain Support Group
HRQoL	health-related quality of life
ICC	intra class correlation coefficient
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IQR	interquartile range
IR	immediate release
ITT	intention-to-treat
LBP	low back pain
LOCF	last observation carried forward
LSM	least squares mean
LSMD	least squares mean difference
MCID	minimal clinically importance difference
MCS	mental component summary
NMA	network meta-analysis
NPSI	Neuropathic Pain Symptom Inventory
NRS	numeric rating scale
NSAIDs	nonsteroidal anti-inflammatory drugs
OA	osteoarthritis
OL	open label

PAC-SYM	Patient Assessment of Constipation Symptoms
PCS	physical component summary
PGIC	Patient Global Impression of Change
PP	per-protocol
PR	prolonged release
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SD	standard deviation
SE	standard error
SF-12	12-item Short Form Health Survey
SF-36	36-item Short Form Health Survey
SOWS	Subjective Opiate Withdrawal Scale
SR	sustained release
TDD	total daily dose
VAS	visual analogue scale
WDAE	withdrawal due to adverse event
WOCF	worst observation carried forward
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Drug	Tapentadol hydrochloride extended-release tablet (Nucynta Extended-Release)
Indication	Management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. Nucynta Extended-Release is not indicated as an as-needed (prn) analgesic.
Reimbursement Request	As per indication
Dosage Form(s)	50 mg, 100 mg, 150 mg, 200 mg, and 250 mg tablets
NOC Date	October 31, 2013
Manufacturer	Paladin Labs Inc.

Executive Summary

Introduction

Chronic pain is generally defined as a painful condition persisting for several months or longer. In terms of approach to management, chronic pain can be broadly classified as either cancer-related pain or non-cancer pain. Common causes or types of chronic non-cancer pain include osteoarthritis (OA), back pain, fibromyalgia, post-surgical chronic pain, and painful diabetic neuropathy.[1,2] Results from Canadian surveys from 1994 to 2008 estimated the prevalence of chronic pain in Canadian adults to be 15% to 19%.[3]

When chronic pain cannot be managed with non-opioid pharmacological or non-pharmacological options, opioid analgesics may be considered. For neuropathic pain, the 2014 Canadian Consensus Statement on Neuropathic Pain recommends anticonvulsants and antidepressant agents as first-line analgesics, opioids as second-line analgesics, cannabinoids as third-line analgesics, and a variety of other types of agents as fourth-line analgesics.[4] There is evidence of varying quality that non-pharmacological interventions (such as exercise, manual therapy, and multidisciplinary treatment programs) may also benefit patients with chronic pain.[5-7] The *2017 Canadian Guidelines for Opioids for Chronic Non-Cancer Pain*[8] strongly recommend optimization of non-opioid analgesic therapy and non-pharmacological therapy before administering a trial of opioids. The guidelines also contain strong recommendations against using opioids in patients with an active substance use disorder and for restricting the dosage to less than 90 mg morphine equivalents daily for patients beginning long-term opioid therapy. The guidelines contain weak recommendations of tapering opioids to the lowest effective dose if patients are using 90 mg morphine equivalents daily or more and rotating to other opioids if patients have persistent problematic pain or adverse effects. Long-term opioid therapy may lead to tolerance of analgesic efficacy and withdrawal symptoms when opioid therapy is discontinued (or if dosage is reduced) abruptly.[9] Product monographs for opioid analgesics list a serious warning: “the risk of opioid addiction, abuse, and misuse which can lead to overdose and death.”

Tapentadol is a centrally acting synthetic analgesic that is thought to act as a mu-opioid receptor agonist and norepinephrine reuptake inhibitor. Another modified release formulation of tapentadol, Nucynta Controlled-Release (CR), was previously reviewed by the CADTH Common Drug Review (CDR) in 2011. Since that review, Health Canada has approved an immediate-release formulation (Nucynta IR) as well as Nucynta Extended-Release (ER), which was shown to be bioequivalent to Nucynta CR, which is no longer available in the Canadian market. Since the two modified release formulations of tapentadol are considered bioequivalent for regulatory purpose they will both be referred to as tapentadol ER in this report.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of tapentadol hydrochloride extended-release tablets (Nucynta Extended-Release) 100 mg to 250 mg twice a day for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. Nucynta Extended-Release is not indicated as an as-needed analgesic.

Results and Interpretation

Included Studies

The systematic review identified eight relevant phase III randomized controlled trials (RCTs). Five of the RCTs were conducted in patients with chronic non-cancer pain, while three RCTs were conducted in patients with cancer-related pain. Patients in the non-cancer pain RCTs had knee or hip OA-related pain or low back pain (LBP). In the non-cancer pain RCTs, oxycodone CR was included as an active comparator in four RCTs and oxycodone/naloxone prolonged-release (PR) was the comparator in one RCT. In the cancer pain RCTs, the active comparators were oxycodone CR, morphine sustained-release (SR), and morphine sulphate CR. Four of the non-cancer pain RCTs had a treatment period of 12 to 15 weeks and the fifth RCT had a treatment period of one year. The treatment periods in the cancer pain RCTs ranged in duration from four to eight weeks.

The following made up the eight relevant RCTs:

- Three 15-week, double-blind (DB), parallel-groups RCTs in patients with pain for at least three months related to knee OA (Study PAI-3008, N = 1,030; Study PAI-3009, N = 990) or non-malignant LBP (Study PAI-3011, N = 981) randomized patients (1:1:1) to either tapentadol ER (100 mg to 250 mg twice daily), oxycodone CR (20 mg to 50 mg twice daily), or placebo. The main comparison in these trials was between tapentadol ER and placebo. The comparison between oxycodone CR and placebo was conducted for assay sensitivity and the comparison of tapentadol ER with oxycodone was conducted as an exploratory analysis.
- One one-year, open-label (OL), parallel-group RCT (Study PAI-3007, N = 1,121) in patients with pain for at least three months related to knee or hip OA or non-malignant LBP randomized patients (4:1) to tapentadol ER (100 mg to 250 mg twice daily) or oxycodone CR (20 mg to 50 mg twice daily). This study was primarily designed to assess safety.
- One 12-week, OL, noninferiority, parallel-group, sequential phase IIIb/IV RCT (Baron 2016, N = 258) in patients with pain for at least three months related to LBP with a neuropathic pain component randomized patients (1:1) to tapentadol ER (50 mg to 250 mg twice daily) or oxycodone/naloxone PR (10 mg/5 mg to 40 mg/20 mg twice daily,

plus oxycodone PR 10 mg twice daily). Following a three-week titration phase, patients could proceed to the nine-week maintenance phase if they had either: a pain intensity score of no more than 4 points on the 11-point numeric rating scale (NRS) with acceptable tolerability, or a pain intensity score of no more than 5 points with satisfactory pain relief and tolerability according the patient and investigator. Patients in the oxycodone/naloxone PR group could switch to a separate tapentadol ER escape arm at any time, but patients in the tapentadol ER group could not switch to another group.

- One four-week, DB, noninferiority, parallel-group RCT (Imanaka 2013; N = 343) in patients with chronic cancer pain randomized patients (1:1) to tapentadol ER (25 mg to 200 mg twice daily) or oxycodone CR (5 mg to 40 mg twice daily).
- One eight-week, OL, parallel-group RCT (Imanaka 2014; N = 100) in patients with chronic cancer pain whose pain was already controlled with an opioid were randomized (1:1) to tapentadol ER (25 mg to 250 mg twice daily) or morphine SR (10 mg to 70 mg twice daily). This study was designed to assess the proportion of patients who maintained pain control; however, treatment groups were not formally compared.
- One six-week, DB parallel-group RCT (Kress 2014; N = 505) was conducted with patients with chronic cancer pain. Patients were initially randomized (2:1) to tapentadol ER (100 mg to 250 mg twice daily) or morphine sulphate CR (40 mg to 100 mg twice daily) for a two-week titration phase. Patients on tapentadol ER who, in the last three days of titration, had a mean pain intensity score on the 11-point NRS of less than 5 and mean daily use of morphine IR of no more than 20 mg were then re-randomized (1:1) to continue tapentadol ER or placebo for a four-week, randomized withdrawal maintenance phase. Due to the second randomization for the maintenance phase, tapentadol ER and morphine sulphate CR could only be compared for the titration phase.

In addition to the above, efficacy and safety results from an OL safety extension trial (Study PAI-3010) and two network meta-analyses (NMAs) are summarized in this report. Four observational studies on additional harms such as drug abuse, overdose, and diversion were also summarized.

Given a number of design limitations with the aforementioned RCTs, informative direct comparisons between tapentadol ER and other long-acting opioids were only available for oxycodone CR and oxycodone/naloxone PR. As noted, statistical comparisons between tapentadol ER and oxycodone CR were not controlled for multiplicity and were considered exploratory in studies PAI-3008, PAI-3009 and PAI-3011. Further, the comparison with morphine SR (Imanaka 2014) was limited by the lack of a formal statistical comparison and the comparison with morphine CR (Kress 2014) was limited by the two-week treatment duration. In terms of generalizability of the trial results, it is unclear whether the patients in the non-cancer pain trials would be considered appropriate candidates for continuous, long-term opioid therapy in the current Canadian setting. Only one of these trials (Baron 2016) specified in the entry criteria that patients had to require treatment with an opioid analgesic according to the investigator. In the cancer pain trials, the treatment durations were eight weeks or less and substantial proportions of patients received dosages of tapentadol ER that were below the minimum recommended dosage.

The systematic review did not identify sufficient evidence on the risk of long-term opioid use such as tolerance and hyperalgesia or the potential risks of opioid use disorder, misuse, overdose, or diversion.

Efficacy

Pain Intensity

Non-Cancer Pain Trials

In the efficacy RCTs in patients with non-cancer pain, the primary efficacy end point was mean change from baseline in pain intensity over the whole of the maintenance phase, based on an 11-point NRS. In studies PAI-3008 and PAI-3009, reduction in pain intensity was greater in the tapentadol ER groups compared with oxycodone CR; least squares mean differences (LSMDs) of –0.3 (95% confidence interval [CI], –0.66 to –0.00) and –0.4 (95% CI, –0.68 to –0.05) (Table 1). While the reductions in pain intensity from baseline were clinically meaningful, differences between the active treatments were less than the smallest minimal clinically important difference of 1.1 identified by CDR and the comparisons were not controlled for multiplicity. The primary end point in Study PAI-3009 was not met (tapentadol ER versus placebo) and assay sensitivity (oxycodone CR versus placebo) was not demonstrated in studies PAI-3008 and PAI-3009. In Study PAI-3011, change in pain intensity was not different between the tapentadol ER and oxycodone CR groups.

In Baron 2016, the upper limit of the 97.5% CI for the LSMD between tapentadol ER and oxycodone/naloxone PR was lower than the noninferiority margin of 1.3 and noninferiority of tapentadol ER to oxycodone/naloxone PR was declared (Table 2). Superiority was demonstrated with a between-group difference of –0.9 in favour of tapentadol ER, though the difference was less than the smallest reported MCID of 1.1. In Study PAI-3007, change in pain intensity from baseline to end of treatment was similar between the two groups (–3.2 [standard error of 2.7] for tapentadol ER and –3.1 [standard error of 3.4] for oxycodone CR), although no statistical analysis was conducted for this outcome.

The validity of the aforementioned findings is compromised by the high frequency of study discontinuation (ranging from 34% to 65% across the active treatment groups), which was differential (being lower in the tapentadol groups in all five trials). Adverse event (AE) was the most common reason for early study discontinuation and occurred less often in the tapentadol ER groups. The imbalance was compounded in the short-term OL trial (Baron 2016), with the availability of an escape arm for patients randomized to oxycodone/naloxone PR but not for patients randomized to tapentadol ER.

The short titration period of three weeks (one week in the safety trial) may be responsible for the high frequency of study withdrawal. According to the clinical expert consulted for this review, patients in clinical practice are titrated and monitored continuously and have a longer time to acclimatize or develop tolerance to side effects. The considerable amount of missing data, which was differential between treatment groups, calls the study findings into question, although the direction of the bias from the LOCF approach for imputing missing data is unclear. Alternative approaches for imputing missing data used in the trials (e.g., baseline, or worst, observation carried forward) likely biased the results in favour of tapentadol ER.

Other than PAI-3007 (the safety study) the trials were of relatively short duration. The OL extension trial, which included patients from three of the non-cancer pain RCTs and one other trial, found that pain intensity remained stable throughout the maintenance phase following titration. However, all patients in the trial received tapentadol ER and there was no control group. There were also substantial proportions of patients discontinuing the extension trial, ranging from 24% to 49%.

Cancer Pain Trials

The efficacy results in the cancer pain RCTs did not show any benefits of tapentadol ER over its comparators.

In Imanaka 2013, the LSMD (95% CI) for reduction in pain intensity on the 11-point NRS for tapentadol ER versus oxycodone CR was –0.06 (–0.51 to 0.38). Given that the upper limit of the 95% CI was less than 1, tapentadol was considered to be noninferior to oxycodone CR. In the tapentadol ER group, mean pain intensity was 5.4 (standard deviation [SD] of 1.5) at baseline and changed by –2.7 (SD of 2.2) over the four-week treatment period. In the oxycodone CR group, mean pain intensity was 5.3 (SD of 1.2) at baseline and changed by –2.6 (SD of 2.0).

In Imanaka 2014, patients were on opioid analgesic therapy at baseline and mean baseline pain intensity on the 11-point NRS was 1.5 (SD of 1.1) in the tapentadol ER group and 1.8 (SD of 1.1) in the morphine SR group. Mean pain intensity did not change appreciably in either the tapentadol ER or morphine SR groups from baseline to the end of treatment, and no formal statistical testing was conducted.

During the two-week, DB titration phase in Kress 2014, mean pain intensity at the end of titration was 3.7 (SD of 1.8) for the morphine CR group and 4.1 (SD of 1.8) for the tapentadol ER group, despite similar baseline values (Table 3). Also, rescue morphine IR was used by more patients (72% versus 58%) and in larger amounts (mean of the mean total daily dose of milligrams of morphine; SD: 13.3 [17.4] versus 8.9 [12.5]) in the tapentadol ER group versus the morphine CR group. Rescue opioid analgesic use was similar between groups in Imanaka 2013 and not reported for the morphine SR group in Imanaka 2014.

Overall, the numerous and significant limitations identified in all of the included RCTs contributed a great amount of uncertainty that prevented conclusions from being drawn regarding the comparative efficacy in lowering pain intensity of tapentadol ER versus oxycodone CR, oxycodone/naloxone PR, or morphine SR or CR. The common limitations potentially impacting internal validity were substantial and unbalanced amounts of missing data from early study discontinuations, short durations of most of the trials (with titration periods shorter than would be expected in clinical practice), lack of blinding in some trials coupled with the use of subjective outcomes, lack of control for type I error, and potential biases introduced by approaches for imputing missing data.

Other Efficacy Outcomes

Efficacy in terms of health-related quality of life (HRQoL), global assessment of change, impact on sleep, impact on work and daily activities, and mental or psychological symptoms were reported mainly in the non-cancer pain trials. Outcomes on caregiver burden were not available. These outcomes shared the same limitations as for pain intensity and were further limited by the lack of formal statistical comparisons and control for type I error.

The EuroQol 5-Dimension (EQ-5D) instrument, 36-item Short Form Health Survey (SF-36, SF-12 in Baron 2016), and sleep questionnaire were administered to patients in all of the non-cancer pain RCTs. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), measuring OA-related HRQoL, was assessed in the two knee OA pain RCTs. Improvements in the EQ-5D-3L index score, EQ-5D visual analogue scale, SF-36 (or SF-12) mental component summary, and SF-36 (or SF-12) physical component summary favoured the tapentadol ER groups versus the active comparator groups in three of the five

trials; however, there was no adjustment for multiplicity in these outcomes. The WOMAC and the sleep questionnaire did not show any consistent differences between the tapentadol ER and oxycodone CR groups in OA-specific HRQoL or impact on sleep. While instruments specific to the impact of pain on work and daily activities were not used, the Brief Pain Inventory pain interference subscale score in the DB RCT in patients with LBP showed no clinically meaningful difference between the tapentadol ER and oxycodone CR groups.

There were consistently greater proportions of patients reporting for the Patient Global Impression of Change that they were very much or much improved from the start of the trial in the tapentadol ER groups than in the oxycodone CR or oxycodone/naloxone PR groups in the trials in patients with non-cancer pain (as well as in Imanaka 2013). However, differences between the response distributions were difficult to interpret without appropriate statistical testing.

Between-group differences in improvement in the Hospital Anxiety and Depression Scale anxiety and depression scores in Baron 2016 favoured tapentadol ER, but the lack of adjustment for multiplicity means these results were inconclusive.

Harms

Adverse Events, Serious Adverse Events, Withdrawals Due to Adverse Events, and Mortality

In all of the trials, AEs were less frequent in the tapentadol ER group than in the active comparator group. In the non-cancer pain RCTs, AEs occurred in 67% to 76% of patients in the tapentadol ER group and 85% to 87% in the oxycodone CR groups in the DB efficacy RCTs (Table 1), 77% and 84% in the tapentadol ER and oxycodone/naloxone PR groups in the OL efficacy RCT (Baron 2016, Table 2), and 86% and 91% in the tapentadol ER and oxycodone CR groups in the safety RCT (Study PAI-3007, Table 2). In the cancer pain trials (Table 3), AEs occurred in 88% and 90% of the tapentadol ER and oxycodone CR groups in Imanaka 2013, 90% and 94% of the tapentadol ER and morphine SR groups in the opioid-switching RCT (Imanaka 2014), and 50% and 64% of the tapentadol ER and morphine CR groups in the third RCT (Kress 2014).

The most common AEs were constipation, nausea, vomiting, and somnolence (notable harms according to the systematic review protocol) in both non-cancer and cancer pain trials. Dizziness, headache, fatigue, pruritus, and hyperhidrosis were also common in the non-cancer pain trials, while diarrhea, decreased appetite, and disease progression were also common in the cancer pain trials. There were notably lower proportions of patients in the tapentadol ER group than in the oxycodone CR and oxycodone/naloxone PR groups who experienced AEs and withdrawals due to AEs of constipation, nausea, and vomiting (Table 1 and Table 2). In the cancer pain trials, gastrointestinal AEs were less commonly reported in the tapentadol ER groups, compared with oxycodone CR (Imanaka 2013), morphine SR (Imanaka 2014), and morphine CR (Kress 2014). The gastrointestinal AEs with opioid agonists are well known, and the clinical expert consulted for this review noted that patients who discontinued in the RCTs may have in the clinical setting been encouraged to stay on therapy and acclimatize to the AEs, since such AEs can become more tolerable over time.

Serious AEs (SAEs) were reported in no more than 4% of patients in the short-term, non-cancer pain trials and in no more than 6% of patients in the one-year trial. SAEs occurred

more frequently in the cancer pain trials, with disease progression and vomiting being the most common SAEs in the Imanaka 2013 and 2014 trials, and neoplasm-related SAEs being the most common in Kress 2014. There were no notable differences in SAEs between tapentadol and its comparators.

There was one death in the non-cancer pain trials; a myocardial infarction in a patient with a history of morbid obesity randomized to oxycodone CR in PAI-3008. Although causes of deaths were not comprehensively reported in the cancer pain trials, disease progression or malignant neoplasm accounted for almost all of the deaths, with the only other cause of death reported being gastrointestinal perforation in one patient randomized to tapentadol ER in Imanaka 2014.

The AE profile in the OL extension trial was similar to that in the RCTs and no new safety signals were apparent.

Notable Harms

Gastrointestinal Symptoms

The Patient Assessment of Constipation Symptoms (PAC-SYM) was administered in the efficacy RCTs for non-cancer pain and was a co-primary end point in Baron 2016, which compared tapentadol ER with oxycodone/naloxone PR. Between-group differences favoured tapentadol ER in Study PAI-3008, Study PAI-3009, and Study PAI-3011 but were inconclusive due to the lack of control for multiplicity. In the OL RCT (Baron 2016), tapentadol ER was found to be noninferior but not superior to oxycodone/naloxone PR for the overall PAC-SYM score. However, the high and unbalanced study withdrawal coupled with the need for considerable data imputation results in uncertain validity of these findings.

In the OL extension trial, the severity of constipation symptoms decreased with tapentadol ER for patients who had received oxycodone CR in the predecessor trial.

Withdrawal Symptoms

The AEs of withdrawal syndrome or drug withdrawal syndrome occurred in no more than 1% of any one treatment group in all trials.

Instruments assessing withdrawal symptoms — the Subjective Opiate Withdrawal Scale (SOWS; range 0 to 60, with higher scores indicative of greater severity) and the Clinical Opiate Withdrawal Scale (COWS); range 0 to 47, with higher scores indicative of greater severity) — were administered in the non-cancer pain RCTs. However, limited data were available as patients who entered the OL extension trial were not administered these instruments and the SOWS was only assessed in patients at English-speaking sites in the US. In addition, SOWS and COWS scores from patients who continued opioid therapy after the end of study treatment were not considered relevant by the clinical expert consulted for this review. It is possible that the SOWS captured a wider range of withdrawal symptoms than the COWS since the COWS relies on observed signs and symptoms.

The SOWS was assessed in two of the DB non-cancer pain RCTs (studies PAI-3008 and PAI-3011) and least squares mean total scores ranged from 6.2 to 8.7 (out of a maximum of 60) in the tapentadol ER groups and from 6.7 to 11.6 in the oxycodone CR groups over all the time points (day 2, 3, 4, or 5 and later following treatment discontinuation). In the OL safety study (Study PAI-3007), SOWS total score ranged from 6.9 to 9.5 in the tapentadol ER group and from 7.5 to 10.1 in the oxycodone CR group. The results favoured tapentadol ER consistently in all three trials (except for one time point in Study PAI-3011), though there

was no control for multiplicity for this outcome and the analyses included only a small subset of randomized patients.

All patients assessed with the COWS in the non-cancer pain trials (studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007) were categorized as having no withdrawal symptoms, mild symptoms, or moderate symptoms regardless of when they were assessed (two to four days versus five to 14 days after treatment discontinuation). There were no consistent differences between active treatment groups in mean COWS total score, although analyses of these data suffer from the same limitations as the SOWS.

According to the clinical expert consulted for this review, patients on opioid therapy for the treatment durations in the trials should be tapered off of the therapy. The lack of a taper regimen following treatment discontinuation may have exacerbated withdrawal symptoms. The clinical expert also indicated that longer durations of opioid therapy necessitate longer taper regimens, suggesting that withdrawal symptoms in the RCTs may not have reflected those experienced in clinical practice.

Serotonin Syndrome

Serotonin syndrome was not reported in any of the trials.

Indirect Comparisons

Due to the lack of sufficient head-to-head trials on data for tapentadol and other opioids for chronic pain management, a search for indirect treatment comparisons was conducted to provide indirect evidence on the efficacy and safety of the available opioids in the study population. Two NMAs were identified for this review. Different approaches and statistical models were adopted in the two NMAs; however, in both cases a major limitation was the decision by the authors to combine all doses and formulations of a drug and treat them as a single intervention in the analysis. This is considered by the CDR reviewer to be inappropriate from a clinical perspective and provides no evidence specific to tapentadol ER, the study drug under review. Thus the usefulness of the results of these analyses is compromised.

Potential Place in Therapy[1]

Nucynta ER has two mechanisms of action: it is a mu-opioid receptor agonist and norepinephrine reuptake inhibitor. The mu-opioid receptor agonist is similar to other opioids, such as morphine or oxycodone, and it mediates the analgesic and adverse effects of morphine such as sedation, drowsiness, nausea, vomiting, and constipation. The colon contains a large population of mu-opioid receptors, and opioid-induced constipation can be a difficult clinical problem. In contrast to tapentadol, oxycodone is a mu-opioid receptor agonist that also may have kappa agonist activity, conferring an advantage to oxycodone for the management of visceral pain like that which occurs in gallbladder and pancreatic disease.[10] Nucynta's mechanism of action is similar to that of tramadol, a weak mu-opioid receptor agonist and weak norepinephrine-serotonin reuptake inhibitor. The potency of tapentadol seems to be between tramadol and morphine.[11] Aside from potency, another way to interpret weak opioids is by defining those that have a ceiling dose and would not be able to treat severe pain that requires higher doses.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

Weak opioids available in Canada include codeine, tramadol, transdermal buprenorphine, and tapentadol. Codeine and tramadol have limited use in patients requiring daily long-term continuous opioid treatment because of their pharmacology; as they require metabolism by the liver to active metabolites, their efficacy can be unpredictable. In contrast, tapentadol exerts its analgesic effects without a pharmacologically active metabolite.[12] Weak opioids are generally used for mild-to-moderate pain, or when it is unlikely that the patient will need to use high doses of opioids. Weak opioids are usually the first-line opioids for patients who are opioid naive. Similar to codeine and tramadol, Nucynta also has a ceiling dose. There is a perception that weak opioids are less addictive than strong opioids. Some physicians report only prescribing weak opioids for patients with chronic pain, and their rational is that they have concerns regarding potential long-term AEs such as addiction and misuse.[13]

The fact that Nucynta has a ceiling dose can be seen as a disadvantage when the patient has severe pain and the dose of the opioid needs to be increased. In such cases, the prescriber will need to switch from Nucynta to a stronger opioid, such as hydromorphone, morphine, oxycodone, or fentanyl. In randomized trials, Nucynta has been compared with oxycodone ER, and this might suggest that Nucynta can be used as a strong opioid analgesic, even for cancer-related pain.[14]

The management of neuropathic pain usually requires polypharmacy with analgesics that have different mechanisms, and Nucynta offers the advantage of having a mu-opioid receptor agonist and norepinephrine reuptake inhibition mechanism in one single drug. The diagnosis of neuropathic pain is by history and physical exam. There is no need for special tests such as imaging or electrodiagnostic tests. Clinicians who are taught about neuropathic pain usually do not have difficulty identifying cases. However, for clinicians who do not have the knowledge or skills to make the diagnosis of neuropathic pain, there might be some confusion about which patients would benefit from Nucynta.

Nucynta may increase the risk of seizures compared with other opioids aside from tramadol. Like other opioids, it has the potential for misuse, diversion, and addiction; may cause withdrawal symptoms if tapered abruptly; has risks of overdose and death; and may cause central nervous system depression and cognitive impairment that are important for driving.

Most drugs are metabolized by the cytochrome P450 system. The major pathway of metabolism of tapentadol is conjugation with glucuronic acid to produce glucuronides, which offers a big advantage of its metabolism not being mediated by the cytochrome P450 system. Therefore, there is very low risk of drug-to-drug interactions with Nucynta.

Conclusions

Based on the eight RCTs included in this systematic review, the comparative efficacy of tapentadol ER versus other long-acting opioids (oxycodone CR, oxycodone/naloxone PR, morphine SR or CR) is uncertain due to important limitations of the reviewed trials, including high and unbalanced study withdrawal and considerable imputation of missing data.

Based on the reviewed trials, tapentadol ER was associated with lower frequency of treatment discontinuations than oxycodone CR or oxycodone/naloxone PR for non-cancer pain, most notably when the reason was AE. AEs in both the cancer and non-cancer pain trials, especially gastrointestinal AEs, were reported less frequently with tapentadol ER than with oxycodone CR, oxycodone/naloxone PR, morphine CR, or morphine SR. AEs and treatment discontinuations were likely not as affected by the numerous threats to internal validity as the other outcomes. However, it is unclear to what extent these benefits would be realized in clinical practice where patients may have more flexibility to adjust doses and clinicians can encourage their patients to acclimatize to the side effects of their treatment.

Table 1: Summary of Results for Double-Blind Non-Cancer Pain Trials

	PAI-3008 Knee Osteoarthritis			PAI-3009 Knee Osteoarthritis			PAI-3011 Low Back Pain		
	PL	**TAP**	**OXY**	**PL**	**TAP**	**OXY**	**PL**	**TAP**	**OXY**
ITT set, N	**336**	**344**	**342**	**336**	**319**	**331**	**316**	**312**	**323**
Mean NRS-11 pain intensity									
Baseline (SD)	7.2 (1.3)	7.4 (1.4)	7.2 (1.3)	7.3 (1.1)	7.3 (1.1)	7.3 (1.1)	7.6 (1.3)	7.5 (1.3)	7.5 (1.2)
Change to average over maintenance phase (SD)	–2.2 (2.4)	–2.9 (2.3)	–2.5 (2.3)	–2.2 (2.1)	–2.5 (2.2)	–2.1 (2.2)	–2.1 (2.2)	–2.8 (2.5)	–2.9 (2.4)
LSMD vs. PL (95% CI)[a]	NA	**–0.7 (–1.00 to –0.33) *P* < 0.001**	–0.3 (–0.67 to –0.00) *P* = 0.049	NA	**–0.2 (–0.55 to 0.07) *P* = 0.14**	0.1 (–0.18 to 0.44) *P* = 0.42	NA	**–0.7 (–1.06 to –0.35) *P* < 0.001**	–0.8 (–1.16 to –0.46) *P* < 0.001
LSMD, TAP vs. OXY (95% CI)[a]	NA	–0.3 (–0.66 to –0.00) *P* = 0.048		NA	–0.4 (–0.68 to –0.05) *P* = 0.02		NA	0.1 (–0.25 to 0.45) *P* = 0.56	
Study discontinuations, N (%[b])	134 (40)	163 (47)	224 (65)	122 (36)	140 (44)	212 (64)	167 (52)	152 (48)	195 (59)
Safety set, N	**337**	**344**	**342**	**337**	**319**	**331**	**317**	**315**	**326**
Patients with ≥ 1 AE, n (%)	206 (61)	261 (76)	299 (87)	187 (56)	214 (67)	281 (85)	190 (60)	240 (76)	278 (85)
Deaths, n (%)	0	0	1 (0.3)	0	0	0	0	0	0
Patients with ≥ 1 SAE, n (%)	6 (2)	4 (1)	10 (3)	4 (1)	2 (1)	13 (4)	3 (1)	7 (2)	11 (3)
WDAEs, n (%)	22 (7)	66 (19)	146 (43)	27 (8)	60 (19)	140 (42)	14 (4)	53 (17)	104 (32)
Notable AEs, n (%)									
Gastrointestinal disorders	88 (26)	148 (43)	230 (67)	92 (27)	133 (42)	224 (68)	84 (26)	139 (44)	203 (62)
Constipation	22 (7)	65 (19)	126 (37)	31 (9)	57 (18)	116 (35)	16 (5)	44 (14)	88 (27)
Nausea	23 (7)	74 (22)	125 (37)	21 (6)	65 (20)	124 (38)	29 (9)	64 (20)	113 (35)
Vomiting	11 (3)	18 (5)	61 (18)	13 (4)	33 (10)	86 (26)	5 (2)	29 (9)	63 (19)
Drug withdrawal syndrome	0	1 (0.3)	2 (0.6)	2 (0.6)	2 (0.6)	4 (1)	0	0	0
Somnolence	14 (4)	37 (11)	67 (20)	13 (4)	34 (11)	48 (15)	8 (3)	42 (13)	53 (16)
Withdrawal syndrome	0	0	3 (0.9)	0	0	1 (0.3)	0	0	0

AE = adverse event; CI = confidence interval; ITT = intention-to-treat; LSMD = least squares mean difference; NA = not applicable; NRS-11 = 11-point numeric rating scale; OXY = oxycodone controlled-release; PL = placebo; SAE = serious adverse event; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus; WDAE = withdrawal due to adverse event.

Note: Boldface font indicates results for the primary end point. All other outcomes are exploratory.

Last observation carried forward was used for imputing missing efficacy values.

[a] Analysis of covariance model adjusted for pooled site and baseline pain intensity.

[b] Out of patients who received ≥ 1 dose of the study drug.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 2: Summary of Results for Open-Label Non-Cancer Pain Trials

	PAI-3007 Knee or Hip Osteoarthritis and Low Back Pain ITT Set		Baron 2016 Low Back Pain With a Neuropathic Component PP Set	
	TAP N = 876	**OXY N = 219**	**TAP N = 117**	**OXN N = 112**
Mean NRS-11 pain intensity	N = 821	N = 178		
Baseline (SD)	7.6 (1.5)	7.6 (1.6)	7.6 (1.0)	7.6 (1.0)
Change to end of treatment (SD)	–3.2 (2.7)	–3.1 (3.4)	NR	NR
LSM change to end of treatment (SE)	NR	NR	–3.7 (0.5)	–2.7 (0.3)
LSM difference, TAP vs. OXN (97.5% RCI)	NA		**–0.9 (–1.8, –0.2)[a]** Noninferiority margin = 1.3 **Noninferiority met** ***P* = 0.003 for superiority**	
Study discontinuations, N (%)	482 (54[b])	145 (65[b])	44 (34[c])	80 (63[c])
Safety set, N	**894**	**223**	**130**	**128**
Patients with ≥ 1 AE, n (%)	766 (86)	202 (91)	100 (77)	107 (84)
Notable AEs, n (%)				
Gastrointestinal disorders	465 (52)	143 (64)	58 (45)	66 (52)
Constipation	202 (23)	86 (39)	20 (15)	33 (26)
Nausea	162 (23)	74 (33)	29 (22)	23 (18)
Vomiting	63 (7)	30 (14)	10 (8)	21 (16)
Drug withdrawal syndrome	9 (1)	1 (0.4)	NR	NR
Somnolence	133 (15)	25 (11)	NR	NR
Withdrawal syndrome	13 (2)	2 (0.9)	NR	NR
Deaths, n (%)	0	0	0	0
Patients with ≥ 1 SAE, n (%)	49 (6)	9 (4)	3 (2)	2 (2)
WDAEs, n (%)	198 (22)	82 (37)	28 (22)	54 (42)

AE = adverse event; ITT = intention-to-treat; LSM = least squares mean; NA = not applicable; NRS-11 = 11-point numeric rating scale; OXY = oxycodone controlled-release; OXN = oxycodone/naloxone prolonged-release; PP = per-protocol; RCI = repeated confidence interval; SAE = serious adverse event; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus; WDAE = withdrawal due to adverse event.

Note: Boldface font indicates results for primary end point. All other outcomes are exploratory.

Last observation carried forward was used for imputing missing efficacy values in Baron 2016.

[a] Analysis of covariance model adjusted for pooled site and baseline value.

[b] Out of patients who received ≥ 1 dose of the study drug.

[c] Out of randomized patients.

Source: Clinical study report for PAI-3007,[18] Baron et al. 2016.[19,20]

Table 3: Summary of Results for Cancer Pain Trials

	Imanaka 2013 PP Set		Imanaka 2014 ITT Set		Kress 2014 FA Set Titration Phase	
	TAP N = 126	**OXY N = 139**	**TAP N = 50**	**MOR N = 50**	**TAP N = 335**	**MOR N = 157**
Mean NRS-11 pain intensity						
Baseline (SD)	5.4 (1.5)	5.3 (1.2)	1.5 (1.1)[a]	1.8 (1.1)[a]	6.3 (1.5)	6.3 (1.6)
Change to end of treatment (SD)	–2.7 (2.2)	–2.6 (2.0)	N = 29 0.0 (0.9)	N = 29 0.0 (1.2)	NR	NR
LSM difference, TAP vs. OXY (95% CI)	**–0.06 (–0.51, 0.38)** Noninferiority margin: 1 **Noninferiority met**		NR		NR	
End of 2 weeks of titration (SD)	NA	NA	NA	NA	4.1 (1.8)	3.7 (1.8)
Rescue opioid analgesic use, n (%)	94 (75)	103 (74)	NR	NR	241 (72)	91 (58)
Mean days of use (SD)	7.6 (7.7)	7.2 (7.8)	15.9 (19.6)	NR	NR	NR
Mean of the mean TDD per patient, mg morphine or MED (SD)	7.0 (2.3)	6.7 (2.2)	3.0 (8.3)	NR	13.3 (17.4)	8.9 (12.5)
Study discontinuations, N (%[a])	55 (33)	49 (29)	22 (44)	21 (42)	59 (18)	29 (18)
Safety set, N	**168**	**172**	**50**	**50**	**338**	**158**
Patients with ≥ 1 AE, n (%)	147 (88)	155 (90)	45 (90)	47 (94)	169 (50)	101 (64)
Most common AEs, n (%)						
Gastrointestinal disorders	93 (55)	116 (67)	19 (38)	27 (54)	NR (30)	NR (47)
Constipation	51 (30)	64 (37)	6 (12)	10 (20)	48 (14)	28 (18)
Nausea	48 (29)	61 (36)	7 (14)	7 (14)	42 (12)	38 (24)
Vomiting	42 (25)	41 (24)	3 (6)	13 (26)	17 (5)	25 (16)
Somnolence	29 (17)	36 (21)	8 (16)	10 (20)	14 (4)	10 (6)
Deaths, n (%)	30 (18)	30 (17)	6 (12)	4 (8)	12 (4)[b]	3 (2)[b]
Disease progression	23 (14)	24 (14)	5 (10)	4 (8)	NR	NR
Patients with ≥ 1 SAE, n (%)	78 (46)	69 (40)	16 (32)	16 (32)	25 (7)	6 (4)
WDAEs, n (%)	22 (13)	29 (17)	14 (28)	19 (38)	29 (9)	11 (7)

AE = adverse event; CI = confidence interval; FA = full analysis; ITT = intention-to-treat; LSM = least squares mean; MED = morphine equivalent dose; MOR = morphine controlled- or sustained-release; NA = not applicable; NR = not reported; NRS-11 = 11-point numeric rating scale; OXY = oxycodone controlled-release; PP = per-protocol; SAE = serious adverse event; SD = standard deviation; TAP = tapentadol extended-release; TDD = total daily dose; vs. = versus; WDAE = withdrawal due to adverse event.

Note: End of treatment was week 4 for Imanaka 2013 and week 8 for Imanaka 2014.

Boldface font indicates primary end point. All other outcomes are exploratory.

Last observation carried forward was used for imputing missing values in Imanaka 2013.

[a] Out of patients who received ≥ 1 dose of the study drug.

[b] Includes deaths occurring up to 30 days after the last dose for patients who discontinued during the titration phase.

Source: Imanaka et al. 2013,[21] Imanaka et al. 2014,[22] Kress et al. 2014.[23]

Introduction

Disease Prevalence and Incidence

Chronic pain is generally defined as a painful condition persisting for several months or longer. In terms of approach to management, chronic pain can be broadly classified as cancer-related pain and non-cancer pain. Common causes or types of chronic non-cancer pain are osteoarthritis (OA), back pain, fibromyalgia, post-surgical chronic pain, and painful diabetic neuropathy.[1,2] Pain can also be classified as nociceptive (caused by actual or potential tissue damage), neuropathic (caused by a lesion or disease of the somatosensory nervous system), or a mix of the two.[1]

Results from Canadian surveys from 1994 to 2008 estimated the prevalence of chronic pain in Canadian adults to be 15% to 19%.[3] Patient input received by the CADTH Common Drug Review (CDR) outlined many of the negative impacts of pain in patients' lives. Pain limits physical function and has negative impacts on work, daily activities, sleep, mood, and relationships with others. Patients with pain can also feel depressed, isolated, and helpless.

Standards of Therapy

When chronic pain cannot be managed well with non-opioid pharmacological or non-pharmacological options, opioid analgesics can be considered. For neuropathic pain, the 2014 Canadian Consensus Statement on Neuropathic Pain recommends anticonvulsants and antidepressant agents as first-line analgesics, opioids as second-line analgesics, cannabinoids as third-line analgesics, and a variety of other types of agents as fourth-line analgesics.[4] There is evidence of varying quality that non-pharmacological interventions (such as exercise, manual therapy, and multidisciplinary treatment programs) may also benefit patients with chronic pain.[5-7]

The World Health Organization (WHO) initially proposed a framework for cancer pain relief in 1986, introducing the three-step pain ladder[24] and updating it in 1996.[25] The first step in the pain ladder is the use of a non-opioid. If there is inadequate pain relief, the second step is the addition of an opioid for mild-to-moderate pain, a group that includes codeine and tramadol. If this is still inadequate, then the third step is the substitution of the Step II opioid for a step III opioid, or opioid for moderate-to-severe pain, a group that includes morphine, methadone, hydromorphone, and oxycodone.

The 2017 *Canadian Guidelines for Opioids for Chronic Non-Cancer Pain*[8] strongly recommend the optimization of non-opioid analgesic therapy and non-pharmacological therapy before administering a trial of opioids. The guidelines also contain strong recommendations against using opioids in patients with an active substance use disorder and for restricting the dosage to less than 90 mg morphine equivalents daily for patients beginning long-term opioid therapy. The guidelines contain weak recommendations of tapering opioids to the lowest effective dose if patients are using 90 mg morphine equivalents daily or more and rotating to other opioids if patients have persistent problematic pain or adverse effects.

Long-term opioid therapy leads to tolerance, which is when efficacy diminishes over time for a constant dosage and patients require higher dosages to maintain the same level of analgesia.[9] Unpleasant withdrawal symptoms also occur with opioid therapy is discontinued (or if dosage is reduced) abruptly.[9] The product monographs for opioid analgesics list as a

serious warning: “the risk of opioid addiction, abuse, and misuse which can lead to overdose and death” (see Table 4). In recommending the restriction of opioid dosages in patients with chronic non-cancer pain to 90 mg morphine equivalent daily or less, the 2017 Canadian guidelines cite evidence for increased risks of non-fatal and fatal opioid overdose with higher daily dosages.

Constipation is a common side effect of opioids and the patient input received by CDR reflected this. Other side effects of pain medications (not necessarily opioids) that were identified by patients were tiredness, drowsiness, nausea, stomach upset, kidney and liver damage, weight gain or loss, loss of appetite, anxiety, hyperactivity, feelings of being unwell, dizziness, headache, dry mouth, mood swings, brain fog, insomnia, irritability, and paranoia. Patients also described difficulty in finding a physician to treat their pain and affordability issues with medications. In terms of expectations for therapy, patients want new treatments that can relieve pain and improve function, are non-addictive and won’t cause withdrawal, have long-lasting effects, have the fewest side effects, and can improve their quality of life (QoL).

Drug

Tapentadol extended-release (Nucynta Extended-Release) tablets are indicated for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. Tapentadol extended-release (ER) tablet is not indicated as an as-needed analgesic. The recommended dosage of tapentadol ER is 100 mg to 250 mg orally twice a day, taken approximately every 12 hours. The recommended limit of 90 mg morphine equivalents daily for patients with chronic non-cancer pain corresponds to 300 mg of tapentadol daily.[12] Tapentadol is a centrally acting synthetic analgesic that is thought to act as a mu-opioid receptor agonist and norepinephrine reuptake inhibitor.

Another modified release formulation of tapentadol, Nucynta controlled-release (CR), was previously reviewed by CDR in 2011 with a recommendation that it not be listed.[26] The reviewed indication was “the management of moderate to moderately severe pain in adults who require continuous treatment for several days or more.” Since that review, Health Canada has approved an immediate-release formulation (Nucynta IR) as well as Nucynta Extended-Release, which was shown to be bioequivalent to Nucynta CR[27] (aside from the 50 mg tablets, which are only used for titration). The Nucynta Extended-Release product replaced the Nucynta CR product in the Canadian market. Nucynta Extended-Release was designed with the intention of making the product tamper resistant; however, Health Canada has not approved tamper-resistant labelling for any opioid formulations marketed in Canada.[28] Given that the two modified release formulations of tapentadol are considered bioequivalent for regulatory purposes,[27] they will both be referred to as tapentadol ER in this report.

Table 4: Key Characteristics of Long-Acting Opioid Analgesics

	Tapentadol ER	Long-Acting Opioid Agonists (Morphine SR, Oxycodone CR, Hydromorphone CR, Methadone, Transdermal Fentanyl, Transdermal or Buccal Film Buprenorphine)	Long-Acting Opioid Agonist-Antagonist Combinations (Oxycodone/Naloxone CR)	Tramadol ER	Codeine CR
Mechanism of action	Thought to act as a mu-opioid receptor agonist and norepinephrine reuptake inhibitor.	Opioid receptor agonist. Buprenorphine is also an agonist at nociceptin receptors.	Opioid receptor agonist combined with an opioid receptor antagonist.	Thought to act as a mu-opioid receptor agonist (both the parent and M1 metabolite) and weak inhibitor of norepinephrine and serotonin uptake.	Opioid receptor agonist.
Indication[a]	Management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. Not indicated as an as-needed analgesic. For fentanyl transdermal system: Only for use in patients who are already receiving opioid therapy at a total daily dose of at least 60 mg/day morphine equivalents.				
Route of administration	Oral	Oral, transdermal, or buccal	Oral	Oral	Oral
Recommended dose range	100 mg to 250 mg b.i.d.	See following information	See following information	Maximum daily dosage of 300 mg	See following information
Recommended initial dose in opioid-naive patients	**Tapentadol ER:** 50 mg b.i.d. **Morphine SR:** 30 mg b.i.d. (recommendation for initial q.d. dose not available) **Oxycodone CR:** 10 mg b.i.d. **Hydromorphone CR**: 4 mg q.d. or 3 mg b.i.d., depending on the product **Methadone:** Contraindicated for opioid-naive patients. Usual initial dose is 2.5 mg to 10 mg every 4 hours. **Transdermal fentanyl:** Contraindicated for opioid-naive patients. Most patients are adequately maintained with transdermal fentanyl administered every 72 hours. **Transdermal buprenorphine:** 5 mcg/h over 7 days **Buccal film buprenorphine**: 75 mcg film q.d. or b.i.d. **Oxycodone/naloxone CR:** 10 mg/5 mg b.i.d. **Tramadol ER:** 100 mg q.d. **Codeine CR:** 50 mg b.i.d.				
Recommended maximum dose and initial dose in patients switching from another opioid analgesic	For the management of chronic non-cancer, non-palliative pain, it is recommended that 90 morphine milligram equivalent not be exceeded per dose (note that the maximum daily dosage of tramadol is 50 morphine milligram equivalent). In patients already on another opioid, the nature of the previous analgesic, its administration, and the mean total daily dose should be taken into account in choosing the initial dose.				
Serious side effects / safety issues	Not recommended for patients < 18 years of age. **Serious warnings:** • Risk of opioid addiction, abuse, and misuse, which can lead to overdose and death. • Life-threatening respiratory depression with overdose (including accidental exposure). • Neonatal opioid withdrawal syndrome, which may be life-threatening. • Possible dangerous additive effect when co-ingested with alcohol.				

	Tapentadol ER	Long-Acting Opioid Agonists (Morphine SR, Oxycodone CR, Hydromorphone CR, Methadone, Transdermal Fentanyl, Transdermal or Buccal Film Buprenorphine)	Long-Acting Opioid Agonist-Antagonist Combinations (Oxycodone/Naloxone CR)	Tramadol ER	Codeine CR
	• Profound sedation, respiratory depression, coma, or death from concomitant use with benzodiazepines or other CNS depressants. • Potential risk (risk for tramadol) for serotonin syndrome, particularly with concomitant administration of serotonergic drugs. **Contraindications:** • hypersensitivity to opioids • known or suspected mechanical gastrointestinal obstruction or diseases or conditions affecting bowel transit • suspected surgical abdomen • management of acute, mild, intermittent, short-duration, or peri-operative pain • use of MAO inhibitors • severe renal or hepatic impairment • acute asthma or obstructive airway • acute respiratory depression, elevated carbon dioxide levels in blood, or cor pulmonale • acute alcoholism, delirium tremens, or convulsive disorders • severe CNS depression, increase intracranial pressure, or head injury • women who are breastfeeding, pregnant, or during labour and delivery • for opioid agonist-antagonist combinations: opioid-dependent patients and for narcotic withdrawal treatment • for methadone and transdermal fentanyl: patients naive to opioids • for tramadol: pediatric patients < 18 years of age who have undergone tonsillectomy and/or adenoidectomy for obstructive sleep apnea syndrome; pediatric patients < 12 years of age • for buprenorphine: myasthenia gravis.			

b.i.d.= twice a day; CNS = central nervous system; CR = controlled release; ER = extended release; MAO = monoamine oxidase; q.d.= once a day; SR = sustained release.

[a] Health Canada indication.

Source: Product monographs for Nucynta Extended-Release,[12] Teva-Morphine SR,[29] Kadian,[30] OxyNEO,[31] Jurnista,[32] Hydromorph Contin,[33] Metadol,[34] Duragesic,[35] BuTrans,[36] Belbuca,[37] Targin,[38] Durela.[39] and Codeine Contin.[40]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of tapentadol hydrochloride ER tablets (Nucynta ER) for the management of pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. Nucynta ER is not indicated as an as-needed analgesic.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CDR and Health Canada, as well as those meeting the selection criteria presented in Table 5.

Table 5: Inclusion Criteria for the Systematic Review

Patient Population	Adults with pain severe enough to require daily, continuous, long-term opioid treatment, and: that is opioid responsive; and for which alternative treatment options are inadequate. **Subgroups:** • pain type (e.g., osteoarthritis, musculoskeletal, neuropathic, cancer) • history of opioid use (e.g., opioid naive, past opioid use, current opioid use) • patients with vs. without depression • baseline pain intensity.
Intervention	Tapentadol hydrochloride extended-release tablets 100 mg to 250 mg twice daily and not as an as-needed analgesic.
Comparators	• Long-acting opioid analgesics (e.g., morphine SR, oxycodone CR, hydromorphone CR, methadone, transdermal fentanyl, transdermal or buccal film buprenorphine, tramadol ER, codeine CR) • Long-acting opioid agonist-antagonist combinations (e.g., oxycodone/naloxone)
Outcomes	**Efficacy outcomes:** • pain intensity[a] • health-related quality of life[a] • patient global assessment of change[a] • impact on sleep (e.g., latency, duration, awakenings, quality[a]) • impact on work and daily activities[a] • need for additional therapy for breakthrough pain • mental or psychological symptoms[a] • caregiver burden.[a] **Harms outcomes:** • AEs, SAEs, WDAEs, mortality • notable harms (gastrointestinal AEs [e.g., constipation, nausea, vomiting], somnolence, withdrawal symptoms, serotonin syndrome) • treatment discontinuation, including reason for discontinuation (e.g., lack of efficacy, adverse effects).
Study Design	Published and unpublished RCTs; phase III and IV

AE = adverse event; CR = controlled release; ER = extended release; RCT = randomized controlled trial; SAE = serious adverse event; SR = sustained release; vs. = versus; WDAE = withdrawal due to adverse event.

[a] Using a validated scale.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was the drug name (tapentadol/Nucynta).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on May 15, 2018. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on September 19, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 6, Table 7, and Table 8. A list of excluded studies is presented in Appendix 3.

Results

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

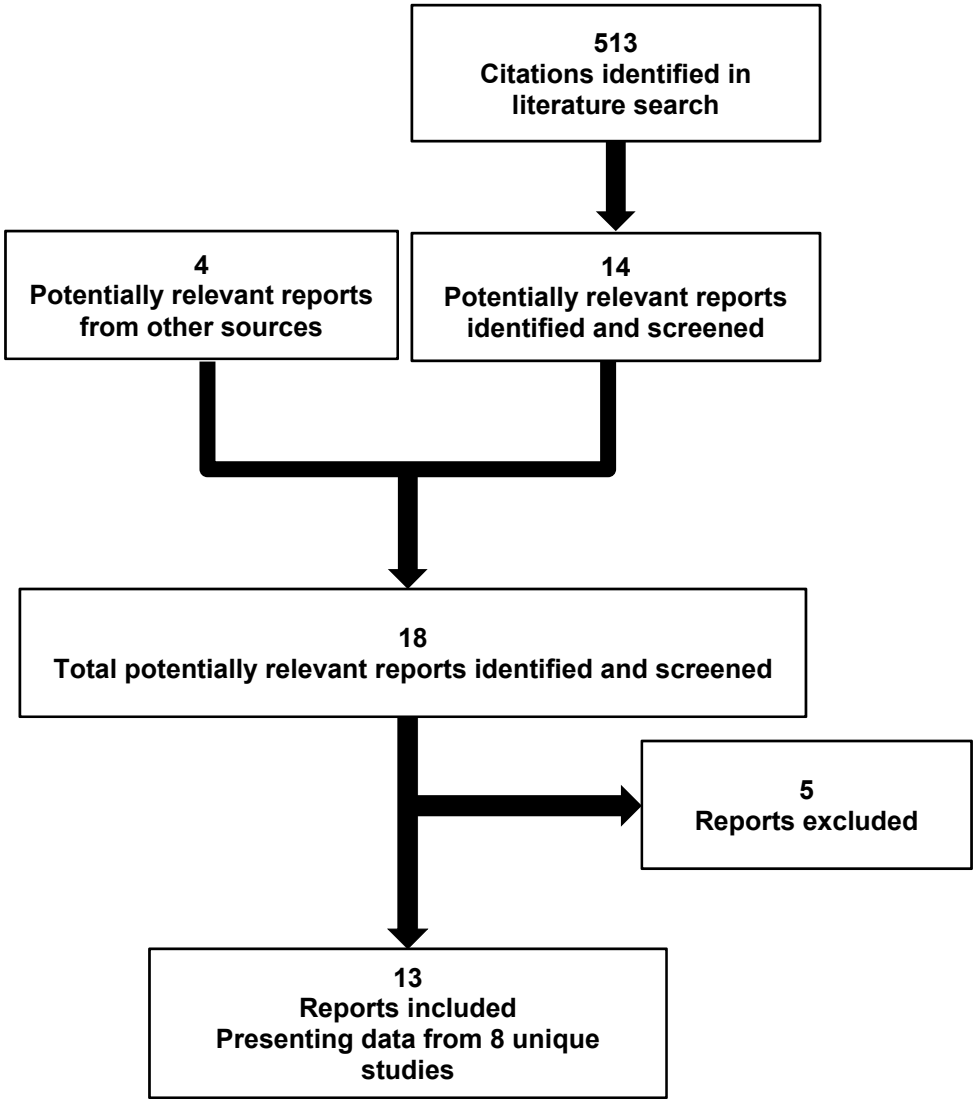


Table 6: Details of Included Studies — Osteoarthritis or Low Back Pain

		PAI-3008 Afilalo 2010	PAI-3009 Serrie 2017	PAI-3011 Buynak 2010	PAI-3007 Wild 2010
Designs and Populations	**Study Design**	DB, parallel-group, phase III RCT	DB, parallel-group, phase III RCT	DB, parallel-group, phase III RCT	OL, parallel-group, phase III RCT
	Years Conducted	2007 to 2008	2007 to 2008	2007 to 2008	2006 to 2008
	Locations	87 sites in the US, 15 sites in Canada, 6 sites in New Zealand, and 4 sites in Australia	79 sites in 12 European countries	85 sites in the US, 15 sites in Canada, 3 sites in Australia	53 sites in North America, 36 sites in Europe
	Randomized (N)	1,030	990	981	1,121
	Inclusion Criteria (Common)	• Taking analgesics (non-opioids or opioids at doses equivalent to ≤ 160 mg oral morphine/day) for ≥ 3 months prior to screening and dissatisfied with current therapy • Average pain intensity score on an 11-point NRS of ≥ 5 during the 3 days prior to randomization			NA
	Inclusion Criteria	• ≥ 40 years of age • Experiencing pain in the reference joint for ≥ 3 months • OA of the knee according to ACR criteria • Functional capacity class I to III		• ≥ 18 years of age • History of non-malignant low back pain for ≥ 3 months	• ≥ 18 years of age • Knee or hip OA with pain in the reference joint for ≥ 3 months or lower back pain of benign origin for ≥ 3 months • Dissatisfied with current analgesic therapy • Pain intensity score of ≥ 4 on an 11-point NRS after washout
	Exclusion Criteria[a]	• Requirement for painful procedures during the study that could affect efficacy or safety assessments • Surgery in the reference joint or lower back area (PAI-3011 and PAI-3007) within 3 months of screening • Conditions potentially influencing the assessment of OA pain or low back pain (PAI-3011 and PAI-3007)			
Drugs	**Intervention**	Tapentadol ER 100 mg to 250 mg b.i.d. See text for more details.			
	Comparator(s)	Oxycodone CR 20 mg to 50 mg b.i.d. Placebo tablets and capsules b.i.d. (except for Study PAI-3007) See text for more details.			
Duration	**Phase**				
	Screening	Up to 2 weeks			
	Washout	3 to 7 days			
	Titration	3 weeks (DB)			1 week (OL)
	Maintenance	12 weeks (DB)			Up to 51 weeks (OL)
	Follow-up	Up to 14 days			10 to 14 days

		PAI-3008 Afilalo 2010	PAI-3009 Serrie 2017	PAI-3011 Buynak 2010	PAI-3007 Wild 2010
Outcomes	**Primary End Point**	US: Change from baseline in average pain intensity at week 12 of the maintenance period Non-US: Change from baseline in average pain intensity over the entire 12-week maintenance period Pain intensity was rated twice daily (morning and evening) for the previous 12 hours on an 11-point NRS			Safety profile (AEs, SAEs, WDAEs)
	Other End Points	**Efficacy** Change from baseline to week 12 of the maintenance period in: • alternative primary end point (depending on region) • responder analysis for average pain intensity (improvement of ≥ 30% and ≥ 50%) • time to treatment discontinuation • WOMAC (PAI-3008 and PAI-3009 only) • BPI-SF (PAI-3011 only) • SF-36 • EQ-5D • Sleep questionnaire • PGIC. **Safety** • AEs, SAEs, WDAEs • PAC-SYM • COWS • SOWS (PAI-3008 and PAI-3011 only)			**Efficacy** • Sleep questionnaire • Pain intensity score on an 11-point NRS • EQ-5D • SF-36 • PGIC **Safety** • AEs, SAEs, WDAEs • PAC-SYM • COWS • SOWS
Notes	**Publications**	Afilalo 2010[41]	Serrie 2017[42]	Buynak 2010[43]	Wild 2010[44]

ACR = American College of Rheumatology; AE = adverse event; b.i.d. = twice daily; BPI-SF = Brief Pain Inventory – Short Form; COWS = clinical opiate withdrawal score; CR = controlled release; DB = double blind; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; ER = extended release; NA = not applicable; NRS = numeric rating scale; OA = osteoarthritis; OL = open label; PAC-SYM = Patient Assessment of Constipation Symptoms; PGIC = Patient Global Assessment of Change; RCT = randomized controlled trial; SAE = serious adverse events; SF-36 = Short Form-36 Health Survey; SOWS = subjective opiate withdrawal score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WDAE = withdrawal due to adverse event.

[a] See text for more details on exclusion criteria.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] PAI-3011,[17] and PAI-3007;[18] Afilalo et al. 2010;[41] Serrie et al. 2017;[42] Buynak et al. 2010;[43] and Wild et al. 2010.[44]

Table 7: Details of Included Studies — Neuropathic Pain

		Baron 2016
Designs and Populations	**Study Design**	OL, parallel-group, adaptive group-sequential phase IIIb/IV RCT
	Years Conducted	2013 to 2014
	Locations	Multiple sites in 3 European countries
	Randomized (N)	258

	Inclusion Criteria	• ≥ 18 years of age
		• Severe low back pain with a neuropathic component for ≥ 3 months prior to enrolment
		• Pain requiring a strong (WHO step III) analgesic (according to the investigator)
		• Average 11-point NRS pain intensity score during the 3 days prior to enrolment of:
		  ○ ≥ 5 for patients taking co-analgesics
		  ○ ≥ 6 for patients not taking co-analgesics
		• 11-point NRS pain intensity score ≥ 6 for all patients at randomization

		Baron 2016
		• painDETECT questionnaire score ≥ 13 (≥ 9 for patients on a stable regimen of centrally acting co-analgesics) at enrolment • painDETECT questionnaire score ≥ 13 at randomization
	Exclusion Criteria[a]	• Condition other than index pain that could confound the assessment of pain (e.g., fibromyalgia or inflammation) • Low back pain caused by cancer and/or metastatic diseases • Acute intoxication with alcohol, hypnotics, centrally acting analgesics, or psychotropic active substances • Autoimmune inflammatory conditions • Hypothyroidism or Addison's disease • Severe respiratory depression with hypoxia and/or hypercapnia or chronic obstructive pulmonary disease, acute or severe bronchial asthma • Paralytic ileus, acute biliary obstruction or pancreatitis
	Criteria for Entering Maintenance Phase	One of the following: • 11-point NRS pain intensity score ≤ 4 and acceptable tolerability as reported by the patient • 11-point NRS pain intensity score ≤ 5; satisfactory pain relief and tolerability as reported by the patient and investigator; and patient on maximum dosage of the study drug (or maximum dosage not reached due to side effects).
Drugs	**Intervention**	Tapentadol ER 50 mg to 250 mg b.i.d. See text for more details.
	Comparator(s)	Oxycodone/naloxone PR 10 mg / 5 mg to 40 mg / 20 mg b.i.d. (plus oxycodone PR 10 mg b.i.d.) See text for more details.
Duration	**Phase**	
	Screening	None
	Washout	3 to 14 days
	Titration	3 weeks
	Maintenance	9 weeks
	Follow-up	None
Outcomes	**Primary End Point**	Co-primary end points: • Change in average 11-point NRS pain intensity from baseline (mean value during the last 3 days of washout) to the end of the maintenance period or at discontinuation • Change in PAC-SYM total score from baseline to end of the maintenance phase or at discontinuation
	Other End Points	**Efficacy** • Change in 11-point NRS pain intensity for pain radiating toward or into the leg • NPSI • PGIC • HADS **Safety** • AEs, SAEs, WDAEs • PAC-SYM
Notes	**Publications**	Baron et al. 2016[19,20]

AE = adverse event; b.i.d. = twice daily; ER = extended release; HADS = Hospital Anxiety and Depression Scale; NPSI = Neuropathic Pain Symptom Inventory; NRS = numeric rating scale; OL = open label; PAC-SYM = Patient Assessment of Constipation Symptoms; PGIC = Patient Global Assessment of Change; PR = prolonged release; RCT = randomized controlled trial; SAE = serious adverse events; WDAE = withdrawal due to adverse event; WHO = World Health Organization.

[a] See text for more details on exclusion criteria.

Source: Baron et al. 2016.[19,20]

Table 8: Details of Included Studies — Cancer Pain

		Imanaka 2013	Imanaka 2014	Kress 2014
Designs and Populations	**Study Design**	DB, parallel-group, phase III RCT	OL, parallel-group, phase III RCT	DB, parallel-group and randomized withdrawal, phase III RCT
	Years Conducted	2010 to 2012	2010 to 2012	2007 to 2012
	Locations	69 sites in Japan and Korea	27 sites in Japan	71 sites in 16 European countries
	Randomized (N)	343	100	505
	Inclusion Criteria	• ≥ 20 years of age • Diagnosis of any type of cancer • Chronic malignant tumour-related pain • Dissatisfied with pain relief on current analgesic treatment for cancer pain • Pain required treatment with an opioid analgesic (according to investigator) • Average pain intensity score over the past 24 hours of ≥ 4 on 11-point NRS at randomization	• ≥ 20 years of age • Diagnosis of any type of cancer • Moderate-to-severe chronic malignant tumour-related pain • Receiving around-the-clock opioid therapy of oral morphine SR (≤ 120 mg/day), oral oxycodone CR (15 to 80 mg/day), or transdermal fentanyl (≤ 3.4 mg/patch to ≤ 8.4 mg/patch, depending on product) • Stable opioid dose during the 3 days before randomization • Average pain intensity score over the past 24 hours of < 4 on 11-point NRS at randomization	• ≥ 18 years of age • Chronic malignant tumour-related pain • Pain intensity score of ≥ 5 on 11-point NRS at randomization • Opioid naive or dissatisfied with prior opioid treatment (dose equivalent of oral morphine ≤ 160 mg/day)
	Exclusion Criteria[a] (Common)	• History of or current disease that could result in increased intracranial pressure, disturbance of consciousness, lethargy, or respiratory problems • Disease for which opioids are contraindicated • History of surgery intended for the cure of primary disease or treatment of cancer pain within 28 days of screening • Psychiatric disorder or concurrent symptoms with accompanying pain that could interfere with efficacy and safety evaluations		• History and/or presence of cerebral tumour or cerebral metastases • HIV infection • Hypercalcemia
	Exclusion Criteria[a] (Study-Specific)	• Use of opioid analgesics (except for ≤ 60 mg/day codeine phosphate or ≤ 30 mg/day dihydrocodeine phosphate as anti-tussives) within 28 days of screening	• History of chemotherapy that might interfere with assessments • Use of opioid medication for purposes other than cancer pain within 3 days of enrolment; or ≥ 3 doses of rescue medication within 3 days of randomization • Opioid antagonist analgesics, nerve block and stimulation analgesia within 7 days of screening	
	Criteria for Entering Maintenance Phase	NA	NA	Mean pain intensity score < 5 and mean total daily dose of rescue medication ≤ 20 mg/day during the last 3 days of titration
Drugs	**Intervention**	Tapentadol ER 25 mg to 200 mg b.i.d. See text for more details.	Tapentadol ER 25 mg to 250 mg b.i.d. See text for more details.	Tapentadol ER 100 mg to 250 mg b.i.d. See text for more details.

		Imanaka 2013	Imanaka 2014	Kress 2014
	Comparator(s)	Oxycodone CR dosage range: 5 mg to 40 mg b.i.d. See text for more details.	Morphine SR dosage range: 10 mg b.i.d to 70 mg b.i.d. See text for more details.	Morphine sulphate CR dosage range: 40 mg b.i.d. to 100 mg b.i.d. See text for more details.
DURATION	**Phase**			
	Screening	1 week	1 to 2 weeks	Up to 7 days
	Titration	4 weeks (DB titration and maintenance)	8 weeks (OL titration and maintenance)	2 weeks (DB parallel-group phase)
	Maintenance			4 weeks (DB randomized withdrawal phase)
	Follow-up	1 week	None	None
OUTCOMES	**Primary End Point**	Mean change in average pain intensity on an 11-point NRS from baseline to the last 3 days of study treatment	Proportion of patients who maintained pain control (change from baseline in mean 24-hour pain intensity score on an 11-point NRS of less than +1.5 and ≤ 2 doses of rescue medication per day for any 3 consecutive days) during the first week of the open-label treatment period	Proportion of patients who completed ≥ 28 days of the maintenance phase and during the maintenance phase had a: • mean 11-point NRS pain intensity score of < 5 • mean total daily dose of ≤ 20 mg/day of rescue medication
	Other End Points	**Efficacy** • Responder analysis for 11-point NRS average pain intensity (improvement of ≥ 30% and ≥ 50%) • PGIC • Rescue medication use **Safety** • AE, SAEs, WDAEs	**Efficacy** • Average weekly pain intensity scores on an 11-point NRS • PGIC • Rescue medication use **Safety** • AEs, SAEs, WDAEs	**Efficacy** • Proportion of patients who completed the titration phase and during the last 3 days of titration had a: ○ mean 11-point NRS pain intensity score of < 5 ○ mean total daily dose of ≤ 20 mg/day of rescue medication • Change from start of titration to each week of titration in mean pain intensity on an 11-point NRS • Change from start of maintenance to each week of maintenance in mean pain intensity on an 11-point NRS **Safety** • AEs, SAEs, WDAEs
NOTES	**Publications**	Imanaka 2013[21]	Imanaka 2014[22]	Kress 2014[23]

AE = adverse event; b.i.d. = twice daily; CR = controlled release; DB = double blind; ER = extended release; NA = not applicable; NR = not reported; NRS = numeric rating scale; OL = open label; PGIC = Patient Global Assessment of Change; RCT = randomized controlled trial; SAE = serious adverse events; SR = sustained release; WDAE = withdrawal due to adverse event.

[a] See text for more details on exclusion criteria.

Source: Imanaka et al. 2013,[21] Imanaka et al. 2014,[22] Kress et al. 2014.[23]

Included Studies

Description of Studies

The systematic review identified eight relevant phase III randomized controlled trial (RCTs). Five of the RCTs were conducted in patients with chronic non-cancer pain while three RCTs were conducted in patients with cancer-related pain. Patients in the non-cancer pain RCTs had knee or hip osteoarthritis (OA)-related pain or low back pain (LBP). In the non-cancer pain RCTs, oxycodone CR was included as an active comparator in four RCTs and oxycodone/naloxone prolonged-release (PR) was the comparator in one RCT. In the cancer pain RCTs, the active comparators were oxycodone CR, morphine sustained-release (SR), and morphine suphate CR. Four of the non-cancer pain RCTs had a treatment period of 12 to 15 weeks and the fifth RCT had a treatment period of one year. The treatment periods in the cancer pain RCTs ranged in duration from four to eight weeks.

The following made up the eight RCTs:

- Three 15-week, double-blind (DB), parallel-group RCTs in patients with knee OA (Study PAI-3008, N = 1,030; Study PAI-3009, N = 990) or non-malignant LBP (Study PAI-3011, N = 981) randomized (1:1:1) to one of placebo, tapentadol ER, or oxycodone CR. Details of these trials are provided in Table 6. Studies PAI-3008 and PAI-3011 were pivotal trials when Nucynta CR was reviewed by Health Canada.
- One one-year, OL, parallel-group RCT (Study PAI-3007, N = 1,121) in patients with knee or hip OA or non-malignant LBP randomized (4:1) to tapentadol ER or oxycodone CR. Details of this trial are provided in Table 6.
- One 12-week, OL, noninferiority, parallel-group, sequential phase IIIb/IV RCT (Baron 2016, N = 258) in patients with LBP with a neuropathic component randomized (1:1) to tapentadol ER or oxycodone/naloxone PR. Following a three-week titration phase, patients could proceed to the nine-week maintenance phase if they had either: a pain intensity score of no more than 4 points the 11-point numeric rating scale (NRS) with acceptable tolerability; or a pain intensity score of no more than 5 points with satisfactory pain relief and tolerability according the patient and investigator. Patients in the oxycodone/naloxone PR group could switch to a separate tapentadol ER escape arm at any time, but patients in the tapentadol ER group could not switch to another group. The co-primary end points of this trial were pain intensity on the 11-point NRS and an evaluation of constipation symptoms, and noninferiority of tapentadol ER compared with oxycodone/naloxone PR was assessed. Although this trial was described as having an adaptive, three-stage, group-sequential design, adaptations and interim analyses were not described and only the final analysis was reported. Details of this trial are provided in Table 7.
- One four-week, DB, noninferiority, parallel-group RCT (Imanaka 2013; N = 343) in patients with cancer pain randomized (1:1) to tapentadol ER or oxycodone CR. Noninferiority of tapentadol ER compared with oxycodone CR was assessed. Details of this trial are provided in Table 8.
- One eight-week, OL, parallel-group RCT (Imanaka 2014; N = 100) in patients with cancer pain whose pain was already controlled with an opioid and who were randomized (1:1) to tapentadol or morphine SR. The primary end point was the proportion of patients who maintained pain control and the treatment groups were not formally compared. Details of this trial are provided in Table 8.

- One six-week, DB, parallel-group RCT (Kress 2014; N = 505) in patients with cancer pain. Patients were initially randomized (2:1) to tapentadol ER or morphine sulphate CR for a two-week, parallel-group titration phase. Patients on tapentadol ER who, in the last three days of titration, had a mean pain intensity score on the 11-point NRS of less than 5 and mean daily use of morphine IR of no more than 20 mg were then re-randomized (1:1) to tapentadol ER or placebo for a four-week, randomized withdrawal maintenance phase. Due to the second randomization for the maintenance phase, tapentadol ER and morphine sulphate CR could only be compared for the titration phase. Details of this trial are provided in Table 8.

The trials with names beginning with "PAI" were sponsored by the manufacturer (Johnson and Johnson and Grünenthal). The other trials were funded by Janssen Research and Development or Grünenthal.

Populations

Study Inclusion and Exclusion Criteria

In four of the RCTs in patients with OA pain or LBP (studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007), patients had experienced pain for at least three months prior to screening and were dissatisfied with their current analgesic therapy (including non-opioid analgesics or opioid analgesics equivalent to no more than oral morphine 160 mg per day). In addition, patients had to have a minimum pain intensity averaged over the three-day baseline pain evaluation period at the end of washout of analgesic medication. The minimum score on an 11-point NRS for pain intensity was 5 points for all of these RCTs except for one (minimum score of 4 for Study PAI-3007).

In the OL RCT in patients with LBP with a neuropathic component (Baron 2016), patients had experienced severe LBP for at least three months prior to enrolment, which required a World Health Organization step III analgesic (i.e., a strong opioid), according to the investigator. A minimum pain intensity score of 6 points on an 11-point NRS and a minimum painDETECT questionnaire score of 13 were required at randomization. The range of scores for the painDETECT questionnaire is 0 to 38, with a higher score indicating a higher probability of a neuropathic pain component being present.[45] A score of 13 to 18 corresponds to the unclear category and a score of 19 to 38 corresponds to the positive category.

In the three RCTs in patients with chronic tumour-related pain (Imanaka 2013, Imanaka 2014, and Kress 2014), patients either had a minimum pain intensity score on an 11-point NRS (4 points for Imanaka 2013 and 5 points for Kress 2014) at randomization and were dissatisfied with current analgesic therapy or a pain intensity score on an 11-point NRS of less than 4 points at randomization while on a stable dosage of strong opioid analgesic (Imanaka 2014).

Common exclusion criteria for the RCTs in patients with non-cancer pain (as well as Kress 2014) were scheduled painful procedures during the study; history of substance abuse, seizure disorder, malignancy, traumatic brain injury, stroke, transient ischemic attack, brain neoplasm, allergy or contraindication to oxycodone or acetaminophen; uncontrolled hypertension; severe renal or hepatic impairment; recent use of neuroleptics, tricyclic antidepressants, antiparkinsonian drugs, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and corticosteroids. In the Imanaka et al. studies, patients were excluded if they had uncontrolled arrhythmia, a recent history of surgery for cancer or

cancer pain or radiotherapy, or a history of disease that could result in increased intracranial pressure, disturbance of consciousness, lethargy, or respiratory problems. Patients in the Imanaka 2013 study were excluded if they recently used opioid analgesics other than anti-tussive doses of codeine or dihydrocodeine. The exclusion criteria regarding recent use of medications in Imanaka 2014 were similar to those in the non-cancer pain RCTs.

Baseline Characteristics

In the four RCTs in patients with OA and LBP (studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007), patients were mostly female (55% to 76% of patients) and white (72% to 99% of patients) and mean ages ranged from 58 to 62 years (OA patients) or 49 to 50 years (LBP)(Table 9 and Table 10). Baseline pain following washout of analgesic medications was 7.2 to 7.6 on the 11-point NRS, with most patients (more than 80% in all groups) having a pain score of 6 points or greater. The most common opioid analgesics used within one month prior to the studies were Vicodin (combined hydrocodone and acetaminophen) in studies PAI-3008 and PAI-3011 and Panadeine Co (combined codeine and acetaminophen) in all four trials. The most common non-opioid analgesics in the four RCTs were acetaminophen, ibuprofen, and acetylsalicylic acid. There were no notable imbalances between treatment groups in any of the trials. The percentage of patients using opioids within three months of screening (referred to as prior opioid users) varied between trials. Prior opioid users made up about a third of patients in Study PAI-3008 (32% to 34%), which was conducted in North America and Australasia, and only 14% to 17% of patients in Study PAI-3009, which was conducted in Europe. There were higher percentages of prior opioid users in studies PAI-3008 and PAI-3007, which ranged from 50% to 56%.

In the RCT in patients with LBP with a neuropathic component (Baron 2016), all patients were white, most patients were female (59% to 66%), and had experienced chronic LBP for a mean of 102 to 116 months. Mean pain intensity score following washout was 7.5 points; most patients fell in the painDETECT score category of positive (74% to 76%), and most patients had a diagnosis of lumbar radiculopathy (59%). There were no notable imbalances between treatment groups (Table 11).

Table 9: Summary of Baseline Characteristics — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2010 Safety Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 337	TAP N = 319	OXY N = 331	PL N = 319	TAP N = 318	OXY N = 328
Mean age, years (SD)	58 (9)	58 (10)	58 (10)	62 (9)	62 (9)	62 (9)	50 (14)	49 (13)	50 (14)
Male, n (%)	137 (41)	128 (37)	140 (41)	80 (24)	88 (28)	112 (34)	135 (42)	124 (39)	147 (45)
Race, n (%)									
White	267 (79)	260 (76)	245 (72)	335 (99)	316 (99)	329 (99)	237 (74)	229 (72)	241 (74)
Black	38 (11)	49 (14)	45 (13)	0	1 (0.3)	1 (0.3)	50 (16)	62 (20)	55 (17)
Hispanic	20 (6)	21 (6)	37 (11)	0	1 (0.3)	0			
Other	32 (9)	35 (10)	52 (15)	2 (0.6)	1 (0.3)	1 (0.3)	32 (10)	27 (8)	32 (10)
Prior opioid use,[a] n (%)	114 (34)	109 (32)	108 (32)	56 (17)	52 (16)	47 (14)	172 (54)	178 (56)	165 (50)
Baseline pain category,[b] n (%)									
Severe	275 (82)	293 (85)	284 (83)	294 (88)	284 (89)	299 (90)	276 (87)	280 (89)	292 (90)
Moderate	61 (18)	49 (14)	58 (17)	42 (13)	35 (11)	32 (10)	42 (13)	35 (11)	33 (10)
Mild	0	2 (1)	0	0	0	0	0	0	0
Mean baseline pain intensity score[c] (SD)	7.2 (1.3)	7.4 (1.4)	7.2 (1.3)	7.3 (1.1)	7.3 (1.1)	7.3 (1.1)	7.6 (1.3)	7.5 (1.3)	7.5 (1.2)
Opioid-naive patients	7.1 (1.3) N = 223	7.2 (1.4) N = 235	7.2 (1.3) N = 234	7.3 (1.1) N = 281)	7.2 (1.1) N = 267	7.2 (1.1) N = 284	7.4 (1.3) N = 146	7.4 (1.4) N = 137	7.4 (1.2) N = 161
Prior opioid users[a]	7.4 (1.3) N = 114	7.8 (1.2) N = 109	7.4 (1.4) N = 108	7.3 (1.3) N = 56	7.5 (1.2) N = 52	7.4 (1.1) N = 47	7.7 (1.3) N = 172	7.6 (1.3) N = 178	7.7 (1.2) N = 164
Prior opioid analgesic use,[d] n (%)	121 (36)	117 (34)	117 (34)	60 (18)	55 (17)	52 (16)	178 (56)	177 (56)	171 (52)
Vicodin (hydrocodone + acetaminophen)	31 (9)	25 (7)	37 (11)	0	0	0	67 (21)	56 (18)	64 (20)
Panadeine Co	17 (5)	23 (7)	15 (4)	10 (3)	11 (3)	7 (2)	31 (10)	29 (9)	21 (6)
Propacet	11 (3)	15 (4)	11 (3)	0	0	0	15 (5)	15 (5)	9 (3)
Tramadol	14 (4)	14 (4)	10 (3)	14 (4)	21 (7)	15 (5)	16 (5)	15 (4)	11 (3)
Tramadol hydrochloride	8 (2)	9 (3)	8 (2)	11 (3)	12 (4)	6 (2)	17 (5)	12 (4)	8 (2)
Ultracet (tramadol + Acetaminophen)	0	1 (0.3)	6 (2)	15 (5)	8 (3)	10 (3)	1 (0.3)	3 (0.9)	3 (0.9)
Hydrocodone	16 (5)	6 (2)	11 (3)	0	0	0	17 (5)	18 (6)	17 (5)
Oxycocet	9 (3)	9 (3)	8 (2)	0	0	0	19 (6)	17 (5)	15 (5)
Prior non-opioid analgesic use,[d] n (%)	293 (87)	297 (86)	300 (88)	315 (94)	301 (94)	311 (94)	262 (82)	259 (81)	271 (83)
Aceclofenac	0	0	0	18 (5)	25 (8)	25 (8)	0	0	0
Acetaminophen	100 (30)	100 (29)	99 (29)	67 (20)	82 (26)	75 (23)	89 (28)	84 (26)	79 (24)
Acetylsalicylic	60 (18)	63 (18)	59 (17)	44 (13)	46 (14)	51 (15)	43 (14)	43 (14)	47 (14)

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2010 Safety Set		
acid									
Celecoxib	36 (11)	48 (14)	34 (10)	15 (5)	12 (4)	13 (4)	18 (6)	12 (4)	13 (4)
Diclofenac/ diclofenac sodium	16 (5)	13 (4)	10 (3)	116 (34)	106 (33)	102 (31)	9 (3)	10 (3)	6 (2)
Etoricoxib	0	0	0	30 (9)	18 (6)	25 (8)	0	0	0
Ibuprofen	80 (24)	94 (27)	98 (29)	52 (15)	48 (15)	57 (17)	110 (35)	124 (39)	119 (36)
Ketoprofen	0	1 (0.3)	3 (0.9)	26 (8)	26 (8)	37 (11)	0	0	0
Meloxicam	23 (7)	17 (5)	27 (8)	27 (8)	27 (9)	35 (11)	11 (3)	12 (4)	13 (4)
Naproxen/ naproxen sodium	48 (14)	47 (14)	50 (15)	5 (2)	3 (0.9)	1 (0.3)	41 (13)	47 (15)	67 (20)
Nimesulide	0	0	0	54 (16)	55 (17)	46 (14)	0	0	0
Piroxicam	4 (1)	4 (1)	5 (2)	38 (11)	30 (9)	20 (6)	3 (0.9)	1 (0.3)	1 (0.3)

PL = placebo; OXY = oxycodone controlled-release; SD = standard deviation; TAP = tapentadol extended-release.

Note: Pain intensity is measured on the 11-point numeric rating scale.

[a] Prior opioid use is defined as taking opioid analgesics during the three months prior to the screening visit.

[b] For the 11-point numeric rating scale pain intensity score, mild was defined as a pain intensity score of 1 to 3; moderate as a pain intensity score of 4 to 5; severe as a pain intensity score of 6 or greater.

[c] Baseline pain intensity score is the average of pain scores over 72 hours prior to randomization.

[d] Data are presented for opioid analgesics used in at least 3% of patients in any treatment group and non-opioid analgesics used in at least 5% of patients in any treatment group. Analgesics taken within one month of screening were recorded.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 10: Summary of Baseline Characteristics – Osteoarthritis and Low Back Pain (PAI-3007)

	PAI-3007 Wild 2010 (OA and LBP) Safety Set	
	TAP N = 894	OXY N = 223
Mean age, years (SD)	56.8 (12.5)	58.1 (11.8)
Male, n (%)	379 (42)	98 (44)
Race, n (%)		
White	792 (89)	203 (91)
Black	60 (7)	13 (6)
Hispanic	26 (3)	4 (2)
Other	16 (2)	3 (1)
Prior opioid use,[a] n (%)	473 (53)	112 (50)
Baseline pain category,[b] n (%)		
Severe	805 (90)	194 (87)
Moderate	89 (10)	29 (13)
Mean baseline pain intensity score[c] (SD)	7.6 (1.5)	7.6 (1.6)
Baseline painDETECT score category,[d] n (%)		
Positive	NR	NR
Unclear	NR	NR

	PAI-3007 Wild 2010 (OA and LBP) Safety Set	
Patients with diagnosed lumbar radiculopathy, n (%)	NR	NR
Mean duration of chronic low back pain, months (SD)	NR	NR
Mean number of previous hospitalizations for pain (SD)	NR	NR
Mean number of analgesic regimens since pain started (SD)	NR	NR
Prior opioid analgesic use,[e] n (%)	473 (53)	112 (50)
Vicodin (hydrocodone + acetaminophen)	108 (12)	28 (13)
Panadeine Co	57 (6)	12 (5)
Propacet	36 (4)	5 (2)
Tramadol	42 (5)	10 (5)
Tramadol hydrochloride	60 (7)	13 (6)
Ultracet (tramadol + acetaminophen)	24 (3)	8 (4)
Hydrocodone	46 (5)	9 (4)
Oxycocet	44 (5)	14 (6)
Oxycodone	27 (3)	6 (3)
Prior non-opioid analgesic use,[e] n (%)	414 (46)	109 (49)
Acetaminophen	145 (16)	42 (19)
Ibuprofen	137 (15)	30 (14)
Acetylsalicylic acid	97 (11)	25 (11)
Naproxen/naproxen sodium	64 (7)	17 (8)

LBP = lower back pain; NR = not reported; OA =osteoarthritis; OXY = oxycodone controlled-release; SD = standard deviation; TAP = tapentadol extended-release.

Note: Pain intensity is measured on the 11-point numeric rating scale.

[a] Prior opioid use is defined as taking opioid analgesics during the three months prior to the screening visit.

[b] Mild is defined as a pain intensity score of 1 to 3; moderate as a pain intensity score of 4 to 5; severe as a pain intensity score of 6 or greater.

[c] Baseline pain intensity score is the average of pain scores over 72 hours prior to randomization.

[d] Positive is defined as a painDETECT score of 19 to 38 and unclear is defined as a painDETECT score of 13 to 18.

[e] Data are presented for opioid analgesics used in at least 3% of patients in any treatment group and non-opioid analgesics used in at least 5% of patients in any treatment group. Analgesics taken within one month of screening were recorded.

Source: Clinical study report for PAI-3007.[18]

Table 11: Summary of Baseline Characteristics — Low Back Pain (Baron 2016)

Characteristic	Oxycodone/ Naloxone PR (*n* = 128)	Tapentadol PR (*n* = 130)
Mean (SD) age, years	58.4 (12.23)	58.1 (11.48)
Gender, *n* (%)		
Female	84 (65.6)	77 (59.2)
Male	44 (34.4)	53 (40.8)
Mean (SD) BMI, kg/m^2	29.0 (5.69)	29.8 (5.55)
Race, *n* (%)		
White	128 (100)	130 (100)
Baseline painDETECT score*		
Positive	97 (75.8)	96 (73.8)
Unclear	27 (21.1)	33 (25.4)

BMI = body mass index; PR = prolonged release; SD = standard deviation.

Source: Table 1 of Effectiveness of Tapentadol Prolonged Release (PR) Compared with Oxycodone/Naloxone PR for the Management of Severe Chronic Low Back Pain with a Neuropathic Component: A Randomized, Controlled, Open-Label, Phase 3b/4 Study by Baron R, Likar R, Martin-Mola E, Blanco FJ, Kennes L, Müeller m, Falke D, and Steigerwald I[20] is licensed under https://creativecommons.org/licenses/by-nc-nd/4.0/.

In the three RCTs in patients with malignant tumour-related pain (Imanaka 2013 and 2014 and Kress 2014), the mean age ranged from 59 to 66 years. About half of the patients were male (50% to 58%). In Imanaka 2013, patients had an 11-point NRS mean pain intensity score of 5.4 to 5.5 points while on non-opioid therapy prior to the trial. In Imanaka 2014, patients were on a strong opioid analgesic and had an 11-point NRS mean pain intensity score of 1.5 to 1.8 points. All patients received prior opioids. In Kress 2014, patients were opioid naive or were dissatisfied with their opioid treatment and had a mean pain intensity score of 6.0 to 6.3 points while on their previous analgesic therapy. The proportions of patients that received prior opioids were 85%, 86%, and 84% in the placebo group, the tapentadol PR group, and the morphine group, respectively. There were no notable imbalances between treatment groups in any of the trials.

Interventions

Study Medication

Prior to randomization in the studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007, patients underwent screening for up to 14 days followed by a three- to seven-day washout period during which use of analgesics was prohibited. Before randomization in Baron 2016, there was a three- to 14-day washout period with no analgesic use. This period was likely also the screening period given that a separate screening period was not defined. In the cancer pain trials, there was no washout of analgesics and the screening periods were one week, one to two weeks, and up to one week in Imanaka 2013, Imanaka 2014, and Kress 2014, respectively.

All of the trials allowed for titration of the study treatment to a dosage representing the optimal balance between efficacy and adverse effects. Following titration, patients remained

on the same dosage for the remainder of the treatment period, with dosage adjustment allowed in some trials.

In studies PAI-3008, PAI-3009, and PAI-3011, a computer-generated randomization schedule with randomly permuted blocks stratified by study site was prepared by the sponsor. Patients were assigned to treatment groups via an interactive voice response system oxycodone CR tablets were encapsulated in grey, opaque capsules, in contrast to the white to blue or blue-green colour of the tapentadol ER film-coated tablets. Placebo tablets and capsules matched the appearance of tapentadol ER tablets or oxycodone capsules, respectively.

In the studies PAI-3008, PAI-3009, and PAI-3011, patients were titrated on study medication for three weeks following washout of previous analgesic medications. Patients on a stable dose of study medication and not taking acetaminophen during the last three days of titration could proceed to the 12-week maintenance phase with follow-up for up to 14 days. In Study PAI-3007, the long-term OL trial, titration only lasted three to seven days, though titration could continue during the maintenance phase until the optimal dosage was achieved. The minimum and maximum dosages during the above-mentioned trials were 100 mg twice daily and 250 mg twice daily of tapentadol ER and 20 mg twice daily and 50 mg twice daily of oxycodone CR. During the titration phase, patients randomized to tapentadol received tapentadol ER 50 mg twice daily for three days, followed by 100 mg twice daily for four days and then further increases in 50 mg twice daily increments no more than once every three days as necessary. Decreases of 50 mg twice daily were allowed at any time. Patients randomized to oxycodone CR followed the same titration regimen except that the starting treatment dosage was 10 mg twice daily, the subsequent dosage was 20 mg twice daily, and increment and decrements of 10 mg twice daily were used. During the maintenance phase, patients remained on the titrated dosage with dosage adjustments (following evaluation by the investigator) kept to a minimum. The formulation used in these four RCTs was the Nucynta CR formulation.

In Imanaka 2013 and 2014, the extended-release formulation of tapentadol was used, according to the FDA medical review for Nucynta ER.[46] For the remaining trials (Baron 2016 and Kress 2014), the formulation of tapentadol (CR or extended-release) could not be confirmed. Since the two formulations are considered by Health Canada to be bioequivalent, they are both referred to in this report as tapentadol ER.

The minimum and maximum dosages and titration regimens for each treatment arm in these trials are provided in Table 7 and Table 8. In the OL phase IIIb/IV RCT (Baron 2016), the methods for randomization and allocation to either tapentadol ER or oxycodone/naloxone PR were not described. Patients in the oxycodone/naloxone PR arm could switch to the tapentadol ER arm at any time during the treatment period. The minimum and maximum dosages of study medication were 50 mg twice daily and 250 mg twice daily of tapentadol ER and 10 mg/5 mg twice daily to 40 mg/20 mg twice daily of oxycodone/naloxone PR plus 10 mg twice daily of oxycodone PR. The starting tapentadol ER dose during the three-week titration phase was 50 mg twice daily, with 50 twice daily increments allowed until the efficacy criteria for entering the nine-week maintenance phase were reached. Oxycodone/naloxone PR was titrated in the same manner with starting and incremental dosages of 10 mg/5 mg twice daily used. During the maintenance phase, a single increment or decrement in dosage was allowed.

Patients in Imanaka 2013 and Kress 2014 were randomized according to a computer-generated list in permuted blocks, stratified by study site, and allocated to their treatment

through an interactive voice response system. Randomization and allocation were not described in Imanaka 2014 aside from randomization being stratified by prior opioid treatment. Methods to maintain patient and investigator blinding in Imanaka 2013 and Kress 2014 were not described.

In Imanaka 2013, dosages of tapentadol ER could range from 25 mg twice daily to 200 mg twice daily and dosages of oxycodone CR could range from 5 mg twice daily to 40 mg twice daily during the four-week DB treatment period. Patients started on the minimum dosage with adjustments allowed (after assessing patients for pain intensity and rescue medication use) after four consecutive doses of the same amount. After titration to the optimal dosage, the dosage was kept stable, though dose adjustments were permitted except during the last three days.

In Imanaka 2014, the dosage ranges were 25 mg twice daily to 250 mg twice daily of tapentadol ER and 10 mg twice daily to 70 mg twice daily of morphine SR. The starting tapentadol ER dose was based on the previous opioid analgesic dose and used for two days, followed by increases of 50 mg per day (if current daily dosage < 200 mg) or 100 mg per day (if current daily dosage ≥ 200 mg) based on pain intensity score and rescue medication use and decreases as needed. The dosage regimen was the same for morphine SR dose except that increases of 10 mg per day (if current daily dosage < 60 mg) or 20 mg per day (if current daily dosage ≥ 60 mg) were used.

In the two-week titration phase of Kress 2014, patients received 100 mg twice daily to 250 mg twice daily tapentadol ER or 40 mg twice daily to 100 mg twice daily morphine CR. Patients started on 100 mg twice daily tapentadol ER (or 40 mg twice daily morphine CR) with increases of 50 mg twice daily tapentadol (or 20 mg twice daily morphine CR) at a minimum of three-day intervals or a decrease to the previous dosage. There were no provisions for dosage adjustments in the maintenance phase.

Allowed Rescue and Concomitant Medications

Medications prohibited within a certain period prior to screening were also prohibited throughout the trials. Patients diagnosed with psychiatric or neurological disorders treated with medications other than the prohibited medications could continue on the same regimen if they were already on a stable dosage.

Analgesics other than allowed rescue medications (see Table 12) were prohibited during the trials. Limited use of acetaminophen was commonly allowed as rescue medication for patients with OA or LBP during titration and maintenance, with patients already on a stable regimen of acetaminophen or nonsteroidal anti-inflammatory drugs allowed to continue this in Baron 2016. Patients with cancer pain were allowed rescue immediate-release morphine with no limit, except in Imanaka 2014, where immediate-release oxycodone or morphine up to one-sixth of the equivalent total daily dose (TDD) of study medication was allowed.

Table 12: Allowed Rescue Analgesic Medication Use

	Washout/Screening Phase	Titration Phase	Maintenance Phase	Follow-Up Phase
PAI-3008 **PAI-3009** **PAI-3011**	Washout: No analgesic medication permitted	Acetaminophen (≤ 1,000 mg/day) up to 3 days before the end of the titration phase	Acetaminophen (≤ 1,000 mg/day) for no more than 3 consecutive days for reasons other than study-related chronic pain	Following discontinuation of study treatment, appropriate analgesic medication for the symptomatic treatment of pain, according to local practice
PAI-3007	NA	Acetaminophen 1,000 mg/day for a maximum of 7 consecutive days and no more than 14 out of 30 days during the study		
Baron 2016	Patients who were on a stable pre-study regimen of NSAIDs or acetaminophen were permitted to continue taking those medications at the same stable dosage			
Imanaka 2013	Screening: No rescue medication permitted	Oral morphine IR 5 mg with no limit on the number and timing of doses per day		
Imanaka 2014	Oral oxycodone IR or oral morphine IR, no more than one-sixth of the total daily dose of around-the-clock opioid analgesics (or the minimal strength available if greater than the permitted amount)			NA
Kress 2014	NR	Morphine sulphate IR 10 mg with no limit on number and timing of doses per day		NA

IR = immediate-release; NA = not applicable; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] PAI-3011,[17] and PAI-3007;[18] Baron 2016;[19,20] Imanaka 2013;[21] Imanaka 2014;[22] and Kress 2014.[23]

Outcomes

For more information on the outcome measures and their validity, see Appendix 4.

In studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007, patients who discontinued treatment early were assessed in the same manner as patients who reached the end of their scheduled treatment period and attended a follow-up four days later. Patients were assessed at the end of their scheduled treatment period and were asked to maintain records of pain intensity and analgesic medications.

Primary End Point

The primary efficacy end point in all of the trials, except for Study PAI-3007 (safety study), Imanaka 2014, and Kress 2014, was mean change in pain intensity on the 11-point NRS from baseline to the end of the treatment period. In Baron 2016, there was a co-primary end point, mean change in Patient Assessment of Constipation Symptoms (PAC-SYM) total score from baseline to the end of treatment. The primary efficacy end point in Imanaka 2014 was the proportion of patients who maintained paint control (experienced a change from baseline in mean on the 11-point NRS pain intensity score of less than +1.5 points) for any consecutive three days during the first week of study treatment, and not more than two doses of rescue medication a day. Imanaka 2014 did not include a formal comparison between treatment arms. The primary efficacy end point in Kress 2014 was the proportion of patients who completed the maintenance phase; had a mean pain intensity score throughout the maintenance phase of less than 5 points; and had a TDD of rescue medication throughout the maintenance phase of no more than 20 mg per day.

Secondary Efficacy Outcomes

Reporting of the relevant efficacy outcomes is summarized in Table 13.

Table 13: Summary of Reported Efficacy Outcomes

Study	Pain Intensity				HRQoL			Global Assessment of Change	Impact on Sleep	Impact on Work and Daily Activities	Need for Additional Therapy		Mental or Psych. Symptoms
	NRS-11	WOMAC	BPI	NPSI	EQ-5D	SF-36	WOMAC	PGIC	Sleep Questionnaire	BPI	Rescue Analgesics	Concomitant Analgesics	HADS
PAI-3008	✓	✓			✓	✓	✓	✓	✓		✓	✓	
PAI-3009	✓	✓			✓	✓	✓	✓	✓		✓	✓	
PAI-3011	✓		✓		✓	✓		✓	✓	✓	✓	✓	
PAI-3007	✓				✓	✓		✓	✓			✓	
Baron 2016	✓			✓	✓	✓[a]		✓	✓				✓
Imanaka 2013	✓							✓			✓		
Imanaka 2014	✓							✓			✓		
Kress 2014	✓										✓		

BPI = Brief Pain Inventory; EQ-5D = EuroQol 5-Dimensions; HADS = Hospital Anxiety and Depression Scale; HRQoL = health-related quality of life; NPSI = Neuropathic Pain Symptom Inventory; NRS-11 = pain intensity on an 11-point numeric rating scale; PGIC = Patient Global Impression of Change; psych. = psychological; SF-36 = 36-Item Short Form Health Survey; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] 12-Item Short Form Health Survey.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] PAI-3011,[17] and PAI-3007;[18] Baron 2016;[19,20] Imanaka 2013;[21] Imanaka 2014;[22] and Kress 2014.[23]

Pain Intensity

The 11-point NRS for pain intensity is an ordinal scale from 0 to 10 with 0 corresponding to "no pain" and 10 corresponding to "pain as bad as you can imagine." It is a valid, reliable, and responsive outcome measure in patients with various musculoskeletal conditions such as neck pain and cervical radiculopathy.[47,48] The minimal clinically important differences (MCIDs) of the 11-point NRS in patients with chronic pain have been identified, ranging from 1.1 to 2.2 — 2 points in patients with LBP,[47] 1.3 points in patients with neck pain,[47] 2.2 points in patients with cervical radiculopathy,[49] and 1.1 points to 2.17 points in patients with shoulder pain.[48,50]

Responder analysis of pain intensity was also conducted with response defined as at least a 30% and a 50% reduction from baseline in pain intensity score in studies PAI-3008, PAI-3009, and PAI-3011. Change in pain intensity was also assessed for pain specifically radiating toward or into the leg in Baron 2016.

Pain intensity was also assessed in the pain subscale of the short form of the Brief Pain Inventory (BPI) in Study PAI-3011. The BPI is a self-administered questionnaire consisting of items on pain, pain relief, and interference of pain with activities. For the pain subscale, four items assess the patient's pain intensity: 1) at its worst in the last 24 hours, 2) at its least in the last 24 hours, 3) average pain, and 4) pain right now. Pain intensity is rated using a 0 to 10 numeric rating scale, with "0" representing "no pain" and "10" representing "pain as bad as you can imagine"; the subscale score is the mean of the individual scores. Although originally developed for evaluation of cancer pain, the BPI has also been shown to be a reliable and valid for evaluating chronic non-cancer pain.[51,52] An overall MCID of the

BPI or its subscales has not been identified from the literature, although a 2-point change was suggested as a reasonable estimate for the MCID of the BPI worst pain item.[53]

Symptoms of neuropathic pain were assessed with the Neuropathic Pain Symptom Inventory (NPSI) in Baron 2016. The NPSI is a self-administered questionnaire with 10 items on different pain sensations rated on an 11-point NRS, one item on duration of spontaneous pain and one item on the number of paroxysmal pain attacks. The recall period for the NPSI is 24 hours. In Baron 2016, the individual scores for the 10 items on pain sensations were summed and divided by 100, yielding an overall score with a possible range of 0 to 1 (with higher scores indicating a greater severity of pain). While the NPSI has been validated,[54] an MCID was not found.

Health-Related Quality of Life

The EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) instrument was used to assess health-related quality of life (HRQoL) in all of the trials in patients with non-cancer pain. Patients choose one of three possible levels (1, 2, or 3) for each of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with the levels corresponding to “no problems,” “some problems,” and “extreme problems.” A scoring function can be used to assign a value (EQ-5D-3L index score) to self-reported health states from a set of population-based preference weights.[55,56] All of the studies reporting EQ-5D-3L results appear to have used a scoring function previously developed in the UK population,[57] aside from Baron 2016, which did not report the scoring function used. EQ-5D-3L index scores of less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states “dead” and “perfect health,” respectively. Estimates of MCIDs for the EQ-5D-3L index score in general have ranged from 0.033 to 0.074[58] and MCIDs specific to patients with chronic pain were not found. The EQ-VAS is a 20 cm visual analogue scale (VAS) that has end points labelled 0 and 100, with respective anchors of “worst imaginable health state” and “best imaginable health state.” An MCID for the EQ-VAS in patients with chronic pain was not found.

The 36-item (12-item in Baron 2016) Short Form Health Survey (SF-36) was also used to assess HRQoL in the non-cancer pain trials. The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[59] For each of the eight categories, a subscale score can be calculated. In addition to subscale score for its eight health domains, the SF-36 provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS). The PCS and MCS scores range from 0 to 100 with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation (SD) of 10 in the general US population. Therefore, all scores above 50 are considered above average for the general US population. The MCID for the SF-36 MCS and PCS is typically between 2.5 points and 5 points.[60-62] MCIDs in patients with chronic pain were not found for the SF-36 MCS and PCS.

Disease-specific QoL was also assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in studies PAI-3008 and PAI-3009. The WOMAC consists of 24 self-administered items rated on an ordinal scale of 0 to 4, with 0 corresponding to the lowest level of symptoms of physical disability. The subscales assess pain, physical function, and joint stiffness due to knee and hip OA. The global score ranges from 0 to 96, with higher scores indicating greater levels of symptoms or physical

disability.[63] It is a valid, reliable, and responsive[64,65] measure of HRQoL with an MCIDs of 0.51 to 1.33 for worsening and 0.67 to 0.75 for improvement.[66]

Patient Global Assessment of Change

Patient Global Impression of Change (PGIC) from the start of the trial was assessed in all of the trials, with the exception of Kress 2014. Patients indicated their perceived change by completing the statement "Since I began trial treatment, my overall status is." In Imanaka 2014, the wording referred to cancer-related pain overall. The seven available responses were: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," and "very much worse." The PGIC is a commonly used and valid outcome measure for clinical pain trials.

Impact on Sleep

A sleep questionnaire was used to assess impact on patients' sleep in all of the trials in patients with non-cancer pain. The self-administered questionnaire was based on the previous night's sleep and patients indicated sleep latency, amount of time slept, number of awakenings, and overall sleep quality. The psychometric properties of the sleep questionnaire used in the studies have not been assessed and an MCID was not found.

Impact on Work and Daily Activities

The degree to which pain interferes with function was assessed in the pain interference subscale of the BPI in Study PAI-3011. The pain interference subscale asks patients to rate on an 11-point NRS (0 or "does not interfere" to 10 or "completely interferes"), based on the past week, how much pain interfered with general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life. The subscale score is calculated as the mean of the individual scores with higher scores indicating greater pain interference. An MCID for the BPI pain interference subscale was not found.

Need for Additional Therapy for Breakthrough Pain

Information on the use of rescue medication during the treatment period was reported in studies PAI-3008, PAI-3009, and PAI-3001, as well as the trials in patients with cancer pain (see Table 12 for allowed rescue medications). Studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007 also reported concomitant use of opioid and non-opioid analgesics during the treatment period.

Mental or Psychological Symptoms

The Hospital Anxiety and Depression Scale (HADS) was assessed in Baron 2016. It consists of 14 items rated on a 4-point scale. The anxiety and depression subscale scores are calculated by summing the individual score for seven items each to give a maximum score of 21 (with higher scores indicating more severe symptoms). Scores of less than 7 indicate non-cases, 8 to 10 indicate mild condition, 11 to 14 indicate moderate condition, and 15 to 21 indicate severe condition. MCIDs were not found for the subscales.

Harms

Reporting of the relevant harms outcomes is summarized in Table 14.

Table 14: Summary of Reported Harms Outcomes

Study	Adverse Events	Gastrointestinal Symptoms	Withdrawal Symptoms		Discontinuation of Drug	
	AEs, SAEs, WDAEs	PAC-SYM	SOWS	COWS	Treatment Discontinuations	Time to Discontinuation Due to Lack of Efficacy
PAI-3008	✓	✓	✓	✓	✓	✓
PAI-3009	✓	✓		✓	✓	✓
PAI-3011	✓	✓	✓	✓	✓	✓
PAI-3007	✓		✓	✓	✓	✓
Baron 2016	✓	✓			✓	
Imanaka 2013	✓				✓	
Imanaka 2014	✓				✓	
Kress 2014	✓				✓	

AE = adverse events, COWS = Clinical Opiate Withdrawal Scale; PAC-SYM = Patient Assessment of Constipation Symptoms; SAE = serious adverse event; SOWS = Subjective Opiate Withdrawal Scale; WDAE = withdrawal due to adverse event.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] PAI-3011,[17] and PAI-3007;[18] Baron 2016;[19,20] Imanaka 2013;[21] Imanaka 2014;[22] and Kress 2014.[23]

Notable Harms

Aside from notable harms captured in adverse event (AE) reporting, studies PAI-3008, PAI-3009, PAI-3011, and Baron 2016 reported PAC-SYM. In Baron 2016, change in total PAC-SYM score from baseline to the end of the maintenance phase or discontinuation was a co-primary end point. The PAC-SYM is a self-administered instrument containing 12 items with a recall period of two weeks. Each item asks about the severity of a symptom and is rated on a 5-point categorical scale ranging from “absent” (0) to “very severe” (4). The overall and subscale scores are calculated as the mean score of the individual items, yielding a possible range of 0 to 4 for each score. Estimates of the MCID for the PAC-SYM overall score range from –0.52 to –0.63.[67] Scores for the abdominal, rectal, and stool subscales (four items each), as well as the total score, were reported.

Withdrawal symptoms following the discontinuation of study treatment were assessed using the patient-reported Subjective Opiate Withdrawal Scale (SOWS) and the investigator-completed Clinician Opiate Withdrawal Scale (COWS). The SOWS used in the trials contained 15 items, each being a first-person statement on experiencing a withdrawal symptom rated by patients on a scale of 0 (“not at all”) to 4 (“extremely”). The total SOWS score is the sum of the individual item scores, with a higher score indicating greater withdrawal severity. In the trials, the range of score was 0 to 60. Ratings are based on how patients are feeling when they are completing the instrument. The SOWS has been found to be responsive, but information demonstrating validity, reliability, or an MCID was not found. The COWS comprises 11 items on the physical symptoms of opiate withdrawal informed by patient questioning and clinical observations. Each item is rated on an ordinal scale ranging from 0 to 4 or 0 to 5, yielding a maximum total score of 47. Higher scores indicate more severe symptoms of withdrawal. The COWS has been shown to be valid and reliable,[68,69] but no MCID was found.

Discontinuation of Drug

The numbers of patients discontinuing study treatment and the reasons for discontinuation during the treatment period and during the titration and maintenance phases, if applicable,

were reported in all of the trials. Time to discontinuation due to lack of efficacy was also reported in studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007.

Statistical Analysis

Primary End Point

In studies PAI-3008, PAI-3009, and PAI-3011, the 11-point NRS pain intensity score was recorded by patients in the morning and evening of every day during the treatment period and was based on the previous 12 hours. In Baron 2016, pain intensity score at each time point was the average pain intensity based on recall of the previous three days. In Study PAI-3007 and Imanaka 2013 and 2014, pain intensity was based on the previous 24 hours. Pain intensity was recorded daily in the Imanaka trials and at each visit in Study PAI-3007.

Baseline pain intensity was the mean of the recorded pain intensity score over the three days prior to randomization in studies PAI-3008, PAI-3009, and PAI-3011. In these RCTs, the primary method for determining pain intensity at the end of the treatment period depended on the regulatory authority. For regulatory approval in the US, pain intensity was averaged over the last week (week 12) of the maintenance phase. For regulatory approval by non-US regulatory authorities, pain intensity was averaged over the entire 12 weeks of the maintenance phase. Individual missing values for pain intensity were linearly interpolated.

In Study PAI-3007, baseline and end-of-treatment pain intensity were the scores recorded at the randomization visit and end-of-treatment visit, respectively.

In Baron 2016, baseline pain intensity was based on recall over the three days prior to randomization and end-of-treatment pain intensity was based on recall over the last three days of the treatment period.

In Imanaka 2013 and 2014, baseline pain intensity was the score recorded at the randomization visit and end-of-treatment pain intensity was averaged over the last three days and last week of the treatment period, respectively. In Kress 2014, pain intensity at baseline was the score recorded at the end of the screening phase and end-of-titration pain intensity was the mean of the score recorded over the last three days of the titration phase.

Details on the statistical methods used, including sensitivity analyses, to evaluate the primary efficacy end point in each trial are provided in Table 15. For continuous outcomes, analysis of covariance adjusted for pooled trial site or country and baseline pain intensity was used. In Baron 2016, this method was used as an exploratory analysis. Superiority of tapentadol ER compared with placebo was evaluated at a 5% significant level in the intention-to-treat set (analysis sets defined in the next section) in most of the trials, while noninferiority of tapentadol ER compared with oxycodone/naloxone PR in Baron 2016 and oxycodone CR in Imanaka 2013 was evaluated in the per-protocol set. In studies PAI-3008, PAI-3009, and PAI-3011, the primary efficacy analysis was repeated for the comparison of oxycodone CR versus placebo for assay sensitivity and for the comparison of tapentadol ER versus oxycodone as an exploratory analysis.

In Imanaka 2013, if the upper limit of the two-sided 95% confidence interval (CI) for the least squares mean difference between tapentadol ER and oxycodone CR was less than 1 point on the 11-point NRS, tapentadol ER was considered to be noninferior to oxycodone CR. No justification was provided for the noninferiority margin.

In Baron 2016, the upper limit of the two-sided 97.5% exact repeated CI for mean change in pain intensity and PAC-SYM total score had to be less than 1.3 and 0.7, respectively, for tapentadol ER to be considered noninferior to oxycodone/naloxone PR. No justification was provided for the noninferiority margins. If noninferiority was established, tapentadol ER was considered superior at a 1.25% significance level to oxycodone/naloxone PR if the upper limit of the 97.5% CI was less than zero. Since Baron 2016 had co-primary end points (pain intensity and PAC-SYM score), the overall one-sided significance level was divided between them (1.25% for each). The 97.5% CI was an exact repeating CI that accounted for the group-sequential design and controlled for overall type I error.

Pain intensity on the 11-point NRS was analyzed by subgroups in the short-term non-cancer pain trials. In PAI-3008, PAI-3009, and PAI-3011, pain intensity was analyzed by baseline pain intensity category and by prior opioid use status. In Baron 2016, pain intensity was reported by painDETECT category and specifically for patients with lumbar radiculopathy. Subgroup analyses did not control for type I error, randomization was not stratified by subgroups, and tests for the interaction terms were not conducted.

The main analyses for the primary efficacy end points used last observation carried forward (LOCF) to impute missing values. In this method, the last available measurement (baseline or post-baseline) was imputed as the end-of-treatment value, regardless of whether the patient completed or discontinued study treatment. Other methods of imputation were used in sensitivity analyses (see Table 15). For baseline observation carried forward (BOCF) and worst observation carried forward (WOCF), the baseline value from the start of DB treatment or the worst value during DB treatment (highest pain intensity score) was carried forward. For placebo mean imputation, post-discontinuation values were imputed as the mean value at that time point of all patients in the placebo group who completed study treatment. In modified BOCF, LOCF was used if PGIC at the end of treatment was “much improved” or “very much improved” with BOCF used otherwise. Although not pre-specified before database lock in studies PAI-3008, PAI-3009, and PAI-3011, analyses were also performed without any imputation of missing data (observed cases only).

Details of calculations to determine sample size were reported for all of the primary efficacy end points to various extents and are provided in Table 16.

Table 15: Summary of Primary Efficacy End Point Analyses

Study	Hypothesis	Set	Model	Factors and Covariates	Sensitivity Analyses
PAI-3008 PAI-3009 PAI-3011	TAP vs. PL, 2-sided test for superiority, 5% significance level	ITT	ANCOVA	Pooled site, baseline pain intensity score	Analysis set: PP Data imputation: BOCF, WOCF, PMI, modified BOCF, observed cases
Baron 2016	2-sided 97.5% exact repeated CI for TAP minus OXN, noninferiority margin of 1.3 points If upper limit of CI < 0: TAP vs. OXN, 1-sided test, 1.25% significance level	PP	ANCOVA (exploratory analysis	Pooled site, baseline pain intensity score	Analysis set: FA
Imanaka 2013	2-sided 95% CI for TAP minus OXY, noninferiority margin of 1	PP	ANCOVA	Country, baseline pain intensity score	Analysis set: FA Data imputation: BOCF, WOCF, observed cases
Kress 2014	TAP vs. PL, 2-sided test for superiority, 5% significance level	FA	Logistic regression	Pooled site, pain intensity at start of maintenance phase	Analysis set: PP

ANCOVA = analysis of covariance; BOCF = baseline observation carried forward; CI = confidence interval; FA = full analysis; ITT = intention-to-treat; OXY = oxycodone controlled-release; OXN = oxycodone/naloxone prolonged-release; PL = placebo, PMI = placebo mean imputation; PP = per-protocol; TAP = tapentadol extended-release; vs. = versus; WOCF = worst observation carried forward.

Note: Last observation carried forward was used to impute missing data in the main analyses of all of the studies.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011;[17] Baron 2016;[19,20] Imanaka 2013;[21] Imanaka 2014;[22] and Kress 2014.[23]

Table 16: Summary of Sample Size Assumptions for Pain Intensity on the 11-Point Numeric Rating Scale

Study	Between-Group Effect Size	Standard Deviation	Statistical Test	Power	Alpha	Dropout	Total Randomized Sample Size
PAI-3008 PAI-3009 PAI-3011	0.7[a]	2.7	2 sample t-test	90%	0.05	NR	942
Baron 2016	Noninferiority margins of 1.3[a] for pain intensity and 0.7 for PAC-SYM total score	NR	2 sample t-test	90%	0.0125 (1-sided)	20% overall	240
Imanaka 2013	Noninferiority margin = 1[a]	2.5	NR	90%	0.025 (1-sided)	15% overall	312 (later extended to 330)
Imanaka 2014	85% response rate for TAP	Lower limit of 2-sided 95% CI > 75%	NA	NA	NA	NR	49 in the TAP group
Kress 2014	20% difference response rate for TAP vs. PL	NR	NR	80%	0.05	35% during titration	498

CI = confidence interval; NA = not applicable; NR = not reported; NRS = numeric rating scale; PAC-SYM = Patient Assessment of Constipation Symptoms; PL = placebo; TAP = tapentadol extended-release; vs. = versus.

[a] On the 11-point numeric rating scale for pain intensity.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011;[17] Baron 2016;[19,20] Imanaka 2013;[21] Imanaka 2014;[22] and Kress 2014.[23]

Secondary Efficacy Outcomes

Beyond the primary end points, none of the trials controlled for multiplicity and all other efficacy outcomes were secondary outcomes. For details on how descriptive statistics were reported and statistical analyses were conducted for the secondary outcomes, see Table 17. In studies PAI-3008, PAI-3009, and PAI-3011, a significance level of 5% was specified for purposes of interpretation. In Study PAI-3007 and Imanaka 2014, statistical analyses were not conducted and missing data were not imputed. Statistical analyses beyond the primary end point in Imanaka 2013 and Kress 2014 were not conducted and a significance level was not specified for secondary outcomes in Baron 2016. In studies PAI-3008, PAI-3009, and PAI-3011, comparisons of tapentadol ER and oxycodone CR with placebo were available for most outcomes while comparisons of tapentadol ER with oxycodone CR were only available for select outcomes (see Table 17).

Pain Intensity

Responder analysis was conducted for a 30% and a 50% improvement in 11-point NRS pain intensity from pre-titration to the end of treatment in studies PAI-3008, PAI-3009, and PAI-3011.

The mean change in NPSI total score from baseline to the end of treatment was compared between treatment groups in Baron 2016. The NPSI was administered at enrolment, randomization, weekly during the titration phase, and three times during the maintenance phase (including end of treatment).

In Kress 2014, noninferiority of tapentadol compared with morphine CR was assessed for titration phase responder rate. Responders were patients who completed the titration phase and had a mean 11-point NRS pain intensity score of less than 5 and mean TDD of rescue medication of no more than 20 mg per day in the last three days of titration. Tapentadol was considered noninferior to morphine CR if the proportion of tapentadol ER responder minus the proportion of morphine CR responders was greater than –20% (Farrington-Manning noninferiority test). The margin was chosen to preserve 50% of the previously measured difference of 32% between tapentadol ER and placebo and account for less stability in the titration phase.

Health-Related Quality of Life

The EQ-5D-3L and SF-36 (SF-12 in Baron 2016) were administered at the start of the titration phase in all of the trials and every four weeks in the maintenance phase in studies PAI-3008, PAI-3009, and PAI-3011. In Study PAI-3007, both instruments were administered at the start of the treatment period, every four weeks for the next four assessments, followed by every 12 weeks for the remainder of the treatment period. In Baron 2016, the EQ-5D-3L and SF-12 were administered weekly in the titration phase and approximately every three weeks in the maintenance phase.

The WOMAC was administered at the start of titration and then weekly from weeks 1 and 3 to 8 of the maintenance phase.

Patient Global Assessment of Change

PGIC was assessed at three time points during the maintenance phase in studies PAI-3008, PAI-3009, and PAI-3011, and Baron 2016. In Baron 2016, PGIC was also assessed weekly during the titration phase. In Imanaka 2013, PGIC was assessed weekly during the

treatment period. In Imanaka 2014, PGIC was assessed at the start of treatment and every other week during the treatment period.

Impact on Sleep

Patients completed the sleep questionnaire based on the previous night. If more than one sleep questionnaire was recorded for a specific day, the first submitted questionnaire was used.

The sleep questionnaire was completed every week during the treatment period in studies PAI-3008, PAI-3009, and PAI-3011. In Study PAI-3007, it was administered at the same time points as the HRQoL assessments. In Baron 2015, the sleep questionnaire was administered at the start of treatment, the end of the titration phase, and the end of the maintenance phase.

Impact on Work and Daily Activities

The BPI was administered in Study PAI-3011 at the start of titration and at weeks 1 and 3 to 8 of the maintenance phase.

Mental or Psychological Symptoms

In Baron 2016, the HADS was completed the start of treatment, the end of the titration phase, and the end of the maintenance phase.

Table 17: Summary of Analysis Methods for Secondary Efficacy and Safety Outcomes

Outcome	Studies	Analysis Methods
Responder analysis for 11-point NRS pain intensity)	PAI-3008 PAI-3009 PAI-3011	Patients with and without a 30% or 50% improvement from baseline to end of treatment; generalized CMH test for general association; early discontinuations imputed as nonresponders; ITT set
NPSI total score	Baron 2016	Mean change from baseline to end of treatment; ANCOVA model adjusted for pooled site and baseline value; LOCF; FA set
WOMAC global score and subscale scores	PAI-3008 PAI-3009	Mean at baseline and weeks 3, 5, 7, 9, 11, 13, and 15; repeated measures model with time point as repeated factor, treatment and pooled site as factors, baseline value as a covariate; ITT set
BPI total and subscale scores (PAI-3011), EQ-5D-3L index score and VAS,[a] SF-36 (SF-12 for Baron 2016) MCS[a] and PCS[a] scores	PAI-3008 PAI-3009 PAI-3011 Baron 2016	Mean change from baseline to end of treatment; ANCOVA model adjusted for pooled site and baseline value; LOCF; ITT set (FA set for Baron 2016)
PGIC	PAI-3008 PAI-3009 PAI-3011	Distribution of responses at end of treatment; CMH test; LOCF; ITT set
	Baron 2016	Distribution of responses at end of treatment; Fisher's exact test; LOCF; FA set
	Imanaka 2013	Distribution of responses at end of treatment; descriptive statistics; LOCF (post-baseline values only)
Sleep questionnaire	PAI-3008 PAI-3009 PAI-3011	Continuous outcomes: descriptive statistics for mean change from baseline to end of treatment; LOCF, ITT set Item 4[a] (overall quality category): distribution at end of treatment; CMH test; LOCF; ITT set
	Baron 2016	Continuous outcomes: mean change from baseline to end of treatment; ANCOVA model adjusted for pooled site and baseline value; LOCF; FA set

Outcome	Studies	Analysis Methods
HADS subscale scores	Baron 2016	Mean change from baseline to end of treatment; ANCOVA model adjusted for pooled site and baseline value; LOCF; FA set
PAC-SYM[a]	PAI-3008 PAI-3009 PAI-3011	Mean change from baseline to end of treatment; ANCOVA model adjusted for pooled site and baseline value; LOCF (post-baseline values only); safety set
	Baron 2016	Mean change from baseline to end of treatment or discontinuation; ANCOVA model adjusted for pooled site and baseline value; missing data imputed as mean of non-missing values within treatment group; PP set
SOWS total score	PAI-3008 PAI-3011	Mean total score at 1, 2, 3, 4, and ≥ 5 days after treatment discontinuation; ANOVA model adjusted for pooled site and baseline value; safety set
COWS total score category	PAI-3008 PAI-3009 PAI-3011	Distribution of categories at 1 day, 2 to 4 days, and ≥ 5 days after treatment discontinuation; CMH test; safety set. Mean total score at 1 day, 2 to 4 days, and ≥ 5 days after treatment discontinuation; ANOVA model adjusted for pooled site; safety set.

ANCOVA = analysis of covariance; ANOVA = analysis of variance; BPI = Brief Pain Inventory; CMH = Cochran–Mantel–Haenszel; COWS = Clinical Opiate Withdrawal Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; FA = full analysis; HADS = Hospital Anxiety and Depression Scale; ITT = intention-to-treat; LOCF = last observation carried forward; MCS = mental component summary; NRS = numerical rating scale; NPSI = Neuropathic Pain Symptom Inventory; PAC-SYM = Patient Assessment of Constipation Symptoms; PCS = physical component summary; PGIC = Patient Global Impression of Change; PP = per-protocol; SF-12 = Short Form-12 Health Survey; SF-36 = Short Form-36 Health Survey; SOWS = Subjective Opiate Withdrawal Scale; VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Statistical comparisons between the tapentadol extended-release and oxycodone controlled-release groups were available for this outcome in studies PAI-3008, PAI-3009, and PAI-3011.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011;[17] Baron 2016;[19,20] Imanaka 2013;[21] Imanaka 2014;[22] and Kress 2014.[23]

Harms

As for the secondary efficacy outcomes, methods of statistical analyses and reporting of descriptive statistics for the safety outcomes are provided in Table 17.

Notable Harms

In studies PAI-3008, PAI-3009, and PAI-3011 and Baron 2016 the PAC-SYM was administered at baseline and at the end of treatment. Subscale and overall scores for the PAC-SYM were calculated as the mean of the non-missing individual item scores. In all the studies, if more than half of the items were missing for a subscale or overall score, the subscale or overall score was set to missing. In Baron 2016, patients who received laxative treatment during the trial completed a PAC-SYM assessment before the treatment and the value was used as the end-of-treatment value. Missing end-of-treatment scores in Baron 2016 were imputed as the mean within the treatment group of the available values at the end of treatment and missing baseline scores were imputed as the mean of all baseline values in the analysis set at baseline.

In studies PAI-3008 and PAI-3007, the SOWS total score was considered missing if at least one item was missing. The COWS was assessed in all of the trials in patients with OA or LBP (except for Baron 2016) and the SOWS was assessed at English-speaking sites in the US in studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007. The SOWS was to be administered 24, 48, and 72 hours after the last dose of study medication. The COWs was to be administered within four days after the last dose of study medication. The SOWS and COWS were not assessed in patients who entered the open-label extension trial and were reported separately for patients who discontinued all opioids and patients who continued opioid therapy following discontinuation of study treatment.

The total COWS score was calculated by adding the scores for the individual items and the total score was considered missing if at least one item was missing. The severity categories for the total COWS score were as follows: no withdrawal (0 to 4), mild (5 to 12), moderate (13 to 24), moderately severe (25 to 36), and severe withdrawal (37 to 48).

For the above-mentioned notable harms in studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007, the last available post-baseline value was used as the end-of-treatment value.

Discontinuation of Drug

A time to treatment discontinuation analysis was performed in studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007 for the distribution of durations from the first dose of the study drug to treatment discontinuation. Patients who completed the treatment period were censored at the end of treatment. The log-rank test was used to compare time to treatment discontinuation between treatment groups in the ITT (intention-to-treat) set in all of the trials except for Study PAI-3007.

Analysis Populations

Intention-to-Treat and Full Analysis Sets

In studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007, the ITT set consisted of all randomized subjects who took at least one dose of the study drug following randomization. Patients were analyzed in the treatment group to which they were randomized. In Baron 2016, the full analysis set (FAS) consisted of patients who took at least one dose of the study drug and had at least one post-baseline pain intensity measurement. In Imanaka 2013 and 2014, the FAS included all randomized patients who took at least one dose of the study drug and had post-baseline efficacy data. In Kress 2014, the FAS for the maintenance phase consisted of patients who were re-randomized to tapentadol ER or placebo, took at least one dose of the study drug during the maintenance phase, and had no Good Clinical Practice compliance issues.

Per-Protocol Set

In studies PAI-3008, PAI-3009, and PAI-3011, the per-protocol (PP) set included those in the ITT set who did not have major protocol deviations that could impact efficacy. In Baron 2016, the PP set included those in the FAS who did not have major protocol deviations that could impact the primary end points (pain intensity and PAC-SYM score).

Safety Set

In studies PAI-3008, PAI-3009, and PAI-3011, the definition of the safety set was identical to the definition of the ITT set. In Study PAI-3007, the safety set included all patients who received at least one dose of the study drug. In Baron 2016, Imanaka 2013, and Imanaka 2014, the safety set consisted of all randomized patients who took at least one dose of the study drug. In Kress 2014, the safety set for the maintenance phase consisted of patients who were re-randomized to tapentadol ER or placebo and took at least one dose of the study drug during the maintenance phase.

Patient Disposition

In the 12-week DB RCTs in patients with non-cancer pain (studies PAI-3008, PAI-3009, and PAI-3011), the proportions of patients in the tapentadol ER and oxycodone CR group discontinuing prematurely ranged from 44% to 65% (Table 18). In the one-year OL trial, Study PAI-3007, 54% and 65% of patients in the tapentadol ER and oxycodone CR groups

discontinued early. In the four trials, the most common reasons for discontinuation were patient choice, AE, and lack of efficacy. The proportion of patients with major protocol deviations ranged from 9% to 22% in the active treatment groups, with the most common deviations being the use of a prohibited concomitant medication (3% to 17%) and less than 80% treatment compliance (2% to 10%). Higher proportions of patients in the oxycodone CR group versus the tapentadol ER group had protocol deviations due to low treatment compliance (5% to 10% versus 2% to 3%).

In Baron 2016, 34% and 63% of patients in the tapentadol ER and oxycodone/naloxone PR groups discontinued during the treatment period. The most common reasons for discontinuing were AE (20% to 41%) and lack of efficacy (6% to 13%). In the oxycodone/naloxone PR group, 19% of patients switched to the tapentadol ER pickup arm, with the most common reasons being AE and lack of efficacy.

In the Imanaka 2013 and 2014 trials in patients with cancer pain, early discontinuations occurred in 29% to 44% of patients. In Kress 2014, 18% of patients in both the tapentadol ER and morphine SR groups discontinued during the titration phase. The reasons for discontinuing treatment are summarized within the results section of this report under treatment discontinuations (Table 55).

There was a consistent imbalance in study discontinuations between the oxycodone CR and tapentadol ER groups in terms of discontinuations due to AE. Groups taking oxycodone CR or oxycodone/naloxone PR had the greater proportions of patients discontinuing due to AE compared with groups taking tapentadol ER.

Table 18: Patient Disposition — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010			PAI-3009 Serrie 2017			PAI-3011 Buynak 2011		
	PL	TAP	OXY	PL	TAP	OXY	PL	TAP	OXY
Screened, N	1,578			1,301			1,589		
Randomized, N	339	346	345	337	320	333	326	321	334
Received ≥ 1 dose of study drug, N	337	344	342	337	319	331	319	318	328
Discontinued study, N (%[a])	134 (40)	163 (47)	224 (65)	122 (36)	140 (44)	212 (64)	167 (52)	152 (48)	195 (59)
Patient choice	43 (13)	50 (15)	48 (14)	33 (10)	44 (14)	58 (18)	59 (18)	39 (12)	43 (13)
Lost to follow-up	3 (0.9)	5 (1)	0	4 (1)	6 (2)	4 (1)	12 (4)	13 (4)	8 (2)
Adverse event	22 (7)	61 (18)	140 (41)	28 (8)	60 (19)	135 (41)	15 (5)	51 (16)	107 (33)
Death	0	0	1 (0.3)	0	0	0	0	0	0
Lack of efficacy	35 (10)	15 (4)	7 (2)	34 (10)	14 (4)	7 (2)	50 (16)	13 (4)	7 (2)
Non-compliance with study drug	4 (1)	6 (2)	7 (2)	5 (1)	6 (2)	3 (0.9)	11 (3)	14 (4)	11 (3)
Other	27 (8)	26 (8)	21 (6)	18 (5)	10 (3)	5 (2)	20 (6)	22 (7)	19 (6)
Completed study, N	203	181	118	215	179	119	152	166	133
ITT, N (%[b])	337 (99)	344 (99)	342 (99)	337 (100)	319 (99.7)	331 (99.4)	316 (97)	312 (98)	323 (98)
PP, N (%[b])	284 (84)	298 (86)	270 (78)	296 (88)	292 (91)	288 (87)	241 (74)	249 (78)	255 (76)
Safety, N (%[b])	337 (99)	344 (99)	342 (99)	337 (100)	319 (99.7)	331 (99.4)	319 (98)	318 (99.1)	328 (98)

	PAI-3008 Afilalo 2010			PAI-3009 Serrie 2017			PAI-3011 Buynak 2011		
	PL	TAP	OXY	PL	TAP	OXY	PL	TAP	OXY
Major protocol deviation, N (%[b])	58 (17)	48 (14)	73 (21)	41 (12)	28 (9)	43 (13)	81 (25)	70 (22)	75 (22)
Prohibited concomitant medication	26 (8)	19 (5)	18 (5)	19 (6)	9 (3)	10 (3)	54 (17)	45 (14)	37 (11)
< 80% of doses taken	9 (3)	7 (2)	36 (10)	6 (2)	7 (2)	27 (8)	10 (3)	11 (3)	18 (5)
Minimum baseline pain intensity score not met	8 (2)	7 (2)	10 (3)	2 (1)	0	0	8 (2)	9 (3)	7 (2)
Medkit number inconsistent	2 (1)	6 (2)	2 (1)	11 (3)	8 (3)	2 (1)	1 (0.3)	2 (0.6)	5 (1)

ITT = intention-to-treat; PL = placebo; OXY = oxycodone controlled-release; TAP = tapentadol extended-release.

Note: Both the ITT and safety sets include patients who received at least one dose of the study drug following randomization. In PAI-3011, seven patients in the safety set were excluded from the ITT set due to major audit findings. The decision to exclude these patients was made before database lock.

PP set includes ITT patients with major protocol deviations that could have an impact on efficacy.

The most common (≥ 3% of at least one treatment group) major protocol deviations are reported.

[a] Denominator is the number of patients who received at least one dose of the study drug.

[b] Denominator is the number of randomized patients.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 19: Patient Disposition — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 (OA and LBP)		Baron 2016 (LBP neuropathic)	
	TAP	OXY	TAP	OXN
Screened, N	**1,458**		367	
Randomized, N	896	225	130	128
Received ≥ 1 dose of study drug, N	894	223	NR	NR
Discontinued study, N (%)	482 (54[a])	145 (65[a])	44 (34[b])	80 (63[b])
Patient choice	93 (10)	31 (14)	5 (4)	9 (7)
Lost to follow-up	42 (5)	7 (3)	1 (0.8)	0
Adverse event	203 (23)	82 (37)	26 (20)	52 (41)
Non-compliance with study drug	41 (5)	15 (7)	0	0
Resolution of pain	2 (0.2)	0	0	0
Lack of efficacy	71 (8)	7 (3)	8 (6)	17 (13)
Protocol violation	0	0	2 (2)	1 (0.8)
Technical problems	0	0	1 (0.8)	1 (0.8)
Other	30 (3)	3 (1)	1 (0.8)	0
Completed study, N	412	78	86	48
Entered open-label extension study (follow-up evaluations not performed), N	249	45	NA	NA
Entered TAP pickup arm, N	NA	NA	NA	50
Adverse event	NA	NA	NA	9
Lack of efficacy	NA	NA	NA	4
Patient choice	NA	NA	NA	1
Technical problems	NA	NA	NA	1

	PAI-3007 Wild 2010 (OA and LBP)		Baron 2016 (LBP neuropathic)	
ITT or FA, N (%[b])	876 (98)	219 (97)	130 (100)	126 (98)
Safety, N (%[b])	894 (99.8)	223 (99.1)	130 (100)	128 (100)
PP, N (%[b])	NA	NA	117 (90)	112 (88)
Major protocol deviation, N (%[b])	99 (11)	23 (10)	NR	NR
Prohibited concomitant medication	53 (6)	15 (7)	NR	NR

FA = full analysis; ITT = intention-to-treat; LBP = low back pain; NA = not applicable; NR = not reported; OA = osteoarthritis; OXN = oxycodone/naloxone prolonged-release; OXY = oxycodone controlled-release; PP = per-protocol; TAP = tapentadol extended-release.

Note: The most common (≥ 3% of at least one treatment group) major protocol deviations are reported.

[a] Denominator is the number of patients who received at least one dose of the study drug.

[b] Denominator is the number of randomized patients.

Source: Clinical study report for PAI-3007,[18] Baron et al. 2016.[19,20]

Table 20: Patient Disposition — Cancer Pain

	Imanaka 2013		Imanaka 2014		Kress 2014		
	TAP	**OXY**	**TAP**	**MOR**	**PL**	**TAP**	**MOR**
Screened, N	374		120		622		
Randomized, N	171	172	50	50	NA	505	
Received ≥ 1 dose of study drug, N	168	172	50	50	NA	338	158
Discontinued study, N (%[a])	55 (33)	49 (29)	22 (44)	21 (42)	NA	NR	NR
Discontinued study during titration, N (%[a])	NA	NA	NA	NA	NA	59 (18)	29 (18)
Completed titration, N (%[a])	NA	NA	NA	NA	NA	279 (83)	129 (82)
Re-randomized for withdrawal,[b] N	NA	NA	NA	NA	112	106	109
Discontinued during withdrawal, N (%[c])	NA	NA	NA	NA	17 (15)	17 (16)	16 (15)
Completed treatment, N (%)	113 (67[a])	123 (72[a])	28 (56[a])	29 (58[a])	95 (85[c])	89 (84[c])	93 (85[c])
Completed study, N (%[a])	110 (66)	121 (70)	NR	NR	NR	NR	NR
Safety, N	168	172	50	50	NA	NA	NA
Full analysis, N	NR	NR	50	NA	NA	NA	NA
PP, N	126	139	NA	NA	NA	NA	NA
Titration phase							
Safety, N	NA	NA	NA	NA	NA	338	158
Full analysis, N	NA	NA	NA	NA	NA	335	157
PP, N	NA	NA	NA	NA	NA	229	100
Maintenance phase							
Safety, N	NA	NA	NA	NA	112	106	109
Full analysis, N	NA	NA	NA	NA	111	105	109

NA = not applicable; NR = not reported; MOR = morphine controlled-release or sustained-release; OXY = oxycodone controlled-release; PL = placebo; PP = per-protocol; TAP = tapentadol extended-release.

Note: The full analysis set includes all randomized patients who took at least one dose of the study drug and had post-baseline efficacy data.

The per-protocol set includes all patients in the full analysis set who did not have a major protocol deviation.

[a] Denominator is the number of patients who received at least one dose of the study drug (safety set).

[b] Excludes one patient who did not take study drug during the withdrawal phase.

[c] Denominator is the number of patients who were re-randomized for the withdrawal phase.

Source: Imanaka et al. 2013,[21] Imanaka et al. 2014,[22] Kress et al. 2014.[23]

Exposure to Study Treatments

In the trials in patients with non-cancer pain, mean treatment duration was consistently lower in the oxycodone groups than in the tapentadol ER groups (42 to 60 days versus 63 to 74 days in the 12- to 15-week RCTs and 161 days versus 211 days in the one-year RCT). This follows the consistent trend of greater proportions of study discontinuations in these groups.

Mean compliance with study treatment in studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007 during treatment duration ranged from 93.0% to 97.7% of expected active treatment doses and differences between treatment groups followed the same trends as for mean treatment duration. Investigators assessed compliance based on medication blister cards dispensed at the previous visit, and missed visits, incomplete diary records, and "questionable usage" of the study drug and medications were recorded.

In the non-cancer pain trials, the modal TDD for each patient was defined as the most frequent TDD for that patient over the maintenance phase. The median modal TDD of tapentadol ER ranged from 200 mg to 400 mg (mean of the mean TDD in Baron 2016 of 379 mg) while the median modal TDD of oxycodone CR ranged from 40 mg to 80 mg (mean of the mean TDD in Baron 2016 of 75 mg) during the maintenance phase.

Median treatment duration was the same across treatment groups in Imanaka 2013 and Kress 2014. Information on treatment compliance was not reported in the trials in patients with cancer pain. Over the treatment period, the median modal TDD of tapentadol ER ranged from 50 mg to 300 mg, the median modal TDD of oxycodone CR in Imanaka 2013 was 10 mg and the median modal TDD of morphine CR in Kress 2014 was 120 mg.

Table 21: Treatment Exposure — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
	PL N = 337	TAP N = 344	OXY N = 341	PL N = 337	TAP N = 319	OXY N = 331	PL N = 319	TAP N = 318	OXY N = 328
Total Treatment Period									
Mean treatment duration, days (SD)	77.1 (41.6)	73.5 (41.9)	50.9 (45.5)	80.4 (37.5)	73.5 (40.7)	52.8 (44.3)	67.6 (44.5)	72.7 (42.8)	60.1 (45.8)
Mean compliance, % of expected doses (SD)	97.0 (7.6)	97.3 (5.3)	93.0 (12.4)	98.1 (5.0)	97.7 (5.4)	94.6 (11.0)	97.0 (6.0)	96.6 (7.7)	95.6 (8.0)
Category of compliance, n (%)									
< 80%	9 (3)	8 (2)	35 (10)	6 (2)	7 (2)	28 (8)	9 (3)	12 (4)	18 (5)
80% to < 90%	10 (3)	7 (2)	28 (8)	7 (2)	10 (3)	21 (6)	12 (4)	6 (2)	19 (6)
90% to < 100%	226 (67)	245 (71)	202 (59)	215 (64)	196 (61)	173 (52)	208 (65)	225 (71)	201 (61)
100%	92 (27)	84 (24)	76 (22)	109 (32)	106 (33)	109 (33)	90 (28)	75 (24)	90 (27)
Titration Phase									
Mean treatment duration, days (SD)	19.3 (5.3)	19.3 (5.3)	15.5 (7.6)	20.5 (3.9)	19.5 (4.7)	16.6 (7.5)	18.8 (5.6)	18.9 (5.7)	16.8 (7.5)

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
Mean modal TDD of study drug, mg (SD)	314 (115)	279 (105)	45 (23)	274 (88)	342 (78)	41 (16)	299 (120)	293 (116)	45 (22)
Median modal TDD of study drug, mg	300	300	40	200	200	40	300	300	40
Maintenance Phase									
Mean treatment duration, days (SD)	76.7 (22.1)	70.7 (27.8)	69.6 (27.2)	72.4 (24.9)	71.1 (26.0)	65.6 (29.3)	74.3 (26.2)	73.3 (25.5)	71.7 (26.1)
Mean modal TDD of study drug, mg (SD)	431 (103)	362 (199)	72 (23)	369 (118)	317 (115)	55 (20)	428 (102)	386 (125)	72 (23)
Median modal TDD of study drug, mg	500	400	80	400	300	40	500	400	80

PL = placebo; OXY = oxycodone controlled-release; SD = standard deviation; TAP = tapentadol extended-release; TDD = total daily dose.

Note: Treatment duration and modal daily dose include zero dose days.

Compliance for each patient was calculated as the number of doses taken relative to the number of doses expected for the patient's treatment duration.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 22: Treatment Exposure — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 Safety Set		Baron 2016 Safety Set	
	TAP N = 894	OXY N = 224	TAP N = 130	OXN N = 128
Mean treatment duration, days (SD)	211 (157)	161 (163)	62.9 (30.8)	42.0 (23.2)
Category of treatment duration, n (%)				
< 3 months	337 (38)	119 (53)	NR	NR
3 months to < 6 months	70 (8)	13 (6)	NR	NR
6 months to < 9 months	42 (5)	9 (4)	NR	NR
9 months to < 12 months	218 (24)	39 (17)	NR	NR
12 months or longer	227 (25)	44 (20)	NR	NR
Mean of the mean TDD of study drug, mg (SD)				
Titration phase	NR	NR	259 (80)	45 (18)
Maintenance phase	NR	NR	379 (130)	75 (24)
Mean modal TDD of study drug, mg (SD)	327 (120) N = 878	57 (30) N = 212	NR	NR
Week 1 to 4	259 (74) N = 894	42 (17) N = 224	NR	NR
Week 9 to 12	375 (111) N = 602	68 (25) N = 114	NR	NR
Week 21 to 24	388 (112) N = 515	73 (25) N = 99	NR	NR
Week 33 to 36	395 (111) N = 467	75 (25) N = 88	NR	NR
Week 49 to 52	393 (113) N = 421	74 (27) N = 80	NR	NR
Median modal TDD of study drug, mg	400 N = 878	40 N = 212	NR	NR

	PAI-3007 Wild 2010 Safety Set		Baron 2016 Safety Set	
	TAP N = 894	OXY N = 224	TAP N = 130	OXN N = 128
Mean compliance, % of expected doses (SD)	97.6 (6.1)	94.4 (11.1)	NR	NR
Patients with < 80% compliance (%)	10 (1)	17 (8)	NR	NR

NR = not reported; OXN = oxycodone/naloxone prolonged-release; OXY = oxycodone controlled-release; SD = standard deviation; TAP = tapentadol extended-release; TDD = total daily dose.

Note: Treatment duration and modal daily dose include zero dose days.

Compliance for each patient was calculated as the number of doses taken relative to the number of doses expected for the patient's treatment duration.

Source: Clinical study report for PAI-3007,[18] Baron et al. 2016.[19,20]

Table 23: Treatment Exposure — Cancer Pain

	Imanaka 2013 Safety Set		Imanaka 2014 Safety Set		Kress 2014 Set Not Specified	
	TAP N = 168	OXY N = 172	TAP N = 50	MOR N = 50	TAP N = 106	MOR N = 109
Expected duration of treatment period, weeks	4		8		Titration: 2 Maintenance: 4	
Median treatment duration, days	28.0	28.0	54.5	NR	Titration: 14 Maintenance: 28	Titration: 14 Maintenance: 28
Patients on study drug for > 21 days, n (%)	121 (72)	133 (77)	NR	NR	NR	NR
Patients on study drug for 29 to 56 days, n (%)	NA	NA	35 (70)	NR	NR	NR
Median of mean total daily dose of study drug, mg	64.5	13.8	NR	NR	NR	NR
Mean of the mean total daily dose of study drug, mg (SD)	NR	NR	173.5 (101.5)	NR	NR	NR
Median modal total daily dose of study drug, mg	50.0	10.0	150.0	NR	300.0	120.0

MOR = morphine controlled-release; NA = not applicable; NR = not reported; OXY = oxycodone controlled-release; SD = standard deviation; TAP = tapentadol extended-release.

Source: Imanaka et al. 2013,[21] Imanaka et al. 2014,[22] Kress et al. 2014.[23]

Critical Appraisal

Internal Validity

Randomization, Allocation, and Blinding

There were no issues with the methods for randomization and allocation in most of the trials. Randomization and allocation were not well described in Baron 2016 and Imanaka 2013 and risk of bias from these sources in unclear in these studies. In the DB trials in patients with OA or LBP (studies PAI-3008, PAI-3009, and PAI-3011), there was low risk of the patients or investigators distinguishing between active treatment and placebo given that placebo tablets and capsules were matched in appearance to the active treatments. However, the tapentadol ER tablets and encapsulated oxycodone CR tablets differed in appearance. Measures to maintain blinding of investigators were not described and treatment compliance was assessed by investigators based on previously dispensed study drug blister cards. If investigators were unblinded to treatment assignment, risk of bias was

high due to the subjective nature of the outcome measures. Study PAI-3007, Baron 2015, and Imanaka 2014 were OL trials and the risk of patients or investigators surmising treatment allocation in Imanaka 2013 and Kress 2014 is unclear as measures to maintain blinding were not well described. There is a risk of bias in all of the outcome measures when patients knew which treatment they were receiving given that all outcome measures were self-reported, subjective, and dependent on patient recall.

Study Design and Interventions

The comparisons of tapentadol ER with placebo arms were appropriate for establishing efficacy of tapentadol ER. The inclusion of oxycodone CR for assay sensitivity in studies PAI-3008, PAI-3009, and PAI-3011 was appropriate as comparisons of oxycodone CR with placebo could aid in the interpretation of the results. When the trials were conducted (2007 to 2008), oxycodone CR was the most common opioid analgesic in trials for the treatment of chronic pain from knee and hip OA[70] and the lack of a statistically significant difference between the oxycodone CR and placebo groups could have signalled potential methodological issues with the study.[71] The comparison of tapentadol with morphine SR in Kress 2014 is insufficient for establishing comparative efficacy and safety in the context of chronic pain as the titration phase was only two weeks long (compared with the FDA-recommended treatment duration of 12 weeks for chronic pain trials[71]).

Baron 2016 and Imanaka 2014 were noninferiority trials, which, according to the FDA, is not appropriate for establishing efficacy given that criteria for noninferiority to another active treatment may be met but this could potentially mean that neither was efficacious.[71]

The titration regimens used in the trials were considered to be reasonable according to the clinical expert consulted for this review. The Health Canada–approved product monograph for Nucynta ER[12] suggests a titration regimen based on clinical studies (including the ones in the present report). The product monograph for OxyNEO[31] (oxycodone CR) states that dosage may be titrated at intervals of 24 to 36 hours, which is shorter than the three-day intervals in the RCTs with oxycodone CR. The product monograph for Targin[38] (oxycodone/naloxone CR) states that dosage may be titrated at intervals of one to two days compared with no minimum interval for adjustments in Baron 2016. The product monograph for Teva-Morphine SR[29] (morphine SR) recommends minimum intervals of 48 hours between dosage adjustments, compared with three days in Kress 2014 for morphine CR.

The use of concomitant analgesics in the DB trials in patients with OA and LBP was limited to acetaminophen with stipulations. The limited use of analgesics allowed in the non-cancer pain trials may have led to higher proportions of discontinuations due to lack of efficacy. Concomitant acetaminophen use was greater in the tapentadol ER groups compared with the oxycodone CR groups in studies PAI-3008, PAI-3009, PAI-3001, and PAI-3007, but it is possible that the greater discontinuations in the oxycodone CR groups led to less exposure to acetaminophen in those groups. In the trials in patients with cancer pain, allowed rescue medication use was more liberal and patients could take immediate-release opioid analgesics. With this design, patients would be expected to achieve similar pain relief between groups and rescue analgesic use would become an important outcome.

Study Population and Attrition

Baseline characteristics were balanced between treatment groups in all of the trials. The criteria for entering the maintenance phase of Baron 2016 enriched the population with patients known to respond favourably to opioid therapy, though the risk of bias is unclear. In addition, the availability of a tapentadol ER escape arm for patients randomized to oxycodone/naloxone PR and the lack of a similar escape arm for patients randomized to tapentadol ER present a high risk of bias in terms of discontinuations, especially in an OL RCT.

All of the trials had high proportions for premature discontinuations, which results in a high risk of bias. Some of the trials attempted to make up for this shortcoming with various imputation methods as discussed below under Statistical Methods. The oxycodone CR and oxycodone/naloxone PR groups consistently had higher proportions of discontinuations than the tapentadol ER groups due to AEs. The differential proportions of discontinuations between treatment groups adds to the risk of bias.

Even with LOCF was used to impute missing data for PGIC and PAC-SYM scores in studies PAI-3008, PAI-3009, and PAI-3011, there were still missing values that were unexplained. There was no imputation of missing data in Study PAI-3007, of which there were substantial amounts.

Assessment of Outcomes

The use of a valid pain intensity patient-reported outcome is recommended to demonstrate efficacy of an analgesic, according to the FDA and European Medicines Agency.[71,72] The FDA recommendation of a recall period of no more than 24 hours was adhered to in the trials. At least some information on psychometric properties (validity, reliability, and/or responsiveness) was available for all of the outcomes, except for the sleep questionnaire. However, MCIDs were only available for the 11-point NRS for pain intensity, the WOMAC, SF-36 MCS and PCS, EQ-5D-3L index score, and the PAC-SYM. Further, the MCIDs for the SF-36 MCS and PCS, the EQ-5D-3L index score, and the PAC-SYM scores were not specific to patients with chronic pain.

The SOWS and COWS were assessed following discontinuation of the study drug without a tapering regimen, which may have resulted in worse withdrawal symptoms than would be experienced by patients tapered off of an opioid in clinical practice.

For efficacy trials in chronic pain, the FDA recommends a minimum of a 12-week treatment period while the European Medicines Agency recommends a minimum of 12 weeks for the maintenance phase alone.[71,72] The trials in patients with non-cancer pain had maintenance phases of 12 weeks or longer, except for Baron 2016. Trials in patients with cancer pain had treatment periods of four to eight weeks in duration. There was one OL, long-term trial comparing the safety profiles of tapentadol ER and oxycodone CR. A treatment duration of 12 weeks is short compared with the long-term opioid therapy that patients with chronic pain may receive in clinical practice.

Noninferiority margins of 1.3 for oxycodone/naloxone PR and 1 for oxycodone CR for pain intensity score (and 0.7 for PAC-SYM total score) were used with no rationale provided.

Statistical Methods

The models used to analyze the outcomes were appropriate and commonly included a pooled analysis site or country factor to control for regional variations as well as either baseline pain intensity or baseline value of the outcome of interest. There was no control for multiplicity (aside from the co-primary end points in Baron 2016) and for all other outcomes there is a risk of type I error, and as such the findings should be considered inconclusive. In studies PAI-3008, PAI-3009, and PAI-3011, the method of measuring the primary end point differed depending on the regulatory authority reviewing the data and there was no control for multiplicity in this case. In the subgroup analyses, according to prior opioid use status and baseline pain intensity category, randomization was not stratified by subgroups, there was no control for type I error, and tests for the interaction terms were not conducted. Subgroup analyses for patients with and without depression were not available in any of the studies.

The analysis sets used for the primary end point analyses were appropriate. The primary analyses in the superiority studies were conducted in the FAS or ITT, depending on the trial. The sets were close to true ITT sets as there were very few patients who were randomized and did not take at least one dose of the study drug. Sensitivity analyses were also conducted in the PP sets. The noninferiority trials used the PP set for the primary efficacy end points with sensitivity analyses in the FAS.

The proportions of patients with major protocol deviations ranged from 9% to 22% in the active treatment groups in studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007, with the most common deviations being the use of a prohibited concomitant medication and low treatment compliance. Concomitant medication use and low compliance could have affected the efficacy outcomes.

The substantial loss of data from early discontinuations cannot be fully mitigated by imputation methods. The LOCF approach was used in studies PAI-3008, PAI-3009, PAI-3011, Baron 2016, and Imanaka 2013 for outcomes using the 11-point NRS pain intensity scale, NPSI, BPI, EQ-5D-3L, SF-36, PGIC, sleep questionnaire, HADS, and PAC-SYM. The LOCF approach can lead to bias toward the null, which is problematic for the noninferiority trials (Baron 2016 and Imanake 2013). Given the greater withdrawal due to adverse events (WDAEs) in the oxycodone CR and oxycodone/naloxone PR groups than in the tapentadol ER groups in non-cancer pain RCTs, results for HRQoL outcomes and the PGIC were potentially biased in favour of tapentadol ER. This was likely also the case in the responder analysis for pain intensity as patients who discontinued were classified as nonresponders. However, direction of bias remains unclear for the other outcomes and the effects of bias could differ according to reason for discontinuation. The BOCF and WOCF approaches may also lead to bias against groups with more discontinuations. The effects of the other imputation methods are unclear. For the PAC-SYM score in Baron 2016, which was a co-primary end point, the use of the analysis set mean to impute missing baseline values and the use of the treatment group mean to impute missing end-of-treatment values may have biased the results toward the null. This is problematic given that noninferiority of tapentadol ER compared with oxycodone/naloxone PR was assessed for this outcome.

All trials randomized sufficient numbers of patients according to their sample size calculations. However, some details on assumptions for the sample size calculations were not provided (Table 16) and studies PAI-3008, PAI-3009, PAI-3011, and Imanaka 2014 did not seem to take dropout into account.

External Validity

Study Population

Study sites in Canada were included for studies in patients with OA and LBP. Studies in patients with LBP with a neuropathic component and in patients with cancer pain were conducted in European and Asian countries, respectively. There are substantial regional variations in opioid prescribing and standards of care for chronic pain, which could translate to regional differences in prior treatment and pain reporting.

Patients with the types of pain studied were considered by the clinical expert consulted for this review to be potential candidates for tapentadol ER according to the Health Canada indication. The clinical expert also considered the minimum post-washout pain scores to be reasonable given that clinicians may use varying thresholds for pain intensity when considering whether to prescribe opioid therapy. Patients with non-cancer pain had a history of at least three months of the index pain and were on analgesic therapy, ensuring that their pain was chronic. In general, patients had to be dissatisfied with their current analgesic therapy, which could mean that their pain was not sufficiently controlled or that they experienced intolerable side effects.

It is not clear how many of the patients fit the Health Canada indication and only Baron 2016 and Imanaka 2013 specified that patients had to require treatment with an opioid analgesic according to the investigator. Although significant proportions of patients had previously received opioid therapy, recommendations regarding the prescription of opioids have changed since the trials were conducted. For example, since the trials with Canadian sites were conducted, the *2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain* were published.[8]

Patients with psychiatric disorders or on medications commonly used to treat such conditions were excluded from all of the RCTs (except for Kress 2014). The product monographs for all strong opioids include a serious warning for risks from concomitant use with benzodiazepines or other central nervous system depressants, the use of monoamine oxidase inhibitors as a contraindication, and a warning for concomitant use of other medication that may cause seizures. However, patients on other medications for psychiatric disorders (e.g., tricyclic antidepressants and neuroleptics) were not included in most of the RCTs.

Interventions

The duration of trials, except for possibly Study PAI-3007, was short relative to actual opioid therapy for chronic pain. In clinical practice, patients and their physicians may require months to find the optimal dosage and to manage side effects. In the trials, patients may have experienced a lack of efficacy or intolerable side effects on their titrated dose because their dose was not fully optimized or they had not become accustomed to the side effects. Over the long-term, patients can develop tolerance to analgesia efficacy and require larger doses to attain the same level of pain relief. Another effect that is not readily assessed in short trials is hyperalgesia.

Tapentadol ER was compared with oxycodone CR, oxycodone/naloxone PR, and morphine SR or CR. Comparisons with morphine were either not statistically tested or involved too short a treatment duration to be informative. Direct comparisons were not available for other long-acting opioids such as oral hydromorphone or methadone, transdermal fentanyl, or transdermal or buccal film buprenorphine, tramadol ER, or codeine CR.

In Imanaka 2013 and 2014 (where initial dosing was 25 mg twice daily; lower than recommended in the Health Canada product monograph), it is possible that a substantial proportion of patients received a dosage of tapentadol ER that was lower than the minimum recommended dosage of 100 mg to 500 mg twice daily since the median modal TDDs of tapentadol ER were 50 mg and 150 mg respectively in those trials.

Outcomes

Many of the outcomes identified in the CDR review protocol were addressed in the trials, more so in the non-cancer pain trials than in the cancer pain trials. Caregiver burden was not assessed in any of the trials and mental or psychological symptoms were assessed in only one trial, possibly due to the exclusion of patients with psychiatric conditions.

Harms related to opioid use disorder, overdose, and diversion were not assessed in the trials.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 5). See Appendix 4 for detailed efficacy data.

Pain Intensity

Over the maintenance phase of studies PAI-3008 and PAI-3009 (DB trials in patients with knee OA pain) the tapentadol ER groups had a greater mean reduction from baseline in pain intensity than the oxycodone CR groups, with least squares mean differences (LSMDs) of –0.3 (95% CI, –0.66 to –0.00) and –0.4 (95% CI, –0.68 to –0.05), respectively (Table 24). However, statistical analyses between tapentadol ER and oxycodone CR were not controlled for multiplicity. In Study PAI-3011 (DB trial in patients with LBP), there was no difference between the tapentadol ER and oxycodone CR groups for change in pain intensity. The results were similar when change from baseline to week 12 of the maintenance phase was measured (analysis for US regulatory).

When BOCF (see Table 57 in Appendix 4), WOCF, and modified BOCF were used to impute missing data instead of LOCF, larger differences in favour of tapentadol ER (ranging from –0.6 to –0.9) were observed in studies PAI-3008, PAI-3009, and PAI-3011 than in the main analyses. When placebo mean imputation was used, the effect sizes were smaller (ranging from –0.2 to 0.0).

Responder analysis (Table 24) of pain intensity revealed that greater proportions of patients in the tapentadol ER groups than in the oxycodone CR groups achieved at least a 30% (tapentadol ER versus oxycodone CR: 43% versus 25% for Study PAI-3008; 41% versus 26% for Study PAI-3009; 40% versus 30% for Study PAI-3011) or 50% (tapentadol ER versus oxycodone CR: 32% versus 17% for Study PAI-3009; 21% versus 22% for Study PAI-3009; 27% versus 23% for Study PAI-3011) reduction in pain intensity from baseline to week 12 of the maintenance phase in all three trials, though statistical analyses did not compare tapentadol ER with oxycodone CR for these outcomes.

Subgroup analyses based on prior opioid use status (Table 58 in Appendix 4) and baseline pain intensity category (Table 59 in Appendix 4) were conducted in studies PAI-3009, PAI-3009, and PAI-3011. In patients with no opioid use in the three months prior to screening, the primary end point results were similar to results in the full population. In patients with prior opioid use, the results were not consistent and tapentadol ER was favoured in Study PAI-3008 while oxycodone CR was favoured in studies PAI-3009 and PAI-3011. The primary end point results in patients with severe baseline pain intensity were similar to the results in the main analyses. Limited data were available for moderate baseline pain intensity in all three trials and for opioid-experienced patients in Study PAI-3009.

In Study PAI-3011, changes in the BPI pain subscale score (Table 24) was similar between the tapentadol ER and oxycodone CR groups (–2.3 [standard error (SE) of 0.1] and –2.2 [SE of 0.1], respectively). These two groups were not statistically compared for the BPI pain subscale score.

Table 24: Change in Pain Intensity — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 336	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
NRS-11 pain intensity									
Mean baseline score (SD)	7.2 (1.3)	7.4 (1.4)	7.2 (1.3)	7.3 (1.1)	7.3 (1.1)	7.3 (1.1)	7.6 (1.3)	7.5 (1.3)	7.5 (1.2)
Overall maintenance									
Mean score (SD)	5.1 (2.5)	4.4 (2.4)	4.7 (2.3)	5.0 (2.2)	4.7 (2.3)	5.1 (2.3)	5.5 (2.5)	4.7 (2)	4.6 (2.4)
Mean change (SD)	–2.2 (2.4)	–2.9 (2.3)	–2.5 (2.3)	–2.2 (2.1)	–2.5 (2.2)	–2.1 (2.2)	–2.1 (2.2)	–2.8 (2.5)	–2.9 (2.4)
LSMD vs. PL (95% CI)[a]	NA	**–0.7 (–1.00 to –0.33) *P* < 0.001**	–0.3 (–0.67, –0.00) *P* = 0.049	NA	**–0.2 (–0.55 to 0.07) *P* = 0.14**	0.1 (–0.18, 0.44) *P* = 0.42	NA	**–0.7 (–1.06 to –0.35) *P* < 0.001**	–0.8 (–1.16, –0.46) *P* < 0.001
LSMD, TAP vs. OXY (95% CI)[a]	NA	–0.3 (–0.66 to –0.00) *P* = 0.048		NA	–0.4 (–0.68 to –0.05) *P* = 0.02		NA	0.1 (–0.25, to 0.45) *P* = 0.56	
Maintenance week 12									
Mean score (SD)	5.0 (2.6)	4.4 (2.5)	4.7 (2.4)	4.8 (2.5)	4.5 (2.5)	5.0 (2.4)	5.5 (2.6)	4.6 (2.7)	4.6 (2.6)
Mean change (SD)	–2.2 (2.5)	–3.0 (2.4)	–2.6 (2.4)	–2.5 (2.3)	–2.7 (2.4)	–2.3 (2.4)	–2.1 (2.33)	–2.9 (2.7)	–2.9 (2.5)
LSMD vs. PL (95% CI)[a]	NA	**–0.7 (–1.04 to –0.33) *P* < 0.001**	–0.3 (–0.68 to 0.02) *P* = 0.069	NA	**–0.3 (–0.61 to 0.09) *P* = 0.15**	0.2 (–0.16, to 0.54) *P* = 0.28	NA	**–0.8 (–1.22 to –0.47) *P* < 0.001**	–0.9 (–1.24 to –0.49) *P* < 0.001
LSMD, TAP vs. OXY (SE)[a]	NA	–0.4 (–0.71 to –0.01) *P* = 0.044		NA	–0.4 (–0.80 to –0.10) *P* = 0.013		NA	0.0 (–0.36 to 0.39) *P* = 0.92	
≥ 30% reduction from baseline to week 12 in pain intensity score	N = 337	N = 344	N = 342	N = 337	N = 319	N = 331	N = 317	N = 315	N = 326
Number of patients, n (%)	121 (36)	148 (43)	85 (25)	138 (41)	131 (41)	86 (26)	86 (27)	125 (40)	99 (30)
P value vs. PL	NA	*P* = 0.058	*P* = 0.002	NA	*P* = 0.98	*P* < 0.001	NA	*P* < 0.001	*P* = 0.37
≥ 50% reduction from baseline to week 12 in pain intensity score	N = 337	N = 344	N = 342	N = 337	N = 319	N = 331	N = 317	N = 315	N = 326
Number of patients, n (%)	82 (24)	110 (32)	59 (17)	91 (27)	99 (31)	73 (22)	60 (19)	85 (27)	76 (23)

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 336	**TAP N = 344**	**OXY N = 342**	**PL N = 336**	**TAP N = 319**	**OXY N = 331**	**PL N = 316**	**TAP N = 312**	**OXY N = 323**
P value vs. PL	NA	*P* = 0.027	*P* = 0.023	NA	*P* = 0.26	*P* = 0.14	NA	*P* = 0.016	*P* = 0.17
BPI pain subscale from baseline to week 12							N = 315	N = 315	N = 325
Mean baseline score (SD)	NR	NR	NR	NR	NR	NR	7.1 (1.4)	7.1 (1.3)	7.0 (1.3)
LSM change (SE)	NR	NR	NR	NR	NR	NR	–1.5 (0.1)	–2.3 (0.1)	–2.2 (0.1)
LSMD vs. PL (95% CI)[b]	NR	NR	NR	NR	NR	NR	NA	–0.8 (–1.14 to –0.45) *P* < 0.001	–0.7 (–1.07 to –0.39) *P* < 0.001

BPI = Brief Pain Inventory; CI = confidence interval; ITT = intention-to-treat; LSM = least squares mean; LSMD = least squares mean difference; NA = not applicable; NR = not reported; NRS-11 = 11-point numeric rating scale; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus.

Note: Boldface font indicates results for primary end point.

Last observation carried forward was used for imputing missing value in the main analysis. Patients who discontinued treatment early were imputed as nonresponders.

Mean pain intensity scores were calculated as the mean of all scores recorded during baseline (three days prior to randomization), week 12 of maintenance, or over the entire maintenance phase. Pain intensity scores were recorded every 12 hours for the preceding 12 hours.

[a] Analysis of covariance model adjusted for pooled site and baseline pain intensity.

[b] Repeated measures model with time point as a repeated factor and adjusting for pooled site and baseline value.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

In the long-term OL trial in patients with OA or LBP (Study PAI-3007), change in pain intensity from baseline to end of treatment (Table 25) was similar between the two groups (–3.2 [SE of 2.7] for tapentadol ER and –3.1 [SE of 3.4] for oxycodone CR).

In the OL trial in patients with severe LBP with a neuropathic component (Baron 2016), the upper limit of the 97.5% repeated CI for the difference in mean change in pain intensity of tapentadol ER minus oxycodone/naloxone PR was less than the noninferiority margin of 1.3 (Table 25). Therefore, noninferiority of tapentadol ER versus oxycodone was established. Since the upper limit of the 97.5% repeated CI was also less than zero, superiority of tapentadol ER versus oxycodone/naloxone PR was declared with a between-group difference of –0.9 in favour of tapentadol ER (P = 0.003). However this between-treatment difference is less than the MCID (range of 1.1 to 2.2) for the 11-point NRS. The manufacturer reported that sensitivity analysis in the FAS supported the results in the PP set.

Beyond the co-primary end points in Baron 2016 (11-point NRS pain intensity and PAC-SYM total score), there was no control for type I error. When pain radiating toward or into the leg was assessed, the improvement in pain intensity was greater in the tapentadol ER group compared with the oxycodone/naloxone PR group (LSMD change [SE]: –3.9 [0.2] versus –2.8 [0.3]). Also, improvement in NPSI overall score was greater in the tapentadol ER group compared with the oxycodone/naloxone PR group (mean change of –0.35 [SE of 0.02] versus –0.25 [SE of 0.02]).

Analyses of pain intensity on the 11-point NRS in subgroups based on pain type in Baron 2016 showed differences in change from baseline to end of treatment that favoured tapentadol ER (Table 60). The LSMD (97.5% CI) for tapentadol ER versus oxycodone/naloxone PR was –1.0 (–1.9 to –0.1) in patients with a positive painDETECT score, –1.2 (–2.9 to 0.6) in patients with an unclear painDETECT score, and –1.3 (–2.3 to –0.4) in patients with lumbar radiculopathy. Again, there was no control for multiplicity for these outcomes.

Table 25: Change in Pain Intensity — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 (OA and LBP) ITT Set		Baron 2016 (LBP Neuropathic) PP Set	
	TAP N = 876	**OXY N = 219**	**TAP N = 117**	**OXN N = 112**
NRS-11 Pain Intensity Score				
Mean at baseline (SD)	7.6 (1.5)	7.6 (1.6)	7.6 (1.0)	7.6 (1.0)
Mean at end of treatment (SD)	4.4 (2.6) N = 821	4.5 (2.2) N = 178	3.9 (2.6)	4.8 (2.4)
Mean change (SD)	–3.2 (2.7)	–3.1 (3.4)	NR	NR
LSM change (SE)	NR	NR	–3.7 (0.5)	–2.7 (0.3)
LSM difference, TAP vs. OXN (97.5% RCI)	NA		**–0.9 (–1.8 to –0.2)** Noninferiority margin = 1.3 **Noninferiority met** ***P* = 0.003 for superiority**	
NRS-11 Pain Intensity Score for Pain Radiating Toward or into the Leg			**Full Analysis Set**	
			N = 130	N = 125
Mean at baseline (SD)	NA	NA	7.5 (1.3)	7.6 (1.1)
Mean at end of treatment (SD)	NA	NA	3.7 (2.8)	4.7 (2.5)
LSM change (SE)	NA	NA	–3.9 (0.3)	–2.8 (0.3)
LSM difference, TAP vs. OXN	NA	NA	*P* = 0.001	
Mean NPSI Overall Score			N = 129	N = 125
LSM change (SE)	NA	NA	–0.35 (0.02)	–0.25 (0.02)
LSM difference, TAP vs. OXN	NA		*P* < 0.001	

ITT = intention-to-treat; LBP = lower back pain; LSM = least squares mean; NA = not applicable; NPSI = Neuropathic Pain Symptom Inventory; NRS-11 = 11-point numeric rating scale; OA = osteoarthritis; OXN = oxycodone/naloxone PR; OXY = oxycodone controlled-release; PP = per-protocol; RCI = repeated confidence interval; TAP = tapentadol extended-release; SD = standard deviation; SE = standard error; vs. = versus.

Note: Boldface font indicates results for primary end point.

In Baron 2016, last observation carried forward was used for imputing missing values, an analysis of covariance model adjusted for pooled site and baseline value was used, and patients rated their pain intensity during the past three days on the NRS-11 at each time point.

Source: Clinical study report for PAI-3007,[18] Baron et al. 2016.[19,20]

In the DB, four-week trial in patients with cancer pain and no recent opioid use (Imanaka 2013, Table 26), the upper limit of the 95% CI for the LSMD of pain intensity for tapentadol ER minus oxycodone CR was less than the noninferiority margin of 1 and noninferiority of tapentadol ER to oxycodone CR was declared. Sensitivity analyses for missing data imputation (BOCF, WOCF, and observed cases) and the FAS were consistent with the main analysis. Responder analysis showed that greater proportions of patients in the tapentadol ER group compared with the oxycodone CR group achieved at least a 30% (64% versus 59%) or a 50% (50% versus 42%) reduction in pain intensity from baseline.

In the OL, eight-week study in patients with cancer pain already on an opioid analgesic (Imanaka 2014, Table 27), mean pain intensity did not change in either the tapentadol ER or morphine SR groups from baseline to the end of treatment. The primary efficacy end point in this trial was the proportion of patients in the tapentadol ER group who maintained pain control during the first week of titration. The proportion of patient who achieved this was 84% in the tapentadol ER group and 98% in the morphine SR group.

During the two-week, DB titration phase in Kress 2014 (patients with cancer pain, Table 27), mean pain intensity at the end of titration was lower in the morphine CR group

compared with the tapentadol ER group (3.7 [SD of 1.8] versus 4.1 [SD of 1.8]), despite similar baseline values. The proportion of responders during the titration period was greater in the morphine CR group than in the tapentadol ER group (83% vs 76%), though the lower margin of the 95% CI of the difference in proportions was greater than the noninferiority margin of –20% and noninferiority of tapentadol ER to morphine CR was declared. Formal comparisons were not available between the morphine CR group and the other treatment groups during the maintenance phase as patients titrated on tapentadol ER were re-randomized to tapentadol ER or placebo.

Table 26: Change in Pain Intensity — Cancer Pain (Imanaka 2013, Per-Protocol Set)

	Tapentadol ER ($n = 126$)	Oxycodone CR ($n = 139$)
Baseline[a]		
Mean (SD)	5.35 (1.488)	5.27 (1.238)
Last 3 days of treatment		
Mean (SD)	2.64 (1.971)	2.71 (1.743)
Change from baseline to last 3 days of treatment[a]		
Mean (SD)	−2.69 (2.223)	−2.57 (2.027)
P value vs oxycodone CR	0.786	
Difference in LS means (SE)	−0.06 (0.226)	
95% CI	−0.506 to 0.383	

CI = confidence interval; CR = controlled release; ER = extended release; LS = least squares; SD = standard deviation; SE = standard error.

Source: Permission obtained from the publisher to use Table 3 from Efficacy and safety of oral tapentadol extended-release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain by Imanaka K, Tominaga Y, Etropolski M, van Hove I, Ohsaka M, Wanibe M, Hirose K, and Matsumura T. 2013.[21]

Table 27: Change in Pain Intensity — Cancer Pain (Imanaka 2014 and Kress 2014)

	Imanaka 2014 ITT Set		Kress 2014 FA Set		
	TAP N = 50	**MOR N = 50**	**PL N = 111**	**TAP N = 105**	**MOR N = 109**
NRS-11 Pain Intensity Score					
Mean at baseline (SD)	1.5 (1.1)	1.8 (1.1)	NR	NR	NR
Mean at end of treatment (SD)	NR	NR	NR	NR	NR
Mean change (SD)	N = 29 0.0 (0.9)	N = 29 0.0 (1.2)	NR	NR	NR
LSM difference (95% CI)	NR		NR		
Mean at start of titration (SD)	NA	NA	6.3 (1.5)		6.3 (1.6)
Maintenance FA set	NA	NA	6.2 (1.5)	6.3 (1.4)	6.0 (1.5)
Mean at end of titration (SD)	NA	NA	4.1 (1.8)		3.7 (1.8)
Responders during the titration phase,[a] % of patients	NR	NR	NA	PP Set N = 229	PP Set N = 100
				76	83
TAP vs. MOR				95% CI: –15.5%, NR Noninferiority margin: –20% Noninferiority met	
Number of patients with ≥ 50% reduction from baseline to end of treatment (%)	NR	NR	NR	NR	NR
Number of patients who maintained pain control during first week of titration (%)[a]	**42 (84)**	49 (98)	NR	NR	NR

CI = confidence interval; FA = full analysis; ITT = intention-to-treat; LSM = least squares mean; MOR = morphine controlled-release or sustained-release; NA = not applicable; NR = not reported; NRS-11 = 11-point numeric rating scale; PL = placebo; PP = per-protocol; SD = standard deviation; TAP = tapentadol extended-release; vs. = versus.

Note: End of treatment was four weeks for Imanaka 2013, eight weeks for Imanaka 2014.

Boldface font indicates primary end point.

Last observation carried forward was used for imputing missing values in Imanaka 2013.

[a] Patients who, for any consecutive three days during the first week of study treatment, had a change from baseline in 11-point NRS pain intensity score of less than 1.5 points and no more than two doses of rescue medication a day.

Source: Imanaka et al. 2014,[22] Kress et al. 2014.[23]

Health-Related Quality of Life

There was no control for multiplicity for the HRQoL outcomes in any of the trials, thus conclusions could not be drawn from the statistical analyses.

Improvement in HRQoL as indicated by the change in mean EQ-5D-3L index score was greater in the tapentadol ER group than in the oxycodone CR group by 0.1 (95% CI, 0.03 to 0.10) and 0.1 (95% CI, 0.03, 0.11) in studies PAI-3008 and PAI-3009, respectively (Table 28). Mean change in EQ-5D-3L health state VAS was also greater in the tapentadol group in both trials (mean [SE]: 6.4 [1.0] mm versus 2.9 [0.9] mm and 12.7 [1.3] mm versus 7.4 [1.2] mm). There was no difference in change in EQ-5D-3L index score and VAS between the tapentadol ER and oxycodone CR groups in Study PAI-3011.

Differences in mean change in SF-36 MCS favoured tapentadol ER in all three trials (least squares mean [LSM] difference [95% CI] for tapentadol ER versus oxycodone CR: 1.9 [0.60 to 3.20], 1.3 [–0.15 to 2.68], and 0.8 [–0.53 to 2.18] for studies PAI-3008, PAI-3009, and PAI-3011). Mean change in SF-36 PCS favoured tapentadol ER over oxycodone CR in studies PAI-3008 and PAI-3009 (LSM difference [95% CI]: 2.5 [1.31 to 3.69] and 1.4 [0.20 to 2.69] respectively). There was no difference in mean change in SF-36 PCS between the tapentadol ER and oxycodone CR groups in Study PAI-3011.

The WOMAC in studies PAI-3008 and PAI-3009 measured OA-specific, HRQoL, though formal comparisons of the two active treatments were not made. Improvements from baseline to the end of the maintenance phase in the global, pain subscale, and physical function subscale scores were similar between the tapentadol ER and oxycodone CR groups (Table 29).

Table 28: Health-Related Quality of Life — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
EQ-5D-3L Index Score									
Mean at baseline (SD)	0.4 (0.30)	0.4 (0.31)	0.4 (0.30)	0.4 (0.29)	0.4 (0.30)	0.4 (0.30)	0.4 (0.32)	0.4 (0.33)	0.4 (0.31)
Mean change to end of treatment (SE)	0.1 (0.02)	0.2 (0.02)	0.1 (0.02)	0.2 (0.02)	0.2 (0.02)	0.1 (0.01)	0.1 (0.02)	0.2 (0.02)	0.2 (0.02)
LSM difference vs. PL (95% CI)	NA	0.1 (0.02 to 0.09) *P* = 0.004	-0.0 (–0.05 to 0.02) *P* = 0.45	NA	0.0 (–0.01 to 0.07) *P* = 0.11	-0.0 (–0.08 to –0.00) *P* = 0.031	NA	0.0 (0.01 to 0.09) *P* = 0.020	0.1 (0.01 to 0.09) *P* = 0.09
LSM difference, TAP vs. OXY (95% CI)	NA	0.1 (0.03 to 0.10) *P* < 0.001		NA	0.1 (0.03 to 0.11) *P* < 0.001		NA	0.0 (–0.04 to 0.04) *P* = 0.99	
EQ-5D VAS, mm									
Mean at baseline (SD)	65.2 (19.5)	66.1 (19.8)	67.6 (20.2)	53.2 (42.7)	50.1 (20.0)	51.3 (19.6)	60.5 (22.2)	61.5 (21.7)	62.6 (19.9)
Mean at end of treatment (SD)	69.1 (19.4)	72.5 (18.1)	70.5 (19.2)	61.3 (20.3)	62.8 (20.2)	58.6 (20.4)	64.9 (20.5)	66.6 (21.1)	67.6 (20.6)
Mean change (SE)	3.9 (0.9)	6.4 (1.0)	2.9 (0.9)	8.0 (2.5)	12.7 (1.3)	7.4 (1.2)	4.5 (1.1)	5.1 (1.1)	5.1 (1.3)
SF-36 Mental Component Summary Score									
Mean at baseline (SD)	52.3 (11.9)	52.9 (11.7)	52.2 (11.9)	48 (12.1)	47.4 (11.4)	47.2 (11.5)	47 (12.2)	47.3 (12.0)	47.7 (11.9)
Mean change to end of treatment (SE)	1.9 (0.5)	0.6 (0.6)	–1.0 (0.5)	1.9 (0.6)	1.6 (0.6)	0.3 (0.5)	1.7 (0.6)	1.8 (0.6)	0.8 (0.5)
LSM difference vs. PL (95% CI)	NA	–1.1 (–2.44 to 0.17) *P* = 0.089	–3.0 (–4.34 to –1.72) *P* < 0.001	NA	–0.7 (–2.09 to 0.73) *P* = 0.34	–1.9 (–3.35 to –0.55) *P* = 0.006	NA	0.1 (–1.28 to 1.45) *P* = 0.90	–0.7 (–2.10 to 0.62) *P* = 0.29
LSM difference, TAP vs. OXY (95% CI)	NA	1.9 (0.60 to 3.20) *P* = 0.004		NA	1.3 (–0.15 to 2.68) *P* = 0.079		NA	0.8 (–0.53 to 2.18) *P* = 0.23	
SF-36 Physical Component Summary Score									
Mean at baseline (SD)	27.6 (7.5)	27.8 (7.8)	28.2 (7.8)	27.6 (7.5)	27.8 (7.8)	28.2 (7.8)	27.6 (7.5)	27.8 (7.8)	28.2 (7.8)
Mean change to end of treatment (SE)	3.5 (0.5)	6.2 (0.5)	3.6 (0.4)	5.8 (0.5)	6.7 (0.5)	5.1 (0.5)	3.2 (0.5)	5.6 (0.5)	5.5 (0.5)

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
LSM difference vs. PL (95% CI)	NA	2.8 (1.56 to 3.95) *P* < 0.001	0.3 (–0.94 to 1.45) *P* = 0.68	NA	0.8 (–0.49 to 1.99) *P* = 0.24	–0.7 (–1.93 to 0.53) *P* = 0.27	NA	2.3 (1.02 to 3.58) *P* < 0.001	2.3 (1.02 to 3.56) *P* < 0.001
LSM difference, TAP vs. OXY (95% CI)	NA	2.5 (1.31 to 3.69) *P* < 0.001		NA	1.4 (0.20 to 2.69) *P* = 0.023		NA	0.0 (–1.26 to 1.28) *P* = 0.99	

CI = confidence interval; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; ITT = intention-to-treat; LSM = least squares mean; NA = not applicable; OXY = oxycodone controlled-release; PL = placebo; SE = standard error; SD = standard deviation; SF-36 = 36-item Short Form Health Survey; TAP = tapentadol extended-release; VAS = visual analogue scale; vs. = versus.

Note: Change was measured from baseline to end of treatment and last observation carried forward was used for imputing missing values.

Analysis of covariance model with treatment and pooled centre as factors and baseline value as a covariate were used for all comparisons.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 29: Western Ontario and McMaster Universities Osteoarthritis Index

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 337	TAP N = 319	OXY N = 331
WOMAC from baseline to week 12 of maintenance	N = 158 at week 12	N = 149 at week 12	N = 92 at week 12	N = 218 at week 12	N = 183 at week 12	N = 115 at week 12
Global Score						
Mean at baseline (SD)	3.5 (0.6)	3.6 (0.7)	3.5 (0.6)	3.4 (0.7)	3.4 (0.7)	3.4 (0.6)
LSM change (SE)	–0.9 (0.05)	–1.1 (0.05)	–1.1 (0.07)	–0.9 (0.05)	–0.9 (0.06)	–1.0 (0.07)
LSMD vs. PL (95% CI)	NA	–0.2 (–0.36 to –0.06) *P* = 0.005	–0.2 (–0.34 to –0.01) *P* = 0.038	NA	–0.0 (–0.15 to 0.13) *P* = 0.869	–0.1 (–0.21 to 0.11) *P* = 0.512
Pain Subscale Score						
Mean baseline (SD)	3.4 (0.7)	3.5 (0.7)	3.4 (0.6)	3.3 (0.7)	3.3 (0.7)	3.3 (0.6)
LSM change (SE)	–0.9 (0.05)	–1.2 (0.05)	–1.0 (0.7)	–0.9 (0.05)	–0.9 (0.06)	–1.0 (0.07)
LSMD vs. PL (95% CI)	NA	–0.3 (–0.42 to –0.13) *P* < 0.001	–0.2 (–0.34 to 0.0) *P* = 0.051	NA	–0.0 (–0.17 to 0.13) *P* = 0.77	–0.1 (–0.26 to 0.08) *P* = 0.29
Physical Function Subscale						
Mean baseline score (SD)	3.8 (0.7)	3.9 (0.7)	3.9 (0.7)	3.4 (0.7)	3.3 (0.7)	3.4 (0.7)
LSM change (SE)	–0.8 (0.06)	–1.0 (0.06)	–1.0 (0.07)	–0.9 (0.05)	–1.0 (0.06)	–1.0 (0.07)
LSMD vs. PL (95% CI)	NA	–0.2 (–0.36 to –0.06) *P* = 0.006	–0.2 (–0.37 to –0.03) *P* = 0.019	NA	–0.1 (–0.23 to 0.07) *P* = 0.28	–0.1 (–0.25 to 0.08) *P* = 0.30

CI = confidence interval; ITT = intention-to-treat; LSM = least squares mean; LSMD = least squares mean difference; NA = not applicable; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

Note: Comparisons used a repeated measures mixed effects model with treatment and pooled site as factors and baseline value as a covariate.

Source: Clinical study reports for PAI-3008[15] and PAI-3009.[16]

In the long-term, OL trial in patients with OA and LBP (Study PAI-3007), mean change in EQ-5D-3L index score was the same in both groups (mean of 0.2 with an SD of 0.4). The mean change (improvement) in the EQ-5D-3L VAS was 11.6 (SD of 26.0) in the tapentadol ER group and 7.7 (SD of 24.0) in the oxycodone CR group. The mean changes in the SF-36 MCS and PCS were 1.2 (SD of 11.8) and 7.2 (SD of 9.6) in the tapentadol group ER and 0.4 (SD of 12.2) and 4.9 (SD of 10.1) in the oxycodone CR groups. No statistical analyses were reported for these data in Study PAI-3007.

In the OL trial in patients with LBP with a neuropathic component (Baron 2016), LSM change from baseline to the end of treatment for the tapentadol ER versus the oxycodone CR group was 0.34 (SE of 0.03) versus 0.24 (SE of 0.03) for the EQ-5D-3L index score, 20.4 mm (SE of 2.0 mm) versus 14.0 mm (SE of 2.1 mm) for the EQ-5D VAS, 3.1 (SE of 0.8) versus 1.2 (SE of 0.9) for the SF-12 MCS, and 9.7 (SE of 0.8) versus 6.2 (SE of 0.8) for the SF-12 PCS. The baseline PCS scores were 30.3 (SD 7.3) and 31.7 (SD 6.8) for tapentadol ER and oxycodone-naloxone, respectively; the baseline MCS scores were 48.7 (SD 11.6) and 45.2 (SD 11.8) for tapentadol ER and oxycodone-naloxone, respectively. No statistical analyses were reported for SF-36 findings and analyses of the EQ-5D results were not controlled for multiplicity.

HRQoL outcomes were not reported for the three studies in patients with cancer pain.

Table 30: Health-Related Quality of Life — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 (OA and LBP) ITT Set		Baron 2016 (LBP Neuropathic) Full Analysis Set	
	TAP N = 876	**OXY N = 219**	**TAP N = 130**	**OXN N = 125**
EQ-5D-3L index score	N = 737	N = 149		
Mean at baseline (SD)	0.4 (0.32)	0.4 (0.31)	0.3 (0.3)	0.3 (0.3)
Mean change (SD)	0.2 (0.35)	0.2 (0.37)	NR	NR
LSM change (SE)	NR	NR	0.34 (0.03)	0.24 (0.03)
LSM difference, TAP vs. OXN	NR		*P* = 0.010	
EQ-5D VAS, mm	N = 737	N = 149		
Mean at baseline (SD)	56.6 (23.7)	55.5 (21.8)	44.3 (20.4)	42.1 (18.6)
Mean change (SD)	11.6 (26.0)	7.7 (24.0)	NR	NR
LSM change (SE)	NR	NR	20.4 (2.0)	14.0 (2.1)
LSM difference, TAP vs. OXN	NR		*P* = 0.024	
SF-36 MCS score (SF-12 for Baron 2016)	N = 737	N = 149		
Mean at baseline (SD)	48.3 (12.5)	48.6 (11.9)	Reported in text	Reported in text
Mean change (SD)	1.2 (11.8)	0.4 (12.2)	NR	NR
LSM change (SE)	NR	NR	3.1 (0.8)	1.2 (0.9)
LSM difference, TAP vs. OXN	NR		NR	
SF-36 PCS score (SF-12 for Baron 2016)	N = 737	N = 149		
Mean at baseline (SD)	28.7 (8.6)	27.9 (8.4)	Reported in text	Reported in text
Mean change (SD)	7.2 (9.6)	4.9 (10.1)	NR	NR
LSM change (SE)	NR	NR	9.7 (0.8)	6.2 (0.8)
LSM difference, TAP vs. OXN	NR		*P* ≤ 0.017	

EQ-5D-3L = EuroQol 5-Dimensions 3-Levels; ITT = intention-to-treat; LBP = low back pain; LSM = least squares mean; MCS = mental component summary; NR = not reported; OA = osteoarthritis; OXN = oxycodone/naloxone prolonged-release; OXY = oxycodone controlled-release; PCS = physical component summary; SD = standard deviation; SE = standard error; SF-12 = Short Form-12 Health Survey; SF-36 = Short Form-36 Health Survey; TAP = tapentadol extended-release; VAS = visual analogue scale; vs. = versus.

Note: Last observation carried forward was used for imputing missing values.

Mean change refers to change over the entire treatment period.

Comparisons in Baron 2016 used an analysis of covariance model adjusted for pooled site and baseline value.
Source: Clinical study report for PAI-3007,[18] Baron et al. 2016.[19,20]

Patient Global Assessment of Change

In studies PAI-3008, PAI-3009, and PAI-3011, statistical analyses were not conducted to compare the distribution of PGIC responses between the tapentadol ER and oxycodone CR groups (Table 31).The proportions of patients indicating that they were very much or much improved since the start of the trial in the tapentadol ER versus the oxycodone CR groups were 51% versus 38% for Study PAI-3008, 48% versus 35% for Study PAI-3009, and 47% versus 46% for Study PAI-3011.

Table 31: Patient Global Impression of Change — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
PGIC category, n (%)	N = 309	N = 317	N = 308	N = 322	N = 296	N = 285	N = 286	N = 286	N = 298
Very much improved	23 (7)	55 (17)	30 (10)	33 (10)	42 (14)	27 (10)	25 (9)	45 (16)	49 (16)
Much improved	77 (25)	107 (34)	86 (28)	96 (30)	100 (34)	72 (25)	62 (22)	90 (32)	87 (29)
Minimally improved	66 (21)	69 (22)	72 (23)	84 (26)	69 (23)	63 (22)	55 (19)	70 (25)	71 (24)
No change	80 (26)	46 (15)	53 (17)	69 (21)	42 (14)	52 (18)	87 (30)	52 (18)	57 (19)
Minimally worse	36 (12)	18 (6)	37 (12)	19 (6)	15 (5)	33 (12)	29 (10)	19 (7)	20 (7)
Much worse	21 (7)	16 (5)	24 (8)	18 (6)	23 (8)	30 (11)	19 (7)	7 (2)	11 (4)
Very much worse	6 (2)	6 (2)	6 (2)	3 (1)	5 (2)	8 (3)	9 (3)	3 (1)	3 (1)
P value, vs. PL	NA	*P* < 0.001	*P* = 0.29	NA	*P* = 0.33	*P* = 0.002	NA	*P* < 0.001	*P* < 0.001

ITT = intention-to-treat; NA = not applicable; OXY = oxycodone controlled-release; PGIC = Patient's Global Impression of Change; PL = placebo; TAP = tapentadol extended-release; vs. = versus.

Note: Comparisons between treatment groups were made using the generalized Cochrane–Mantel–Haenzel test.

PGIC is patient-perceived change in overall status from the start of treatment to the end of the maintenance phase.

Last observation carried forward was used for imputing missing values.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Similar results were observed for PGIC in the OL trials (Study PAI-3007 and Baron 2016) as reported in Table 32. Greater proportions of patients reported being very much or much improved since the start of the trial in the tapentadol ER groups (approximately 49% versus 41% when compared with oxycodone CR in Study PAI-3007 and 54.3% versus 29.6% when compared with oxycodone/naloxone PR in Baron 2016). Statistical analyses were not conducted in Study PAI-3007 and there was no control for multiplicity for this outcome in Baron 2016.

Table 32: Patient Global Impression of Change — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 (OA and LBP) ITT Set		Baron 2016 (LBP Neuropathic) Full Analysis Set	
	TAP N = 876	**OXY N = 219**	**TAP N = 130**	**OXN N = 126**
PGIC category, n (%)	N = 819	N = 177	N = 129	N = 125
Very much improved	102 (13)	15 (9)	(20.9)	(14.4)
Much improved	292 (36)	58 (33)	(33.3)	NR (15.2)
Minimally improved	218 (27)	55 (31)	NR (24.8)	NR (36.8)
No change	132 (16)	21 (12)	NR (16.3)	NR (23.2)
Minimally worse	41 (5)	17 (10)	NR (2.3)	NR (4.8)
Much worse	26 (3)	10 (6)	NR (1.6)	NR (3.2)
Very much worse	8 (1)	1 (0.6)	NR (0.8)	NR (2.4)
P value for distribution	NR		*P* = 0.005	
Percentage of patients much improved or very much improved	NR	NR	54.3	29.6
P value	NR		*P* < 0.001	

ITT = intention-to-treat; LBP = low back pain; NR = not reported; OA = osteoarthritis; OXY = oxycodone controlled-release; OXN = oxycodone/naloxone prolonged-release; PGIC = Patient Global Impression of Change; TAP = tapentadol extended-release.

Note: PGIC is patient-perceived change in overall status from start to end of treatment.

Last observation carried forward was used for imputing missing values.

Comparisons used Fisher's exact test.

Source: Clinical study report for PAI-3007,[18] Baron et al. 2016.[19,20]

Statistical tests for between-groups differences were not conducted for PGIC in Imanaka 2013 and Imanaka 2014 (Table 33). In Imanaka 2013, greater proportions of patients who were very much or much improved were observed in the tapentadol ER group compared with the oxycodone CR group (59% versus 50%). A comparison of the response distributions in Imanaka 2014 is limited by the small sample sizes, and unlike other trials the objective in Imanaka 2014 was to determine the percentage of patients who maintained pain control.

Table 33: Patient Global Impression of Change — Cancer Pain

	Imanaka 2013 PP Set		Imanaka 2014 Full Analysis Set	
	TAP N = 126	OXY N = 139	TAP N = 50	MOR N = 50
PGIC category, n (%)	N = 126	N = 139	N = 28	N = 28
Very much improved	17.5	12.2	0	3 (11)
Much improved	41.3	38.1	3 (11)	2 (7)
Minimally improved	31.0	32.4	8 (29)	4 (14)
No change	4.0	12.9	15 (54)	13 (46)
Minimally worse	2.4	3.0	2 (7)	4 (14)
Much worse	4.0	0.7	0	2 (7)
Very much worse	0	0.7	0	0
Patients with any improvement, n (%)	113 (90)	115 (83)	NR	NR
Patients very much improved or much improved, n (%)	74 (59)	70 (50)	NR	NR

MOR = morphine controlled-release; OXY = oxycodone controlled-release; PGIC = Patient Global Impression of Change; PP = per-protocol; TAP = tapentadol extended-release.

Note: PGIC is patient-perceived change in overall status from the start of treatment to the end of the maintenance phase.

Last observation carried forward was used for imputing missing values in Imanaka 2013.

Source: Imanaka et al. 2013,[21] Imanaka et al. 2014.[22]

Impact on Sleep

Differences in mean change in sleep latency between the tapentadol ER and oxycodone CR groups did not exceed 0.1 hours in the three trials (Table 34). There were no notable differences in the distribution of number of awakenings between the tapentadol ER and oxycodone CR group at the end of the maintenance phase. Differences between the tapentadol ER and oxycodone CR groups in the change in mean time slept did not exceed 0.2 hours and the effect was inconsistent across the trials. The distributions in overall quality of sleep categories at the end of the maintenance phase were not noticeably different between the tapentadol ER and oxycodone CR groups.

Table 34: Sleep Questionnaire — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
Mean Sleep Latency, Hours (SD)									
Baseline	1.2 (1.5)	1.2 (1.8)	1.3 (1.9)	1.0 (1.8)	0.8 (1.1)	0.8 (0.8)	1.5 (1.6)	1.8 (2.4)	1.6 (1.9)
Week 12	1.5 (2.4)	1.4 (2.8)	1.5 (2.3)	1.4 (3.3)	1.1 (2.2)	1.0 (2.1)	1.4 (2.1)	1.6 (2.7)	1.4 (2.0)
Change (SE)	0.3 (0.2)	0.2 (0.2)	0.1 (0.1)	0.4 (0.2)	0.2 (0.1)	0.2 (0.1)	–0.1 (0.1)	–0.2 (0.2)	–0.2 (0.1)
Number of Awakenings Category, n (%)									
Baseline									
0 to 1	84 (27)	76 (24)	92 (29)	88 (27)	86 (28)	86 (27)	62 (21)	66 (23)	66 (21)
2 to 3	140 (45)	164 (52)	149 (47)	184 (56)	154 (51)	162 (52)	144 (50)	131 (45)	159 (51)
≥ 4	88 (28)	76 (24)	79 (25)	55 (17)	65 (21)	66 (21)	84 (29)	95 (33)	88 (28)
End of Maintenance Phase									
0 to 1	116 (35)	120 (35)	127 (38)	144 (43)	136 (43)	113 (34)	89 (29)	126 (41)	115 (36)
2 to 3	145 (44)	168 (50)	149 (44)	150 (45)	140 (44)	150 (46)	159 (51)	138 (44)	147 (45)
≥ 4	70 (21)	51 (15)	61 (18)	43 (13)	43 (14)	65 (20)	64 (21)	47 (15)	62 (19)
Mean Time Slept, Hours (SD)									
Baseline	6.1 (1.9)	6.1 (1.7)	6.1 (1.7)	6.1 (1.7)	6.2 (1.9)	6.2 (1.5)	5.7 (1.9)	5.8 (2.1)	5.8 (1.8)
Week 12	6.3 (1.7)	6.6 (1.7)	6.5 (1.9)	6.3 (1.8)	6.4 (1.9)	6.5 (1.9)	6.1 (1.8)	6.5 (1.8)	6.3 (1.8)
Change (SE)	0.3 (0.1)	0.6 (0.1)	0.4 (0.1)	0.2 (0.1)	0.2 (0.1)	0.3 (0.11)	0.4 (0.1)	0.7 (0.1)	0.5 (0.11)
Overall Quality of Sleep									
Baseline									
Excellent	10 (3)	8 (3)	20 (6)	11 (3)	8 (3)	5 (2)	9 (3)	8 (3)	10 (3)
Good	100 (32)	109 (35)	110 (34)	134 (41)	122 (40)	118 (38)	61 (21)	67 (23)	57 (18)
Fair	120 (39)	122 (39)	124 (39)	146 (45)	138 (45)	151 (48)	122 (42)	117 (40)	146 (47)
Poor	82 (26)	77 (24)	66 (21)	36 (11)	37 (12)	40 (13)	98 (34)	100 (34)	100 (32)
End of Maintenance Phase									
Excellent	34 (10)	33 (10)	42 (13)	10 (3)	15 (5)	19 (6)	20 (6)	31 (10)	38 (12)
Good	147 (44)	169 (50)	157 (47)	174 (52)	177 (56)	158 (48)	114 (37)	135 (43)	118 (36)
Fair	100 (30)	99 (29)	96 (29)	124 (37)	107 (34)	125 (38)	119 (38)	105 (34)	111 (34)
Poor	50 (15)	38 (11)	42 (13)	29 (9)	20 (6)	26 (8)	59 (19)	40 (13)	57 (18)
P value, vs. PL	NA	*P* = 0.21	*P* = 0.17	NA	*P* = 0.07	*P* = 0.60	NA	*P* = 0.003	*P* = 0.09
P value, TAP vs. OXY	NA	*P* = 0.88		NA	*P* = 0.22			*P* = 0.24	

ITT = intention-to-treat; NA = not applicable; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus.

Note: Baseline was the start of the titration phase.

Last observation carried forward was used for imputing missing values.

Comparisons between treatment groups were made using the generalized Cochrane–Mantel–Haenzel test.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

In Study PAI-3007, there were no differences between treatment groups in sleep latency or hours slept and there were no notable differences in number of awakenings and sleep quality (Table 35).

In Baron 2016, the tapentadol ER group had greater improvements than the oxycodone/naloxone PR groups for sleep latency (LSM change [SE]: –0.30 [1.11] versus –0.18 [0.10]) and number of awakenings (LSM change [SE]: –0.8 [0.2] versus –0.5 [0.2]) while there were no notable differences in hours slept (LSM change [SE]: 0.46 [0.17] versus 0.41 [0.18]). Compared with baseline, the overall sleep quality improved at the end of the maintenance phase in both treatment groups. The proportion of patients with "excellent" (tapentadol ER changed from 1.5% to 10.5%; oxycodone/naloxone PR changed from 3.2% to 8.7%) or "good" (tapentadol ER changed from 28.5% to 47.6%: oxycodone/naloxone PR changed from 21.6% to 36.5%) sleep quality increased, while the proportion of patients with "fair" (tapentadol ER changed from 37.7% to 28.2%; oxycodone/naloxone PR changed from 53.6% to 41.7%) or "poor" (tapentadol ER changed from 32.3% to 13.7%, oxycodone/naloxone PR changed from 21.6% to 13.0%) sleep quality decreased from baseline. Statistical test were not performed in either trial.

Impact on sleep was not measured in any of the trials in patients with cancer pain.

Table 35: Sleep Questionnaire — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 (OA and LBP) Safety Set	
	TAP N = 894	**OXY N = 223**
Mean hours until sleep (SD)	N = 747	N = 151
Baseline	0.9 (1.1)	0.8 (1.0)
End of treatment	0.8 (1.3)	1.0 (1.9)
Change	–0.1 (1.6)	–0.1 (1.7)
LSM change (SE)	NR	NR
Number of awakenings category, n (%)	N = 748	N = 151
Baseline		
0 to 1	230 (26)	59 (27)
2 to 3	400 (45)	91 (41)
≥ 4	263 (29)	71 (32)
Mean (SD)	NR	NR
End of treatment		
0 to 1	303 (41)	51 (34)
2 to 3	329 (44)	71 (47)
≥ 4	116 (16)	29 (19)
Mean (SD)	NR	NR
LSM change (SE)	NR	NR
Mean hours slept (SD)	N = 748	N = 151
Baseline	6.0 (1.8)	5.9 (1.9)
End of treatment	6.6 (1.7)	6.2 (1.7)
Change	0.6 (2.1)	0.5 (2.1)
LSM change (SE)	NR	NR
Overall quality of sleep, n (%)		
Baseline	N = 893	N = 222

	PAI-3007 Wild 2010 (OA and LBP) Safety Set	
Excellent	24 (3)	10 (5)
Good	237 (27)	55 (25)
Fair	360 (40)	95 (43)
Poor	272 (31)	62 (28)
End of maintenance phase	N = 749	N = 151
Excellent	71 (10)	13 (9)
Good	338 (45)	59 (39)
Fair	234 (31)	56 (37)
Poor	106 (14)	23 (15)

LBP = low back pain; LSM = least squares mean; NR = not reported; OA = osteoarthritis; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release.

Note: Baseline refers to the start of treatment.

Last observation carried forward was used for imputing missing values.

LSM change was estimated in Baron 2016 used an analysis of covariance model adjusted for baseline value.

Source: Clinical study report for PAI-3007.[18]

Impact on Work and Daily Activities

Instruments specific to the impact of pain on work and daily activities were not used in any of the trials. In Study PAI-3011, the BPI pain interference subscale score was reported. The tapentadol ER group had a larger improvement in the subscale score than the oxycodone CR group (LSM change [SE]: –2.3 [0.1] versus –2.0 [0.1]), though the difference was not statistically tested.

Table 36: Brief Pain Inventory — Low Back Pain

	PAI-3011 Buynak 2011 ITT Set		
	PL N = 317	**TAP N = 315**	**OXY N = 326**
BPI pain interference subscale	N = 315	N = 314	N = 323
Mean baseline score (SD)	6.4 (2.0)	6.4 (2.0)	6.3 (2.0)
Mean change (SD)	NR	NR	NR
LSM change (SE)	–1.6 (0.1)	–2.3 (0.1)	–2.0 (0.1)
LSM difference vs. PL (95% CI)	NA	–0.7 (–1.04 to –0.29) *P* < 0.001	–0.4 (–0.80 to –0.06) *P* = 0.023

BPI = Brief Pain Inventory; CI = confidence interval; ITT = intention-to-treat; LSM = least squares mean; NA = not applicable; NR = not reported; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release.

Note: Last observation carried forward was used for imputing missing values.

Change is from baseline (randomization) to week 12 of maintenance phase.

Comparisons used an analysis of covariance model adjusted for pooled site and baseline value.

Source: Clinical study report for PAI-3011.[17]

Need for Additional Therapy for Breakthrough Pain

Greater proportions of patients used acetaminophen during the treatment period in studies PAI-3008, PAI-3009, and PAI-3011 in the tapentadol ER groups than in the oxycodone CR groups (64% vs. 59% in Study PAI-3008, 56% versus 47% in Study PAI-3009, and 69% versus 60% in Study PAI-3011). Among those who used acetaminophen, the mean days of use was consistently higher in the tapentadol ER group versus the oxycodone CR group for each trial (Table 37). Acetaminophen use specifically for reference pain (the pain meeting study entry criteria) tended to be used by more patients in the tapentadol ER group than in the oxycodone CR group in each trial in the titration and maintenance phases. In patients who used acetaminophen for reference pain, exposure during the titration phase was consistently higher in the tapentadol ER group versus the oxycodone CR group (mean days [SD]: 6.2 [5.8] versus 4.4 [4.7] in Study PAI-3008, 6.1 [5.6] versus 5.2 [4.7] in Study PAI-3009, and 6.0 [5.3] versus 5.4 [5.5] in Study PAI-3011). There was no consistent trend in acetaminophen exposure for reference pain in the maintenance phase across the trials, possibly due to the smaller amounts of patients using acetaminophen as it was prohibited during this phase.

Table 37: Acetaminophen Use — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 337	TAP N = 319	OXY N = 331	PL N = 319	TAP N = 318	OXY N = 328
Total DB treatment period, n (%)	232 (69)	221 (64)	202 (59)	222 (66)	180 (56)	156 (47)	232 (73)	220 (69)	198 (60)
Mean days of use (SD)	9.5 (11.1)	7.6 (7.3)	6.2 (6.3)	8.2 (10.0)	7.1 (5.9)	5.6 (5.2)	9.2 (8.2)	8.1 (8.9)	7.0 (9.9)
Median days of use (range)	7 (1,101)	5 (1,44)	4 (1,36)	5 (1, 89)	5 (1, 24)	3.5 (1, 22)	7 (1,50)	5.5 (1,86	4 (1,109)
Use for reference pain during titration phase, n	185	176	164	185	150	114	205	172	154
Mean days (SD)	7.5 (5.8)	6.2 (5.8)	4.4 (4.7)	6.1 (5.2)	6.1 (5.6)	5.2 (4.7)	7.1 (5.8)	6.0 (5.3)	5.4 (5.5)
Median days (range)	6 (1, 21)	4 (1, 25)	3 (1, 19)	5 (1, 21)	4 (1, 24)	3 (1, 22)	6 (1, 23)	4 (1, 21)	3 (1, 21)
Use for reference pain during maintenance phase, n	31	21	18	20	17	6	30	19	23
Mean days (SD)	7.8 (18.7)	2.6 (3.1)	3.1 (6.5)	7.6 (19.2)	1.4 (0.7)	1.0 (0.0)	5.5 (8.7)	5.5 (14.6)	7.1 (19.0)
Median days (range)	2 (1, 81)	1 (1, 14)	1 (1, 29)	1 (1, 82)	1 (1,3)	1 (1,1)	2 (1, 37)	1 (1, 65)	1 (1, 88)

DB = double blind; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; TAP = tapentadol extended-release.

Note: Acetaminophen was allowed as rescue medication during the titration period, except for the last three days of titration. Acetaminophen was allowed only for reasons other than study-related chronic pain during the maintenance period.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

During the treatment periods of studies PAI-3008, PAI-3009, and PAI-3011, proportions of patients in the active treatment groups reporting concomitant opioid analgesic use ranged from 3% to 11% and proportions of patients reporting concomitant non-opioid analgesic use (other than acetaminophen) ranged from 23% to 32% (Table 38). There were no notable differences in reported concomitant analgesic use between the tapentadol ER and oxycodone CR groups in any of the three trials.

Table 38: Concomitant Analgesic Use — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
Total DB Treatment Period									
Patients taking opioids[a] (%)	22 (7)	12 (4)	12 (4)	13 (4)	10 (3)	13 (4)	40 (13)	36 (11)	25 (8)
Vicodin	3 (1)	1 (0.3)	3 (1)	0	0	0	12 (4)	10 (3)	10 (3)
Tramadol or tramadol hydrochloride	3 (1)	0	0	5 (2)	5 (2)	7 (2)	9 (3)	2 (0.6)	3 (1)
Panadeine Co	2 (1)	2 (1)	2 (1)	0	2 (0.6)	2 (0.6)	2 (1)	5 (2)	1 (0.3)
Morphine or morphine sulphate	0	2 (1)	0	0	0	0	3 (1)	6 (2)	1 (0.3)
Patients taking non-opioid analgesics[b] (%)	113 (34)	95 (28)	100 (29)	85 (25)	77 (24)	76 (23)	109 (34)	102 (32)	101 (31)
Acetylsalicylic acid	57 (17)	58 (17)	48 (14)	44 (13)	39 (12)	46 (14)	41 (13)	37 (12)	40 (12)
Paracetamol	30 (9)	30 (9)	31 (9)	20 (6)	20 (6)	13 (4)	33 (10)	39 (12)	22 (7)
Ibuprofen	8 (2)	7 (2)	15 (4)	6 (2)	6 (2)	5 (2)	20 (6)	9 (3)	15 (5)

DB = double blind; OXY = oxycodone controlled-release; PL = placebo; TAP = tapentadol extended-release.

Note: Concomitant opioid use was considered a protocol deviation.

Use of acetylsalicylic acid was allowed for cardiovascular prophylaxis.

[a] Any analgesics taken by at least 2% of patients in any group were included.

[b] Any analgesics taken by at least 5% of patients in any group were included.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

In the long-term, OL trial (Study PAI-3007), rescue acetaminophen was used by a greater proportion of patients in the tapentadol ER group than in the oxycodone CR group (84% versus 71%, see Table 39). Non-rescue, concomitant analgesic use was similar between the groups for opioids (10% in both treatment groups) and non-opioids (20% versus 17% for tapentadol ER versus oxycodone CR).

Table 39: Concomitant Analgesic Use — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 Safety Set	
	TAP N = 894	**OXY N = 223**
Rescue acetaminophen use, n (%)	754 (84)	159 (71)
Days of use category, n (%)	N = 882	N = 219
0	137 (16)	66 (30)
1 to 7	228 (26)	54 (25)
8 to 14	87 (10)	15 (7)
15 to 28	135 (15)	24 (11)
29 to 90	208 (24)	40 (18)
> 90	87 (10)	20 (9)
Opioid analgesic use,[a] n (%)	86 (10)	22 (10)
Vicodin	14 (2)	2 (0.9)
Oxycodone or oxycodone hydrochloride	11 (1)	11 (5)
Tramadol or tramadol hydrochloride	22 (3)	4 (2)
Non-opioid analgesic use,[b] n (%)	178 (20)	38 (17)
Acetylsalicylic acid	87 (10)	25 (11)
Acetaminophen	54 (6)	9 (4)

OXY = oxycodone controlled-release; TAP = tapentadol extended-release.

Note: Use of acetylsalicylic acid was allowed for cardiovascular prophylaxis.

Limited use of acetaminophen was allowed as rescue medication during entire treatment period.

[a] Any analgesics taken by at least 2% of patients in any group were included.

[b] Any analgesics taken by at least 5% of patients in any group were included.

Source: Clinical study report for PAI-3007.[18]

Use of rescue morphine IR in Imanaka 2013 was similar between the tapentadol ER and oxycodone CR groups in terms of proportions of patients, days of use, average daily doses, and average TDD in morphine IR (Table 40). The tapentadol ER group had a higher mean of the average days of use (mean [SD]: 7.6 [7.7] days versus 7.2 [7.8] days) and mean of the average TDD (7.0 [2.3] mg versus 6.7 [2.2] mg of morphine IR) compared with the oxycodone CR group. In Imanaka 2014, the mean of the average daily doses was 0.4 in both groups. In the titration phase of Kress 2014, the tapentadol ER group had a greater proportion of patients using rescue morphine IR (72% versus 58%) and a higher mean of the average TDD of rescue morphine IR (mean [SD]: 13.3 [17.4] mg versus 8.9 [12.5] mg) versus the morphine CR group. These trends continued in the maintenance phase of Kress 2014, though a formal comparison of the tapentadol ER and morphine CR groups was not planned due to limitations in the study design (re-randomization of tapentadol ER patients for the maintenance phase).

Information on the use of concomitant analgesic medications was not reported in the Baron et al. 2016 publications.

Table 40: Rescue Opioid Analgesic Medication Use — Cancer Pain

	Imanaka 2013 PP Set		Imanaka 2014 ITT Set		Kress 2014 Full Analysis Set		
	TAP N = 126	OXY N = 139	TAP N = 50	MOR N = 50	PL N = 111	TAP N = 105	MOR N = 109
Total treatment period (DB titration phase for Kress 2014)					N = 335		N = 157
Rescue medication use, n (%)	94 (75)	103 (74)	NR	NR	241 (72)		91 (58)
Mean number of days of use (SD)	7.6 (7.7)	7.2 (7.8)	15.9 (19.6)	NR	NR		NR
Mean of the per-patient average number of doses/day (SD)	1.4 (0.5)	1.4 (0.4)	0.4 (0.6)	0.4 (0.5)	NR		NR
Mean of the per-patient average total dose/day, mg morphine or morphine equivalent dose (SD)	7.0 (2.3)	6.7 (2.2)	3.0 (8.3)	NR	13.3 (17.4)		8.9 (12.5)
DB Maintenance Phase							
Rescue medication use, n (%)	NA	NA	NA	NA	80 (72)	75 (71)	67 (62)
Mean of the average total dose/day, mg morphine (SD)	NA	NA	NA	NA	13.7 (13.7)	11.2 (12.7)	8.9 (15.0)

DB = double blind; MOR = morphine controlled-release or sustained-release; NA = not applicable; NR = not reported; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; TAP = tapentadol extended-release.

Note: Rescue medications allowed were morphine immediate-release in Imanaka 2013 and Kress 2014 and morphine immediate-release or oxycodone immediate-release in Imanaka 2014. In Imanaka 2014, the dose per intake of rescue medication could be no more than 1/6 of the total daily dose of around-the-clock opioid analgesic.

Source: Imanaka et al. 2013,[21] Imanaka et al. 2014,[22] Kress et al. 2014.[23]

Mental or Psychological Symptoms

Overall, there were reductions (improvements) in the mean anxiety and depression scores of the HADS from baseline to the end of the maintenance phase in both treatment groups in Baron 2016 (Table 41). The LSMD (SE) in change for the tapentadol ER versus the oxycodone/naloxone PR group was –2.1 (0.34) versus –1.1 (0.35) for the anxiety and –2.4 (0.34) versus –1.1 (0.36) for the depression score. Statistical analyses of these data were not controlled for multiplicity.

Table 41: Hospital Anxiety and Depression Subscales — Neuropathic Pain

	Baron 2016 Full Analysis Set	
	TAP N = 130	OXN N = 125
Mean anxiety score	N = 124	N = 114
Baseline (SD)	7.3 (4.1)	8.2 (4.3)
End of maintenance phase (SD)	5.3 (4.4)	6.7 (4.6)
LSM change (SE)	–2.1 (0.34)	–1.1 (0.35)
LSM difference, TAP vs. OXN	*P* = 0.032	
Mean depression score	N = 124	N = 114
Baseline (SD)	7.4 (4.1)	8.0 (4.1)
End of maintenance phase (SD)	5.1 (4.2)	6.5 (4.9)
LSM change (SEM)	–2.4 (0.34)	–1.1 (0.36)
LSM difference, TAP vs. OXN	*P* = 0.011	

LSM = least squares mean; OXN = oxycodone/naloxone prolonged-release; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus.

Note: Baseline refers start of maintenance phase.
Last observation carried forward was used for imputing missing values.
Comparisons used an analysis of covariance model adjusted for pooled site and baseline value.
Source: Baron et al. 2016.[19,20]

Caregiver Burden

There were no outcomes related to caregiver burden that were reported in the included studies.

Harms

Only those harms identified in the review protocol are reported below.

Adverse Events

AEs occurred in 67% to 76% of patients in the tapentadol ER groups and 85% to 87% of patients in the oxycodone ER groups in the three 15-week, DB trials in patients with OA pain or LBP (Table 42). In the 12-week OL trial in patients with LBP (Baron 2016), AEs occurred in 77% of the tapentadol ER group and 84% of the oxycodone/naloxone PR group. In the long-term OL trial (PAI-3007), AEs occurred in 86% in the tapentadol ER group and 91% in the oxycodone CR group (Table 43).

In the non-cancer pain trials, the most common AEs (occurring in at least 10% of any treatment group) were nausea, constipation, vomiting, somnolence, dizziness, headache, fatigue, pruritus, and hyperhidrosis. Nausea, constipation, vomiting, and somnolence were identified as harms of interest in the systematic review protocol and are reported under Notable Adverse Events. Among the other common AEs, the only consistent imbalance between the active treatment groups was pruritus, which occurred in lower percentages of patients in the tapentadol ER versus the oxycodone CR groups (1% to 7% versus 11% to 17%).

In the cancer pain trials, AEs were reported for the entire treatment period in Imanaka 2013 and 2014, while AEs were reported separately for the titration and maintenance phases in Kress 2014 (Table 45, Table 46, and Table 47). AEs occurred in 88% of patients taking

tapentadol ER and 90% of patients taking oxycodone CR in Imanaka 2013 and 90% of patients taking tapentadol ER and 94% of patients taking morphine CR in Imanaka 2014. During the two-week titration phase of Kress 2014, 50% of patients taking tapentadol ER and 64% of patients taking morphine CR experienced an AE. During the maintenance phase, AEs occurred in 62% of patients in both groups (Table 47).

The most common AEs in the cancer pain trials (occurring in at least 10% of any treatment group) were nausea, constipation, vomiting, diarrhea, somnolence, decreased appetite, and disease progression (Table 47). Aside from the notable harms, differences between treatment groups were observed for disease progression (32% of the tapentadol ER group versus 40% of the morphine CR group in Imanaka 2014) and pruritus (2% of the tapentadol ER group versus 8% of the morphine CR group in Imanaka 2014).

Serious Adverse Events

In the three 15-week, DB trials in patients with OA pain or LBP, serious AEs (SAEs) occurred in 1% to 2% of patients in the tapentadol ER groups and 3% to 4% of patients in the oxycodone CR groups (Table 42). In Baron 2016, 2% of patients in both treatment groups (three in the tapentadol ER group and two in the oxycodone/naloxone PR group) experienced an SAE. In the long-term OL trial, 6% of patients on tapentadol ER and 4% of patients on oxycodone/naloxone PR experienced an SAE (Table 43).

SAEs occurred in 46% and 40% of patients in the tapentadol ER and oxycodone CR groups, respectively, in Imanaka 2013 and in 32% of patients in both treatment groups in Imanaka 2014. The most common SAEs were disease progression (20% to 24% of each group) and vomiting (2% to 6% of each group). During the two-week titration phase of Kress 2014, 7% of patients taking tapentadol ER and 4% of patients taking morphine CR experienced an SAE. During the maintenance phase, SAEs occurred in 11% and 6% of patients in the tapentadol ER and morphine CR groups, respectively (Table 47).

Withdrawals Due to Adverse Events

In the three 15-week, DB trials in patients with OA pain or LBP, WDAEs occurred in 17% to 19% of patients in the tapentadol ER groups and 32% to 43% of patients in the oxycodone CR groups (Table 42). The most common reasons for WDAE also occurred more often in the oxycodone CR groups than in the tapentadol ER groups, with the most notable differences being in nausea (2% to 5% versus 11% to 18%), constipation (1% to 4% versus 4% to 9%), and vomiting (1% to 5% versus 7% to 15%). In the Baron 2016, WDAEs occurred in 22% and 42% of patients in the tapentadol ER and oxycodone/naloxone PR groups, with the most common reasons being nausea (8% versus 9% of patients in the tapentadol ER and oxycodone/naloxone PR groups), vomiting (6% versus 9%), dizziness (3% versus 13%), fatigue (4% versus 5%), and pruritus (2% versus 5%). In the long-term PAI-3007 study, WDAEs occurred in 22% and 37% of patients in the tapentadol ER and oxycodone CR groups, with the most common reasons being nausea (3% versus 12%), constipation (2% versus 7%), vomiting (3% versus 7%), dizziness (3% versus 7%), and fatigue (2% versus 5%) (Table 43).

Mortality

One patient in the oxycodone CR group of Study PAI-3008 died from a myocardial infarction and had a history of morbid obesity. In Imanaka 2013 and 2014, deaths occurred in 8% to 18% of patients in each group, with the most common cause of death being

disease progression (8% to 14% of patients in each group). In Imanaka 2014, the only other cause of death was gastrointestinal perforation in the tapentadol ER group. Other causes of death were not reported in Imanaka 2013. In Kress 2014, there were 19 deaths in patients who took tapentadol ER and three deaths in the morphine CR group (Table 47); note that the safety set in Kress 2014 in the titration phase included 338 in the tapentadol ER group and 158 in the morphine CR group. The most common cause of death or associated AE in Kress 2014 was malignant neoplasm, with other causes of death not reported.

Notable Adverse Events

In the three 15-week, DB trials in patients with OA pain or LBP, gastrointestinal AEs occurred in 42% to 44% of patients in the tapentadol ER groups compared with 62% to 68% of patients in the oxycodone CR groups (Table 42). Differences between the tapentadol ER and oxycodone CR groups were also observed, specifically for nausea (20% to 22% versus 35% to 38%), constipation (14% to 19% versus 27% to 37%), and vomiting (5% to 10% versus 18% to 26%). Somnolence occurred in 11% to 13% of patients in the tapentadol ER groups compared with 15% to 20% of patients in the oxycodone CR groups. Drug withdrawal syndrome and withdrawal syndrome were reported in no more than 1% of patients in each treatment group. Notable SAEs (constipation, vomiting, nausea, and drug withdrawal syndrome) occurred in less than 1% of patients in each group, while notable WDAEs (nausea, constipation, vomiting, and somnolence) were more common in the oxycodone CR groups than in the tapentadol groups (4% to 18% versus 0.9% to 5%).

In the one-year OL trial, gastrointestinal AEs occurred in 52% of patients on tapentadol ER and 64% of patients on oxycodone CR (Table 43). Notable AEs occurring in the tapentadol ER and oxycodone CR groups were constipation (23% and 39%), nausea (23% and 33%), vomiting (7% and 14%), somnolence (15% and 11%), withdrawal syndrome (2% and 0.9%), and drug withdrawal syndrome (1% and 0.4%). Each of the observed notable SAEs (constipation, nausea, somnolence, substance abuse, and drug withdrawal syndrome) occurred once in the tapentadol ER group. None of these SAEs were reported in the oxycodone/naloxone PR group. The most common notable WDAEs were nausea, constipation, vomiting, and somnolence (ranging from 2% to 3% of the tapentadol ER group and 4% to 12% of the oxycodone CR group), with drug withdrawal syndrome and withdrawal syndrome occurring in less than 1% of patients in each group.

In Baron 2016, gastrointestinal AEs occurred in 45% and 52% of patients in the tapentadol ER and oxycodone/naloxone PR groups (Table 44). Notable AEs occurring in at least 5% in a group were constipation (15% and 26% in the tapentadol ER and oxycodone/naloxone PR groups), nausea (22% and 18%), and vomiting (8% and 16%). There were no notable SAEs. Notable WDAEs occurring in at least 2% of patients in one group were nausea (8% and 9% in the tapentadol ER and oxycodone/naloxone PR groups), constipation (0.8% and 6%), and vomiting (6% and 9%).

In Imanaka 2013, gastrointestinal AEs occurred in 55% of the tapentadol ER group and 67% of the oxycodone CR group (Table 45). Reported notable AEs were constipation (30% for tapentadol ER and 37% for oxycodone CR), nausea (29% and 36%), vomiting (25% and 24%), and somnolence (17% and 21%). The only reported notable SAE was vomiting (2% in both groups) and the only reported notable WDAEs were nausea (0.6% and 4%) and vomiting (2% in both groups).

In Imanaka 2014, gastrointestinal AEs occurred in 38% of the tapentadol ER group and 54% of patients in the morphine SR group (Table 46). Reported notable AEs were

constipation (12% for tapentadol ER and 20% for morphine SR), nausea (14% and 14%), vomiting (6% and 26%), and somnolence (16% and 20%). The only reported notable SAE was vomiting (2% for tapentadol ER and 6% for morphine SR), and the only reported notable WDAE was nausea (0 and 8%).

In the titration phase of Kress 2014, notable AEs were more common in the morphine CR group compared with the tapentadol ER group, namely constipation (18% versus 14%), nausea (24% versus 12%), vomiting (16% versus 5%), and somnolence (6% versus 4%). Occurrences of notable AEs were less common overall in the maintenance phase and between-group differences were smaller (Table 48). The only notable SAE reported for the titration phase was vomiting, which occurred in one patient in the tapentadol ER group. Reasons for WDAE were not reported. The only notable SAE in the maintenance phase was withdrawal syndrome, which occurred in one patient who was randomized to placebo following treatment with tapentadol ER in the titration phase.

Table 42: Adverse Events — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 337	TAP N = 319	OXY N = 331	PL N = 319	TAP N = 316	OXY N = 328
Patients With ≥ 1 AE, n (%)	206 (61)	261 (76)	299 (87)	187 (56)	214 (67)	281 (85)	190 (60)	240 (76)	278 (85)
Most Common AEs,[a] n (%)									
Gastrointestinal disorders[b]	88 (26)	148 (43)	230 (67)	92 (27)	133 (42)	224 (68)	84 (26)	139 (44)	203 (62)
Constipation[b]	22 (7)	65 (19)	126 (37)	31 (9)	57 (18)	116 (35)	16 (5)	44 (14)	88 (27)
Nausea[b]	23 (7)	74 (22)	125 (37)	21 (6)	65 (20)	124 (38)	29 (9)	64 (20)	113 (35)
Vomiting[b]	11 (3)	18 (5)	61 (18)	13 (4)	33 (10)	86 (26)	5 (2)	29 (9)	63 (19)
Dry mouth	8 (2)	22 (6)	15 (4)	7 (2)	19 (6)	13 (4)	7 (2)	26 (8)	12 (4)
Diarrhea	20 (6)	16 (5)	17 (5)	15 (5)	16 (5)	26 (8)	23 (7)	19 (6)	8 (2)
Dyspepsia	3 (0.9)	3 (0.9)	1 (0.3)	8 (2)	7 (2)	7 (2)	8 (2)	16 (5)	6 (2)
Abdominal pain upper	3 (0.9)	7 (2)	3 (0.9)	20 (6)	13 (4)	15 (5)	4 (1)	1 (0.3)	5 (2)
Abdominal pain	9 (3)	6 (2)	4 (1)	7 (2)	4 (1)	18 (5)	0	4 (1)	6 (2)
Somnolence[b]	14 (4)	37 (11)	67 (20)	13 (4)	34 (11)	48 (15)	8 (3)	42 (13)	53 (16)
Arthralgia	17 (5)	10 (3)	6 (2)	8 (2)	12 (4)	7 (2)	4 (1)	9 (3)	4 (1)
Back pain	22 (7)	7 (2)	5 (2)	10 (3)	9 (3)	7 (2)	4 (1)	1 (0.3)	2 (0.6)
Dizziness	16 (5)	61 (18)	65 (19)	29 (9)	70 (22)	89 (27)	18 (6)	38 (12)	56 (17)
Fatigue	15 (5)	37 (11)	35 (10)	11 (3)	25 (8)	33 (10)	13 (4)	21 (7)	24 (7)
Headache	56 (17)	51 (15)	50 (15)	31 (9)	33 (10)	27 (8)	44 (14)	63 (20)	55 (17)
Hyperhidrosis	1 (0.3)	11 (3)	16 (5)	8 (2)	29 (9)	27 (8)	0	12 (4)	17 (5)
Insomnia	8 (2)	16 (5)	14 (4)	5 (2)	11 (3)	8 (2)	9 (3)	13 (4)	25 (8)
Pruritus	4 (1)	24 (7)	43 (13)	6 (2)	4 (1)	36 (11)	6 (2)	23 (7)	55 (17)
Vertigo	0	0	3 (0.9)	7 (2)	19 (6)	21 (6)	1 (0.3)	0	2 (0.6)
Other Notable AEs, n (%)									
Drug withdrawal syndrome	0	1 (0.3)	2 (0.6)	2 (0.6)	2 (0.6)	4 (1)	0	0	0
Withdrawal syndrome	0	0	3 (0.9)	0	0	1 (0.3)	0	0	0

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
Deaths, n (%)	0	0	1 (0.3)	0	0	0	0	0	0
Patients with ≥ 1 SAE, n (%)	6 (2)	4 (1)	10 (3)	4 (1)	2 (1)	13 (4)	3 (1)	7 (2)	11 (3)
Notable SAEs, n (%)									
Gastrointestinal disorders	1 (0.3)	0	1 (0.3)	0	1 (0.3)	4 (1)	1 (0.3)	1 (0.3)	1 (0.3)
Constipation	0	0	0	0	1 (0.3)	2 (0.6)	0	0	0
Nausea	0	0	0	0	0	1 (0.3)	0	0	0
Vomiting	0	0	0	0	1 (0.3)	0	0	0	0
Drug withdrawal syndrome	0	0	1 (0.3)	0	0	0	0	0	0
WDAEs, n (%)	22 (7)	66 (19)	146 (43)	27 (8)	60 (19)	140 (42)	14 (4)	53 (17)	104 (32)
Most Common Reasons,[a] n (%)									
Constipation[b]	0	6 (2)	32 (9)	2 (0.6)	13 (4)	21 (6)	0	4 (1)	14 (4)
Nausea[b]	3 (0.9)	14 (4)	49 (14)	4 (1)	15 (5)	58 (18)	1 (0.3)	5 (2)	37 (11)
Somnolence[b]	2 (0.6)	3 (0.9)	22 (6)	0	3 (0.9)	16 (5)	0	9 (3)	19 (6)
Vomiting[b]	2 (0.6)	4 (1)	29 (9)	5 (2)	17 (5)	51 (15)	0	8 (3)	23 (7)
Dizziness	2 (0.6)	18 (5)	32 (9)	6 (2)	15 (5)	38 (12)	0	7 (2)	21 (6)
Other Notable WDAEs, n (%)									
Withdrawal syndrome	0	0	2 (0.6)	0	0	0	0	0	0

AE = adverse event; OXY = oxycodone controlled-release; PL = placebo; SAE = serious adverse event; TAP = tapentadol extended-release; WDAE = withdrawal due to adverse event.

[a] Occurring in at least 5% of patients in at least one treatment group.

[b] Identified as a notable harm in the systematic review protocol.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 43: Adverse Events — Osteoarthritis and Low Back Pain (PAI-3007)

	PAI-3007 Wild 2010 Safety Set	
	TAP N = 894	**OXY N = 223**
Patients with ≥ 1 AE, n (%)	766 (86)	202 (91)
Most common AEs,[a] n (%)		
Gastrointestinal disorders[b]	465 (52)	143 (64)
Constipation	202 (23)	86 (39)
Nausea	162 (23)	74 (33)
Dry mouth	81 (9)	10 (5)
Diarrhea	71 (8)	12 (5)
Vomiting	63 (7)	30 (14)
Somnolence[b]	133 (15)	25 (11)
Dizziness	132 (15)	43 (19)
Headache	119 (13)	17 (8)
Insomnia	60 (7)	9 (4)
Fatigue	87 (10)	23 (10)
Pruritus	48 (5)	23 (10)

	PAI-3007 Wild 2010 Safety Set	
Nasopharyngitis	49 (6)	6 (3)
Sinusitis	33 (4)	13 (6)
Hyperhidrosis	40 (5)	8 (4)
Other Notable AEs, N (%)		
Withdrawal syndrome[b]	13 (2)	2 (0.9)
Drug withdrawal syndrome[b]	9 (1)	1 (0.4)
Deaths, n (%)	0	0
Patients with ≥ 1 SAE, n (%)	49 (6)	9 (4)
Notable SAEs, n (%)		
Gastrointestinal disorders	8 (0.9)	2 (0.9)
Constipation	1 (0.1)	0
Nausea	1 (0.1)	0
Somnolence	1 (0.1)	0
Substance abuse	1 (0.1)	0
Drug withdrawal syndrome	1 (0.1)	0
WDAEs, n (%)	198 (22)	82 (37)
Most Common Reasons,[c] n (%)		
Constipation[b]	14 (2)	16 (7)
Nausea[b]	30 (3)	27 (12)
Somnolence[b]	30 (3)	9 (4)
Vomiting[b]	23 (3)	15 (7)
Diarrhea	8 (0.9)	2 (0.9)
Dizziness	27 (3)	15 (7)
Dry mouth	6 (0.7)	2 (0.9)
Fatigue	16 (2)	10 (5)
Headache	7 (0.8)	2 (0.9)
Hyperhidrosis	2 (0.2)	2 (0.9)
Pruritus	5 (0.6)	6 (3)
Other Notable WDAEs, n (%)		
Drug withdrawal syndrome	1 (0.1)	1 (0.4)
Withdrawal syndrome	1 (0.1)	0

AE = adverse event; OXY = oxycodone; SAE = serious adverse event; TAP = tapentadol extended-release; WDAE = withdrawal due to adverse event.

[a] Occurring in at least 5% of patients in at least one treatment group.

[b] Identified as a notable harm in the systematic review protocol.

[c] Occurring in at least 2% of patients in at least one treatment group.

Source: Clinical study report for PAI-3007.[18]

Table 44: Adverse Events — Osteoarthritis and Low Back Pain (Baron 2016)

System Organ Class, *n* (%) Preferred Term, *n* (%)	Titration Period		Overall Treatment Period	
	Oxycodone/ Naloxone PR (*n* = 128)	Tapentadol PR (*n* = 130)	Oxycodone/ Naloxone PR (*n* = 128)	Tapentadol PR (*n* = 130)
Gastrointestinal disorders	64 (50.0)	53 (40.8)	66 (51.6)	58 (44.6)
Constipation	33 (25.8)	16 (12.3)*	33 (25.8)	20 (15.4)*,†
Nausea	23 (18.0)	28 (21.5)	23 (18.0)	29 (22.3)
Vomiting	21 (16.4)	9 (6.9)*	21 (16.4)	10 (7.7)*,‡
Dry mouth	7 (5.5)	8 (6.2)	7 (5.5)	9 (6.9)
Nervous system disorders	33 (25.8)	34 (26.2)	35 (27.3)	38 (29.2)
Dizziness	22 (17.2)	22 (16.9)	22 (17.2)	24 (18.5)
Headache	5 (3.9)	9 (6.9)	5 (3.9)	10 (7.7)
General disorders and administration site conditions	32 (25.0)	40 (30.8)	35 (27.3)	40 (30.8)
Fatigue	30 (23.4)	39 (30.0)	31 (24.2)	39 (30.0)
Skin and subcutaneous tissue disorders	22 (17.2)	14 (10.8)	24 (18.8)	16 (12.3)
Hyperhidrosis	10 (7.8)	7 (5.4)	13 (10.2)	8 (6.2)
Pruritus	11 (8.6)	7 (5.4)	11 (8.6)	8 (6.2)
Infections and infestations	6 (4.7)	4 (3.1)	11 (8.6)	19 (14.6)
Nasopharyngitis	2 (1.6)	2 (1.5)	5 (3.9)	8 (6.2)

PR = prolonged release.

Source: Table 2 of Effectiveness of Tapentadol Prolonged Release (PR) Compared with Oxycodone/Naloxone PR for the Management of Severe Chronic Low Back Pain with a Neuropathic Component: A Randomized, Controlled, Open-Label, Phase 3b/4 Study by Baron R, Likar R, Martin-Mola E, Blanco FJ, Kennes L, Müeller m, Falke D, and Steigerwald I[20] is licensed under https://creativecommons.org/licenses/by-nc-nd/4.0/.

Table 45: Adverse Events — Cancer Pain (Imanaka 2013)

System organ class, *n* (%) Preferred term, *n* (%)	Tapentadol ER (*n* = 168)	Oxycodone CR (*n* = 172)
Gastrointestinal disorders	93 (55.4)	116 (67.4)
Constipation	51 (30.4)	64 (37.2)
Nausea	48 (28.6)	61 (35.5)
Vomiting	42 (25.0)	41 (23.8)
Diarrhea	11 (6.5)	19 (11.0)
General disorders and administration site conditions	58 (34.5)	65 (37.8)
Disease progression	36 (21.4)	33 (19.2)
Pyrexia	11 (6.5)	14 (8.1)
Malaise	6 (3.6)	12 (7.0)
Nervous system disorders	45 (26.8)	55 (32.0)
Somnolence	29 (17.3)	36 (20.9)
Metabolism and nutrition disorders	32 (19.0)	34 (19.8)
Decreased appetite	23 (13.7)	24 (14.0)
Psychiatric disorders	28 (16.7)	18 (10.5)
Delirium	10 (6.0)	6 (3.5)
Insomnia	9 (5.4)	11 (6.4)
Blood and lymphatic system disorders	12 (7.1)	23 (13.4)
Anemia	4 (2.4)	12 (7.0)

CR = controlled release; ER = extended release.

Source: Permission obtained from the publisher to use Table 4 from Efficacy and safety of oral tapentadol extended release in Japanese and Korean patients with moderate to severe, chronic malignant tumor-related pain by Imanaka K, Tominaga Y, Etropolski M, van Hove I, Ohsaka M, Wanibe M, Hirose K, and Matsumura T. 2013.[21]

Table 46: Adverse Events — Cancer Pain (Imanaka 2014)

System organ class TEAE	Tapentadol ER ($n = 50$)	Morphine SR ($n = 50$)
General disorders and administration-site conditions	21 (42.0)	20 (40.0)
Disease progression	16 (32.0)	17 (34.0)
Malaise	4 (8.0)	0
Pyrexia	3 (6.0)	4 (8.0)
Nervous system disorders	18 (36.0)	17 (34.0)
Somnolence	8 (16.0)	10 (20.0)
Headache	1 (2.0)	4 (8.0)
Gastrointestinal disorders	19 (38.0)	27 (54.0)
Nausea	7 (14.0)	7 (14.0)
Constipation	6 (12.0)	10 (20.0)
Vomiting	3 (6.0)	13 (26.0)
Diarrhea	3 (6.0)	4 (8.0)
Blood and lymphatic system disorders	8 (16.0)	3 (6.0)
Anemia	4 (8.0)	1 (2.0)
Psychiatric disorders	5 (10.0)	1 (2.0)
Insomnia	4 (8.0)	0
Injury, poisoning, and procedural complications	4 (8.0)	4 (8.0)
Fall	4 (8.0)	1 (2.0)
Investigations	8 (16.0)	13 (26.0)
γ-Glutamyltransferase increased	1 (2.0)	4 (8.0)
Skin and subcutaneous tissue disorders	8 (16.0)	10 (20.0)
Pruritus	1 (2.0)	4 (8.0)

ER = extended release; SR = sustained release; TEAE = treatment-emergent adverse event.

Source: Table 5 of Ready Conversion of Patients with Well-Controlled, Moderate to Severe, Chronic Malignant Tumor-related Pain on Other Opioids to Tapentadol Extended-Release by Imanaka K, Tominaga Y, Etropolski M, Ohashi H, Hirose K, and Matsumura T[22] is licensed under https://link.springer.com/article/10.1007%2Fs40261-014-0204-3#copyrightInformation.

Table 47: Adverse Events — Cancer Pain (Kress 2014)

	Kress 2014 Safety Set Titration Phase	
	TAP N = 338	**MOR N = 158**
Patients with ≥ 1 AE, n (%)	169 (50)	101 (64)
Most common AEs,[a] n (%)		
Gastrointestinal disorders[b]	NR (30)	NR (47)
Constipation[b]	48 (14)	28 (18)
Nausea[b]	42 (12)	38 (24)
Vomiting[b]	17 (5)	25 (16)
Diarrhea	NR	NR
Dry mouth	4 (1)	10 (6)
Somnolence[b]	14 (4)	10 (6)
Anemia	NR	NR
Decreased appetite	NR	NR
Delirium	NR	NR
Disease progression	NR	NR
Dizziness	17 (5)	10 (6)
Fall	NR	NR
Fatigue	10 (3)	8 (5)
Gamma-glutamyltransferase increased	NR	NR
Headache	NR	NR
Insomnia	NR	NR
Malaise	NR	NR
Pruritus	NR	NR
Pyrexia	NR	NR
Deaths, n (%)	12 (4)[c]	3 (2)[c]
Disease progression	NR	NR
Patients with ≥ 1 SAE, n (%)	25 (7)	6 (4)
Most common SAEs,[d] n (%)		
Disease progression	NR	NR
Vomiting[b]	1 (0.3)	0
WDAEs, n (%)	29 (9)	11 (7)
Most common WDAEs,[d] n (%)		
Gastrointestinal disorders[b]	NR	NR
Nausea[b]	NR	NR
Vomiting[b]	NR	NR
Disease progression	NR	NR

AE = adverse event; NR = not reported; MOR = morphine controlled-release or sustained-release; SAE = serious adverse event; TAP = tapentadol extended-release; WDAE = withdrawal due to adverse event.

[a] Occurring in at least 5% of patients in at least one treatment group.

[b] Identified as a notable harm in the systematic review protocol.

[c] Includes deaths occurring up to 30 days after the last dose for patients who discontinued during the titration phase.

[d] Occurring in at least 2% of patients in at least one treatment group.

Source: Kress et al. 2014.[23]

Table 48: Adverse Events During Maintenance — Cancer Pain

	Kress 2014 Safety Set Maintenance Phase		
	PL N = 112	**TAP N = 106**	**MOR N = 109**
Patients with ≥ 1 AE, n (%)	63 (56)	66 (62)	68 (62)
Most common AEs,[a] n (%)			
Gastrointestinal disorders[b]	NR	NR	NR
Constipation[b]	13 (12)	12 (11)	12 (11)
Dry mouth	2 (2)	3 (3)	1 (0.9)
Nausea[b]	17 (15)	16 (15)	11 (10)
Vomiting[b]	3 (3)	8 (8)	6 (6)
Somnolence[b]	2 (2)	3 (3)	6 (6)
Decreased appetite	6 (5)	8 (8)	6 (6)
Fatigue	6 (5)	4 (4)	6 (6)
Hyperhidrosis	1 (0.9)	4 (4)	7 (6)
Deaths, n (%)	2 (2)	7 (7)	0
Patients with ≥ 1 SAE, n (%)	10 (9)	12 (11)	6 (6)
Notable SAEs, n (%)			
Withdrawal syndrome	1 (0.9)	0	0
WDAEs, n (%)	5 (5)	5 (5)	7 (6)

AE = adverse event; NR = not reported; MOR = morphine controlled-release; PL = placebo; SAE = serious adverse event; TAP = tapentadol extended-release; WDAE = withdrawal due to adverse event.

Note: Deaths during the titration period include deaths occurring up to 30 days after the last dose for patients who dropped out during the titration period.

[a] Occurring in at least 5% of patients in at least one treatment group.

[b] Identified as a notable harm in the systematic review protocol.

Source: Kress et al. 2014.[23]

Gastrointestinal Harms

For the overall PAC-SYM score and subscale scores, substantial proportions of patients were missing post-baseline assessments in each group of each of the PAI-3008, PAI-3009, and PAI-3011 studies (Table 49). Mean scores in the tapentadol ER and oxycodone CR groups increased (worsened) in most cases or remained the same, with the largest increases observed in the mean overall stool score. The LSM difference in overall PAC-SYM score change for tapentadol ER versus oxycodone CR was –0.3 (95% CI, –0.43 to –0.16) for Study PAI-3008, –0.3 (95% CI, –0.37 to –0.15) for Study PAI-3009, and –0.2 (95% CI, –0.32 to –0.03)) for Study PAI-3011. The differences were less than the MCIDs found (range of –0.52 to –0.63).

In Baron 2016, the PAC-SYM overall score LSMD and its 97.5% CI between tapentadol ER and oxycodone/naloxone PR was –0.07 and –0.26 to 0.12. Since the upper limit was less than the noninferiority margin of 0.7, tapentadol was declared to be noninferior to oxycodone/naloxone PR for this co-primary end point. The test for superiority of tapentadol ER over oxycodone/naloxone PR for the PAC-SYM score was not statistically significant.

The between-group difference in change in abdominal subscale score ranged from –0.3 to –0.2 in favour of tapentadol ER in studies PAI-3008 and PAI-3009, while no between-group difference was observed in Study PAI-3011. The between-group difference in change in

rectal subscale score ranged from –0.2 to –0.1 and the between-group difference in change in overall stool score ranged from –0.4 to –0.3, both in favour of tapentadol. MCIDs were not available for the subscales.

Table 49: Patient Assessment of Constipation Symptoms — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set		PAI-3009 Serrie 2017 Safety Set		PAI-3011 Buynak 2011 Safety Set		Baron 2016 PP Set	
	TAP N = 344	OXY N = 342	TAP N = 319	OXY N = 331	TAP N = 315	OXY N = 326	TAP N = 117	OXN N = 112
Mean overall PAC-SYM score	N = 192	N = 155	N = 235	N = 197	N = 168	N = 152		
Baseline (SD)	0.4 (0.5)	0.4 (0.6)	0.4 (0.6)	0.4 (0.5)	0.5 (0.7)	0.5 (0.6)	0.6 (0.6)	0.6 (0.7)
End of maintenance (SD)	0.5 (0.7)	0.8 (0.8)	0.6 (0.6)	0.8 (0.8)	0.6 (0.7)	0.7 (0.8)	0.7 (0.7)	0.7 (0.7)
LSM change (SE)	0.1	0.4	0.2	0.4	0.1	0.3	0.07 (0.06)	0.14 (0.06)
LSM difference, TAP vs. OXY (95% CI)	–0.3 (–0.43 to –0.16) *P* < 0.001		–0.3 (–0.37 to –0.15) *P* < 0.001		–0.2 (–0.32 to –0.03) *P* = 0.020		–0.07 (–0.26 to 0.12) ***P* < 0.001** ***P* = 0.26 for superiority**	
Mean Overall Abdominal Score								
Baseline (SD)	0.5 (0.7)	0.5 (0.8)	0.5 (0.7)	0.5 (0.7)	0.6 (0.8)	0.6 (0.8)	NR	NR
End of maintenance (SD)	0.5 (0.7)	0.8 (0.9)	0.6 (0.7)	0.8 (0.8)	0.7 (0.8)	0.6 (0.8)	NR	NR
LSM change	–0.1	0.3	0.1	0.3	0.1	0.1	NR	NR
LSM difference, TAP vs. OXY (95% CI)	–0.3 (–0.47 to –0.18) *P* < 0.001		–0.2 (–0.35 to –0.10) *P* < 0.001		0.0 (–0.16 to 0.17) *P* = 0.96		NR	
Mean Overall Rectal Score								
Baseline (SD)	0.3 (0.5)	0.3 (0.6)	0.3 (0.6)	0.2 (0.6)	0.3 (0.6)	0.3 (0.6)	NR	NR
End of maintenance (SD)	0.4 (0.7)	0.6 (0.7)	0.4 (0.6)	0.6 (0.9)	0.4 (0.6)	0.5 (0.7)	NR	NR
LSM change	0.1	0.3	0.1	0.3	0.1	0.2	NR	NR
LSM difference, TAP vs. OXY (95% CI)	–0.2 (–0.30 to –0.03) *P* = 0.018		–0.2 (–0.31 to –0.09) *P* < 0.001		–0.1 (–0.28 to –0.01) *P* = 0.038		NR	
Mean Overall Stool Score								
Baseline (SD)	0.5 (0.7)	0.5 (0.6)	0.5 (0.7)	0.4 (0.7)	0.5 (0.8)	0.5 (0.7)	NR	NR
End of maintenance (SD)	0.7 (0.9)	1.0 (1.0)	0.7 (0.8)	1.0 (1.0)	0.7 (0.8)	NR	NR	NR
LSM change	0.2	0.5	0.2	0.6	0.1	0.5	NR	NR
LSM difference, TAP vs. OXY (95% CI)	–0.4 (–0.54 to –0.19) *P* < 0.001		–0.3 (–0.48 to –0.19) *P* < 0.001		–0.3 (–0.51 to –0.14) *P* < 0.001		NR	

CI = confidence interval; LSM = least squares mean; NR = not reported; OXN = oxycodone/naloxone prolonged-release; OXY = oxycodone controlled-release; PAC-SYM = Patient Assessment of Constipation Symptoms; PP = per-protocol; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release.

Note: Baseline refers to the start of the titration phase in PAI-3008, PAI-3009, and PAI-3011 and the start of the maintenance phase in Baron 2016. Change is from baseline to the end of the maintenance phase (week 12).

Boldface font indicates a co-primary end point.

Treatment groups were compared using an analysis of covariance model adjusted for pooled site and baseline value.

In Baron 2016, missing values were imputed as the treatment group arithmetic mean value.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011[17]; Baron et al. 2016.[19,20]

Withdrawal Symptoms

Studies PAI-3008, PAI-3011, and PAI-3007 included the SOWS and COWS as outcomes, while Study-3009 only included the COWS. Limited data are available for withdrawal symptoms as patients who entered the OL extension trial were not administered the SOWS or COWS and the SOWS was only assessed in patients at English-speaking sites in the US. In addition, SOWS and COWS scores from patients who continued opioid therapy after the end of study treatment were not considered relevant by the clinical expert consulted for this review. Statistical testing was not conducted to compare the tapentadol ER and oxycodone CR groups.

Subjective Opiate Withdrawal Scale

In studies PAI-3008 and PAI-3011, LSM SOWS total scores ranged from 6.2 to 8.7 in the tapentadol ER groups and from 6.7 to 11.6 in the oxycodone CR groups over all the time points following treatment discontinuation (Table 50). In Study PAI-3007, SOWS total score ranged from 6.9 to 9.5 in the tapentadol ER group and from 7.5 to 10.1 in the oxycodone CR group. The difference in SOWS total score between tapentadol ER and oxycodone CR favoured tapentadol ER consistently in all three trials, except when assessed five days or more after treatment discontinuation in Study PAI-3011. However between-group differences for tapentadol ER versus oxycodone CR were not statistically compared.

Table 50: Subjective Opiate Withdrawal Scale — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3011 Buynak 2011 Safety Set			PAI-3007 Wild 2010 Safety Set	
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 317	TAP N = 315	OXY N = 326	TAP N = 894	OXY N = 223
SOWS Total Score by Number of Days Following Treatment Discontinuation								
2 days	N = 34	N = 32	N = 32	N = 29	N = 18	N = 25	N = 116	N = 27
Mean (SD)	NR	NR	NR	NR	NR	NR	9.5 (9.8)	12.3 (10.9)
LSM	4.7	6.9	7.3	6.3	6.6	10.4	NR	NR
LSMD vs. PL (95% CI)	NA	2.2 (–1.58 to 5.97) *P* = 0.25	2.5 (–1.53 to 6.55) *P* = 0.22	NA	0.4 (–5.54 to 6.26) *P* = 0.90	4.2 (–1.66 to 10.01) *P* = 0.15	NR	NR
3 days	N = 37	N = 42	N = 36	N = 31	N = 20	N = 29	N = 117	N = 30
Mean (SD)	NR	NR	NR	NR	NR	NR	9.2 (10.8)	10.1 (10.9)
LSM	5.3	7.5	11.6	7.4	7.4	9.9	NR	NR
LSMD vs. PL (95% CI)	NA	2.2 (–1.93 to 6.32) *P* = 0.29	6.3 (1.97 to 10.58) *P* = 0.005	NA	0.1 (–6.71 to 6.84) *P* = 0.99	2.6 (–4.44 to 9.58) *P* = 0.46	NR	NR
4 days	N = 38	N = 38	N = 42	N = 37	N = 22	N = 36	N = 121	N = 30
Mean (SD)	NR	NR	NR	NR	NR	NR	6.9 (9.1)	8.4 (10.6)
LSM	5.1	8.7	9.5	3.8	6.2	9.8	NR	NR
LSMD vs. PL (95% CI)	NA	3.6 (–0.40 to 7.62) *P* = 0.08	4.4 (0.57 to 8.27) *P* = 0.025	NA	2.3 (–4.63 to 9.27) *P* = 0.50	6.0 (–0.89 to 12.93) *P* = 0.09	NR	NR
≥ 5 days	N = 63	N = 75	N = 88	N = 50	N = 46	N = 74	N = 134	N = 40
Mean (SD)	NR	NR	NR	NR	NR	NR	6.9 (9.5)	7.5 (9.0)
LSM	5.7	6.6	10.7	5.0	7.1	6.7	NR	NR

	PAI-3008 Afilalo 2010 Safety Set			PAI-3011 Buynak 2011 Safety Set			PAI-3007 Wild 2010 Safety Set	
LSMD vs. PL (95% CI)	NA	0.9 (–2.06 to 3.93) *P* = 0.54	5.0 (2.10 to 7.93) *P* < 0.001	NA	2.1 (–2.06 to 6.19) *P* = 0.32	1.7 (–2.17 to 5.48) *P* = 0.39	NR	NR

CI = confidence interval; LSM= least squares mean; LSMD = least squares mean difference; NA = not applicable; NR = not reported; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; SOWS = subjective opiate withdrawal total score; TAP = tapentadol extended-release; vs. = versus.

Note: Assessments were performed only for patients enrolled at US English-speaking sites who did not enter the open-label extension study.

Results are only reported for patients who did not use opioid medications following treatment discontinuation.

Treatment groups were compared using an analysis of variance model adjusted for pooled site.

Source: Clinical study reports for PAI-3008,[15] PAI-3011,[17] and PAI-3007.[18]

Clinical Opiate Withdrawal Scale

All patients assessed with the COWS in studies PAI-3008, PAI-3009, PAI-3011, and PAI-3007 were categorized as having no withdrawal symptoms, mild symptoms, or moderate symptoms (Table 51 and Table 52).

In studies PAI-3008, PAI-3009, and PAI-3011, mean COWS total score was consistently higher in the tapentadol ER group two to four days after treatment discontinuation and consistently lower in the tapentadol ER group at least five days after treatment discontinuation compared with the oxycodone CR group (Table 51). Statistical testing was not conducted for comparisons between tapentadol ER and oxycodone CR.

In Study PAI-3007, mean COWS total score was lower in the tapentadol ER group than in the oxycodone CR group (mean [SD]: 2.8 [3.8] versus 3.6 [4.3]) two to four days after treatment discontinuation (Table 52). The mean COWs total score was the same in both groups at least five days after treatment discontinuation.

Table 51: Clinical Opiate Withdrawal Scale — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
	PL N = 337	TAP N = 344	OXY N = 342	PL N = 337	TAP N = 319	OXY N = 331	PL N = 319	TAP N = 318	OXY N = 328
2 to 4 Days After Discontinuation									
COWS score category, n (%)	N = 23	N = 35	N = 37	N = 139	N = 112	N = 102	N = 23	N = 15	N = 23
No withdrawal	23 (100)	29 (83)	32 (87)	133 (96)	90 (80)	81 (79)	21 (91)	12 (80)	20 (87)
Mild	0	6 (17)	5 (14)	6 (4)	16 (14)	19 (19)	2 (9)	2 (13)	3 (13)
Moderate	0	0	0	0	6 (5)	2 (2)	0	1 (7)	0
vs. PL[a]	NA	*P* = 0.038	*P* = 0.068	NA	*P* < 0.001	*P* < 0.001	NA	*P* = 0.22	*P* = 0.64
Mean COWS total score (SD)	1.0 (1.2)	2.5 (2.9)	1.6 (2.2)	0.9 (1.5)	2.8 (4.4)	1.7 (2.9)	1.2 (1.9)	3.0 (4.7)	1.7 (2.3)
LSMD (95% CI) vs. PL[b]	NA	1.9 (0.47 to 3.25) *P* = 0.01	1.3 (–0.03 to 2.67) *P* = 0.06	NA	1.8 (1.09 to 2.55) *P* < 0.001	1.7 (0.93 to 2.46) *P* < 0.001	NA	–0.0 (–2.35 to 2.28) *P* = 0.98	–0.2 (–2.20 to 1.73) *P* = 0.81
≥ 5 Days After Discontinuation									
COWS score category, n (%)	N = 59	N = 70	N = 84	N = 141	N = 135	N = 120	N = 35	N = 46	N = 67

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
No withdrawal	54 (92)	69 (99)	72 (86)	133 (94)	118 (87)	96 (80)	32 (91)	46 (100)	62 (93)
Mild	5 (9)	1 (1)	10 (12)	8 (6)	15 (11)	20 (17)	2 (6)	0	3 (4)
Moderate	0	0	2 (2)	0	2 (1)	4 (3)	1 (3)	0	2 (3)
vs. PL[a]	NA	*P* = 0.059	*P* = 0.20	NA	*P* = 0.030	*P* < 0.001	NA	*P* = 0.06	*P* = 0.91
Mean COWS total score (SD)	1.2 (1.8)	1.1 (1.4)	2.0 (3.0)	1.0 (2.0)	1.7 (2.9)	2.7 (3.8)	1.5 (2.4)	0.7 (1.2)	1.7 (3.1)
LSMD (95% CI) vs. PL[b]		0.1 (–0.78 to 0.98) *P* = 0.82	0.9 (0.08 to 1.81) *P* = 0.03	NA	0.8 (0.13 to 1.45) *P* = 0.02	1.7 (0.95 to 2.35) *P* < 0.001	NA	–1.1 (–2.34 to 0.05) *P* = 0.06	–0.2 (–1.37 to 0.88) *P* = 0.67

CI = confidence interval; COWS = Clinical Opiate Withdrawal Scale; LSMD = least squares mean difference; NA = not applicable; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; TAP = tapentadol extended-release; vs. = versus.

Note: Assessments were performed only for patients who did not enter the open-label extension study.

Results are only reported for patients who did not use opioid medications following treatment discontinuation.

[a] Cochran–Mantel–Haenszel test.

[b] Analysis of variance model adjusted for pooled site.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 52: Clinical Opiate Withdrawal Scale — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 Safety Set	
	TAP N = 894	**OXY N = 223**
2 to 4 Days After Discontinuation		
COWS score category, n (%)	N = 125	N = 22
None	97 (78)	16 (73)
Mild	22 (18)	5 (23)
Moderate	6 (5)	1 (5)
Mean COWS total score (SD)	2.8 (3.8)	3.6 (4.3)
≥ 5 Days After Discontinuation		
COWS score category, n (%)	N = 166	N = 50
None	146 (88)	42 (84)
Mild	18 (11)	7 (14)
Moderate	2 (1)	1 (2)
Mean COWS total score (SD)	1.9 (2.8)	1.9 (3.0)

COWS = Clinical Opiate Withdrawal Scale; OXY = oxycodone controlled-release; SD = standard deviation; TAP = tapentadol extended-release.

Note: For PAI-3007, patients who entered the open-label extension study were excluded.

Results are only reported for patients who did not use opioid medications following treatment discontinuation.

COWS total score withdrawal categories are none for 0 to 4, mild for 5 to 12, moderate for 13 to 24, moderately severe for 25 to 36, and severe for 37 to 48.

Source: Clinical study report for PAI-3007.[18]

Treatment Discontinuations

Treatment discontinuations were reported separately for the titration and maintenance phases in studies PAI-3008, PAI-3009, and PAI-3011 (Table 53). In each trial, the percentage of patients discontinuing during the titration phase was greater in the oxycodone CR group (range of 39% to 49%) compared with the tapentadol ER group (range of 23% to 26%). Treatment discontinuations during the maintenance phase occurred in similar percentages of patients in both groups (range of 18% to 20% for tapentadol ER and range of 15% to 19% for oxycodone CR). The most common reasons for discontinuing were AE, lack of efficacy, and patient choice. Between-group differences in the titration phase were mainly driven by AEs (11% to 12% for tapentadol ER and 27% to 36% for oxycodone CR). The distribution of the percentage of patients discontinuing over time due to lack of efficacy did not differ between the tapentadol ER and oxycodone CR groups in the three trials, according to the log-rank test.

In the subgroup summaries by prior opioid use status (Table 61 in Appendix 4), the only consistent difference between subgroups was in WDAEs in the oxycodone CR groups. WDAEs in the titration phase with oxycodone CR tended to be more common in patients with no prior opioid use than in patients with prior opioid use (28% to 40% versus 25% to 28%).

Table 53: Treatment Discontinuations — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010			PAI-3009 Serrie 2017			PAI-3011 Buynak 2011		
	PL	**TAP**	**OXY**	**PL**	**TAP**	**OXY**	**PL**	**TAP**	**OXY**
Received ≥ 1 dose of study drug, N	337	344	342	337	319	331	319	318	328
Discontinued treatment during titration, N (%[a])	83 (25)	80 (23)	169 (49)	58 (17)	77 (24)	148 (45)	108 (34)	83 (26)	129 (39)
Patient choice	17 (5)	17 (5)	24 (7)	12 (4)	19 (6)	34 (10)	18 (6)	19 (6)	19 (6)
Lost to follow-up	1 (0.3)	1 (0.3)	0	0	1 (0.3)	0	8 (3)	4 91)	2 (0.6)
Adverse event	13 (4)	37 (11)	124 (36)	16 (5)	38 (12)	103 (31)	8 (3)	34 (11)	87 (27)
Lack of efficacy	41 (12)	17 (5)	8 (2)	25 (7)	11 (3)	5 (2)	51 (16)	13 (4)	7 (2)
Non-compliance with study drug	4 (1)	1 (0.3)	8 (2)	0	4 (1)	3 (0.9)	12 (4)	9 (3)	9 (3)
Other	7 (2)	7 (2)	5 (2)	5 (2)	4 (1)	3 (0.9)	11 (3)	4 (1)	5 (2)
Discontinued treatment during maintenance, N (%[a])	47 (14)	67 (20)	52 (15)	58 (17)	56 (18)	62 (19)	50 (16)	63 (20)	57 (17)
Patient choice	11 (3)	21 (6)	11 (3)	14 (4)	16 (5)	15 (5)	12 (4)	13 (4)	17 (5)
Lost to follow-up	0	1 (0.3)	0	0	0	0	4 (1)	7 (2)	4 (1)
Adverse event	9 (3)	29 (8)	23 (7)	12 (4)	22 (7)	38 (12)	7 (2)	19 (6)	19 (6)
Death	0	0	1 (0.3)	0	0	0	0	0	0
Lack of efficacy	15 (5)	5 (2)	5 (2)	18 (5)	10 (3)	7 (2)	15 (5)	5 (2)	2 (0.6)
Non-compliance with study drug	4 (1)	5 (2)	4 (1)	5 (2)	3 (0.9)	1 (0.3)	8 (3)	12 (4)	5 (2)
Other	8 (2)	6 (2)	8 (2)	9 (3)	5 (2)	1 (0.3)	4 (1)	7 (2)	10 (3)

	PAI-3008 Afilalo 2010			PAI-3009 Serrie 2017			PAI-3011 Buynak 2011		
Time to Treatment Discontinuation Due to Lack of Efficacy[b]									
P value vs. PL	NA	*P* < 0.001	*P* < 0.001	NA	*P* = 0.027	*P* = 0.006	NA	*P* < 0.001	*P* < 0.001
P value, OXY vs. TAP	NA	*P* = 0.63		NA	*P* = 0.43		NA	*P* = 0.16	

OXY = oxycodone controlled-release; PL = placebo; TAP = tapentadol extended-release; vs. = versus.

[a] Denominator is the number of patients who received at least one dose of the study drug.

[b] Pairwise log-rank test.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

The percentages of patients discontinuing treatment was lower in the tapentadol ER group compared with the oxycodone CR group in Study PAI-3007 (54% versus 65%) and compared with the oxycodone/naloxone PR group in Baron 2016 (34% versus 63%, see Table 54. The most common reasons for treatment discontinuations were AE, lack or efficacy, and patient choice, and the differences in discontinuations was mainly driven by WDAEs (23% versus 37% for tapentadol ER versus oxycodone CR and 20% versus 41% for tapentadol ER versus oxycodone/naloxone PR).

Table 54: Treatment Discontinuations — Osteoarthritis and Low Back Pain

	PAI-3007 Wild 2010 (OA and LBP) Safety Set		Baron 2016 (LBP neuropathic) Safety Set	
	TAP N = 894	**OXY N = 223**	**TAP N = 130**	**OXN N = 128**
Discontinued treatment, N (%)	481 (54)	145 (65)	44 (34)	80 (63)
Patient choice	94 (11)	31 (14)	5 (4)	9 (7)
Lost to follow-up	40 (5)	7 (3)	1 (0.8)	0
Adverse event	203 (23)	82 (37)	26 (20)	52 (41)
Non-compliance with study drug	42 (5)	15 (7)	NR	NR
Resolution of pain	2 (0.2)	0	NR	NR
Lack of efficacy	72 (8)	7 (3)	8 (6)	17 (13)
Protocol violation	NR	NR	2 (2)	1 (0.8)
Technical problems	NR	NR	1 (0.8)	1 (0.8)
Other	28 (3)	3 (1)	1 (0.8)	0

LBP = low back pain; NR = not reported; OA = osteoarthritis; OXN = oxycodone/naloxone prolonged-release; OXY = oxycodone controlled-release; TAP = tapentadol extended-release.

Note: Patients in the oxycodone/naloxone PR group of Baron 2016 were allowed to switch to the tapentadol ER group during the trial.

Source: Clinical study report for PAI-3007,[18] Baron et al. 2016.[19,20]

Percentages of patients discontinuing in Imanaka 2013 and Imanaka 2014 were similar between the treatment groups (33% versus 29% for tapentadol ER versus oxycodone CR and 44% versus 42% for tapentadol ER versus morphine SR [see Table 55]). The most common reasons for discontinuation in Imanaka 2013 and Imanaka 2014 were progressive disease and AE. In the titration phase of Kress 2014, treatment discontinuations were also similar between treatment groups. However, a higher percentage of patients in the tapentadol ER group than in the morphine SR group failed to meet the response criteria for entering the maintenance phase (17% versus 13%). During the randomized withdrawal phase, discontinuations between the tapentadol ER and morphine SR groups were similar (16% and 15%).

Table 55: Treatment Discontinuations — Cancer Pain

	Imanaka 2013		Imanaka 2014		Kress 2014		
	TAP	OXY	TAP	MOR	PL	TAP	MOR
Received ≥ 1 dose of study drug, N	168	172	50	50	NA	338	158
Discontinued treatment during study, N (%[a])	55 (33)	49 (29)	22 (44)	21 (42)	NA	**Discontinued Treatment During Titration, N (%[a])**	
						59 (18)	29 (18)
Adverse event	12 (7)	14 (8)	5 (10)	8 (16)	NA	22 (7)	12 (8)
Progressive disease	11 (7)	15 (9)	9 (18)	11 (22)	NA	NR	NR
Withdrawal of consent	8 (5)	8 (5)	2 (4)	0	NA	NR	NR
Physician decision	8 (5)	1 (0.6)	1 (2)	1 (2)	NA	NR	NR
Protocol violation	5 (3)	5 (3)	NR	NR	NA	NR	NR
Lack of efficacy	4 (2)	1 (0.6)	3 (6)	1 (2)	NA	10 (3)	0
Non-compliance with study drug	1 (0.6)	4 (2)	NR	NR	NA	4 (1)	1 (0.6)
Patient choice	NR	NR	NR	NR	NA	16 (5)	13 (8)
Death	0	1 (0.6)	NR	NR	NA	4 (1)	2 (1)
Other	6 (4)	0	2 (4)	0	NA	3 (0.9)	1 (0.6)
Completed titration, N (%[a])	NA	NA	NA	NA	NA	279 (83)	129 (82)
Discontinued treatment following titration, N (%[a])	NA	NA	NA	NA	NA	61 (22[b])	20 (16[b])
Lack of efficacy (did not meet response criteria)	NA	NA	NA	NA	NA	48 (17)	17 (13)
Adverse event	NA	NA	NA	NA	NA	6 (2)	0
Patient choice	NA	NA	NA	NA	NA	2 (0.7)	2 (2)
Non-compliance with study drug	NA	NA	NA	NA	NA	0	1 (0.8)
Other	NA	NA	NA	NA	NA	5 (2)	0
Re-randomized for withdrawal,[c] N	NA	NA	NA	NA	112	106	109
Discontinued treatment during withdrawal, N (%[d])	NA	NA	NA	NA	17 (15)	17 (16)	16 (15)
Adverse event	NA	NA	NA	NA	6 (5)	5 (5)	6 (6)
Patient choice	NA	NA	NA	NA	3 (3)	6 (6)	7 (6)
Death	NA	NA	NA	NA	2 (2)	3 (3)	0
Lack of efficacy	NA	NA	NA	NA	4 (4)	2 (2)	2 (2)
Non-compliance with study drug	NA	NA	NA	NA	1 (0.9)	0	0
Resolution of pain	NA	NA	NA	NA	1 (0.9)	0	0
Other	NA	NA	NA	NA	0	1 (0.9)	1 (0.9)

NA = not applicable; MOR = morphine controlled-release or sustained-release; OXY = oxycodone controlled-release; PL = placebo; TAP = tapentadol extended-release.

[a] Denominator is the number of patients who received at least one dose of the study drug (safety set).

[b] Denominator is the number of patients who completed the titration period.

[c] Excludes one patient who did not take the study drug during the withdrawal phase.

[d] Denominator is the number of patients who were re-randomized for the withdrawal phase.

Source: Imanaka et al. 2013, Imanaka et al. 2014, Baron et al. 2016.

Discussion

Summary of Available Evidence

There were eight phase III RCTs, consisting of four RCTs comparing tapentadol ER with oxycodone CR in patients with OA pain and LBP, one RCT comparing tapentadol ER with oxycodone/naloxone PR in patients with severe LBP with a neuropathic component, two RCTs comparing tapentadol ER with morphine CR or SR in patients with cancer-related pain, and one RCT comparing tapentadol ER with oxycodone CR in patients with cancer-related pain.

There was an OL extension trial with 1,154 patients who had completed treatment with tapentadol ER (up to 15 weeks or one year), oxycodone CR (up to 15 weeks or one year), or placebo in four preceding RCTs (including studies PAI-3008, PAI-3011, and PAI-3007) and who were followed for up to one year.

Interpretation of Results

Efficacy

Pain Intensity

Tapentadol ER was shown to lower pain intensity by a greater amount than oxycodone CR in two DB, parallel-group RCTs in patients with knee OA pain (studies PAI-3008 and PAI-3009). However, the primary end point in these RCTs was change in pain intensity from baseline to the average of the 12-week maintenance phase between the tapentadol ER and placebo groups, and all other comparisons, including those between tapentadol ER and oxycodone CR, were not controlled for multiplicity. Therefore, these results are inconclusive. Also, the differences in change in pain intensity between tapentadol ER and oxycodone CR were less than the MCID. In a third trial of similar design but in patients with LBP (Study PAI-3011), no difference was found between the tapentadol ER and oxycodone CR groups. In all three trials, substantial proportions of early study discontinuations, which were unbalanced across treatment groups, comprised a significant source of potential bias that contributed a large amount of uncertainty to the results.

In relation to the missing data resulting from early treatment discontinuation, the direction of bias from the LOCF approach for handling missing data was unclear. The short titration period of three weeks may not reflect clinical practice where, according to the clinical expert consulted for this review, patients are titrated and monitored continuously and have a longer time to acclimatize or develop tolerance to side effects. It is possible that patients who discontinued the trials due to AEs had a unfavourable value for reduction in pain intensity carried forward, which could potentially have biased the results against oxycodone CR (and therefore in favour of tapentadol ER). The BOCF and WOCF approaches in the sensitivity analyses would likely have biased the results in favour of tapentadol ER as baseline pain intensity was measured after washout of analgesics.

The primary efficacy end point was not met in Study PAI-3009. Oxycodone CR was not found to be effective compared with placebo in this trial and assay sensitivity was not confirmed. Therefore, Study PAI-3009 does not support the claim of efficacy of tapentadol ER. Subgroup analyses were not informative due to methodological limitations.

Responder analysis of patients who achieved a 30% and a 50% reduction in pain intensity in studies PAI-3008, PAI-3009, and PAI-3011 was inconclusive as statistical testing was not done for tapentadol ER versus oxycodone CR and imbalances in discontinuations would likely have biased these results in favour of tapentadol ER.

In the one-year, OL, safety RCT in patients with knee or hip OA pain or LBP (Study PAI-3007), tapentadol ER and oxycodone/naloxone PR lowered pain intensity by similar amounts. Some of the limitations of this study include the substantial proportions of patients who discontinued the trial (54% and 65%), the lower proportion of WDAEs and greater treatment compliance in the tapentadol ER group, and the lack of blinding of the patients and investigators.

In a 12-week long, OL, phase IIIb/IV RCT in patients with severe LBP with a neuropathic component (Baron 2016), tapentadol ER was shown to lower pain intensity by a greater amount than oxycodone/naloxone PR, though the difference was not considered clinically relevant based on a range of MCIDs of 1.1 to 2.2. The results for pain intensity for pain radiating toward or into the leg as well as pain intensity in subsets of patients categorized by painDETECT score (positive and unclear) and patients with lumbar radiculopathy were also favourable for tapentadol ER, but these analyses were limited by the lack of stratification at randomization and lack of control for type I error. Neuropathic pain symptoms assessed on the NPSI also improved by a greater amount in the tapentadol ER group, though an MCID for this outcome was not identified by CDR. Limitations of the trial included the numbers of treatment discontinuations (34% and 63%), the greater proportions of WDAEs in the oxycodone/naloxone PR group, the lack of blinding of patients and investigators, and the asymmetrical trial design in which an escape arm (with tapentadol ER treatment) was available to patients on oxycodone/naloxone PR but not those on tapentadol ER. Despite being an adaptive trial, there were no descriptions of planned adaptations or interim analyses and the potential impact of these on the results could not be evaluated by CDR.

While the use of additional rescue analgesic therapy could have provided complementary information on the management of pain in the trial patients, the imbalance in treatment discontinuations may have confounded the results for this outcome. Use of rescue acetaminophen in the DB non-cancer pain trials was reported by less than 8% of patients in each group during the maintenance phase. Concomitant opioid analgesic use, though prohibited in the trials, occurred in 11% or less of each active treatment group in the DB trials and the one-year OL trial while concomitant non-opioid analgesic use was more common. There were no notable differences between the treatment groups and it is not clear if concomitant analgesic use may have biased the pain intensity results.

The trials in patient with cancer-related pain were of short duration (four to eight weeks) and were therefore limited in their ability to inform on the comparative efficacy of tapentadol ER with oxycodone CR and morphine SR and CR in chronic cancer-related pain. In one four-week, DB trial in patients with cancer pain (Imanaka 2013), tapentadol ER was shown to be noninferior to oxycodone CR in lowering pain intensity, and larger proportions of patients on tapentadol ER achieved at least a 30% or a 50% reduction in pain intensity. However, there were substantial discontinuations (33% and 29%), the noninferiority margin was not well justified, and there was no statistical testing for the responder analysis.

The eight-week, OL trial in patients switching from another opioid analgesic to either tapentadol ER or morphine SR for their cancer pain (Imanaka 2014) showed no change in pain intensity when switching from their previous opioid to the study treatment, regardless

of treatment group. However, there were no formal comparisons between the tapentadol ER and morphine SR groups, there were substantial discontinuations (44% and 42%), and rescue opioid analgesic use was not reported for the morphine SR group.

In the six-week, DB trial in patients with cancer pain, tapentadol ER was compared with morphine CR for the initial two-week titration phase. The results suggested that tapentadol ER was less effective than morphine CR in reducing pain intensity and was accompanied by more rescue opioid analgesic use. However, the main focus on the trial was the subsequent withdrawal phase comparing tapentadol ER with placebo. There was a substantial amount of discontinuations (18% during titration).

Overall, the numerous and significant methodological issues identified in all of the included trials limited the ability to draw conclusions regarding the comparative efficacy (either superiority or noninferiority) in lowering pain intensity of tapentadol ER versus oxycodone CR, oxycodone/naloxone PR, or morphine SR or CR. Common limitations were the substantial missing data from discontinuations, the imbalance in WDAEs between treatment groups, the short durations of the trials, lack of blinding in some trials, lack of control for type I error, and potential biases introduced by the approaches for imputing missing data.

The OL extension trial found that pain intensity remained stable throughout the maintenance phase following titration. However, all patients in the trial received tapentadol ER and there was no control group. There were also substantial proportions of patients (ranging from 24% to 49%) discontinuing early.

Other Efficacy Outcomes

The other efficacy outcomes were subject to the same limitations identified for the pain intensity outcomes, and statistical tests were not conducted for most comparisons between tapentadol ER and active comparators. There was no control for multiplicity in any of the trials for these outcome and between-group differences are not conclusive due to the risk of type I error.

The EQ-5D-3L and SF-36 (or SF-12) were used to assess HRQoL in the non-cancer pain trials. The EQ-5D-3L index score showed clinically meaningful differences in improvement between the treatment groups in three of the five trials. The EQ-5D VAS, SF-36 (or SF-12) MCS, and SF-36 (or SF-12) PCS showed consistently greater improvements in the tapentadol ER groups, though the differences were less than the MCIDs for the respective instruments. These results were potentially biased in favour of tapentadol ER in the one-year OL trial by the substantial amount of missing data in the absence of LOCF imputation. The WOMAC did not show any consistent or clinically meaningful differences between the tapentadol ER and oxycodone CR groups in OA-specific HRQoL.

There were greater proportions of patients reporting for the PGIC that they were very much or much improved since the start of the trial in the tapentadol ER groups than in the oxycodone CR or oxycodone/naloxone PR groups in four of the five trials in patients with non-cancer pain (and one trial in patients with cancer pain). However, differences between the response distributions were difficult to interpret without statistical testing.

There were no notable differences observed in sleep latency, time slept, number of awakenings, or overall sleep quality between the tapentadol ER and oxycodone CR groups in the non-cancer pain trials. There were consistently greater improvements in sleep outcomes in the Baron 2016 trial in the tapentadol ER group compared with the

oxycodone/naloxone PR group. However, information on the validity and MCID of the sleep questionnaire was not found.

Between-group differences in improvement in the HADS anxiety and depression scores in the OL trials in patients with severe LBP with a neuropathic component favoured tapentadol ER, but it is not known if they were clinically meaningful.

The patient input submission (Appendix 1) emphasized the negative impacts of pain on physical function and mental health and the ramifications of these. These impacts include impaired ability to stay active, perform daily and recreational activities, sleep, and/or remain employed; depression; isolation; and caregiver burden. As for expectations for analgesic therapy, patients indicated the importance of relieving pain, improving physical function, and improving QoL. Therefore, the efficacy outcomes assessed in the RCTs were outcomes important to patients living with chronic pain.

Harms

Adverse Events, Serious Adverse Events, Withdrawals Due to Adverse Events, and Mortalities

In all of the trials, the tapentadol ER group had lower proportions of patients experiencing at least one AE than the active comparator group. The most common AEs were constipation, nausea, vomiting, and somnolence in both non-cancer and cancer pain trials. Dizziness, headache, fatigue, pruritus, and hyperhidrosis were also common in the non-cancer pain trials while diarrhea, decreased appetite, and disease progression were also common in the cancer pain trials. There were lower proportions of patients on tapentadol ER than on oxycodone CR or oxycodone/naloxone PR who experienced AEs and WDAEs of constipation, nausea, and vomiting. AE profiles were similar in the tapentadol ER and morphine CR groups in one trial while the AEs of constipation and vomiting were more common in the morphine SR group than in the tapentadol ER group in another trial. Withdrawal symptoms and serotonin syndrome were also identified as notable harms in the review protocol, but serotonin syndrome was not reported in any of the trials and withdrawal syndrome or drug withdrawal syndrome were reported in no more than 2% of any one treatment group.

SAEs were reported in no more than 4% of patients in the short-term, non-cancer pain trials and in no more than 6% of patients in the one-year trial. SAEs occurred more frequently in the cancer pain trials, with disease progression and vomiting being the most common SAEs in the Imanaka 2013 and 2014 trials and neoplasm-related SAEs being the most common in Kress 2014.

There was one death in the non-cancer pain trials, which was a myocardial infarction in a patient with a history of morbid obesity. Although causes of deaths were not comprehensively reported in the cancer pain trials, disease progression or malignant neoplasm accounted for almost all of the deaths, with the only other cause of death reported being gastrointestinal perforation in one patient.

The AE profile in the OL extension trial was similar to that in the RCTs and no new safety signals were apparent.

Notable Harms

In the three DB non-cancer pain RCTs, the PAC-SYM results favoured tapentadol ER, though there were no clinically meaningful differences in the scores. Despite using LOCF,

there were still substantial amounts of missing PAC-SYM results. Also, LOCF analysis may have introduced bias in favour of tapentadol ER due to the imbalance in the missing data. Patients who discontinued in the RCTs may have in the clinical setting, possibly with a more flexible titration regimen, been encouraged instead to stay on therapy and acclimatize to the side effects. According to the clinical expert consulted for this review, side effects may become more tolerable over time. In the OL extension trial, the severity of constipation symptoms decreased with tapentadol ER for patients who had previously received oxycodone CR.

In the OL trial comparing tapentadol ER with oxycodone/naloxone PR, which is expected to cause less constipation than oxycodone CR, the PAC-SYM overall score was similar with both treatments.

Results from assessments of withdrawal symptoms suggested that clinician-assessed symptoms were absent, mild, or moderate following treatment discontinuation. Clinician- and patient-reported withdrawal symptoms tended to be less severe on average after discontinuing tapentadol ER than after discontinuing oxycodone CR, though the clinical meaningfulness of these differences was unclear and sample sizes were limited. According to the clinical expert consulted for this review, patients on opioid therapy for the treatment durations in the trials should be tapered off of the therapy. The lack of a taper regimen following treatment discontinuation may have exacerbated withdrawal symptoms. The clinical expert also indicated that longer durations of opioid therapy necessitate longer taper regimens, suggesting that withdrawal symptoms in the RCTs may not have reflected those experienced in clinical practice. There were no notable differences in the SOWS and COWS results between the 15-week trials and the one-year trial.

In the OL extension trial, the COWS and SOWS results were not notably different from those in the RCTs, though the SOWS was not reported in detail and COWS assessment were only available for about a third of the enrolled patients.

Treatment discontinuations followed the trends reported for study discontinuations. In the non-cancer pain trials, the most common reasons for discontinuing treatment were AEs, lack of efficacy, and patient choice, with AEs accounting for most of the imbalances between treatment groups. Treatment discontinuations in the cancer trials were similar between the treatment groups, with progressive disease and AEs most commonly reported. The time to discontinuation due to lack of efficacy curves did not differ between the tapentadol ER and oxycodone CR groups in the non-cancer pain trials.

In the patient input submission (Appendix 1), patients stressed the importance for new analgesic therapies to reduce gastrointestinal side effects (particularly severe constipation), withdrawal symptoms, and abuse potential. Therefore, the safety outcomes in the RCTs were relevant from the patient perspective.

Indirect Comparisons

Due to the lack of sufficient head-to-head trials on data for tapentadol and other opioids for chronic pain management, a search for indirect treatment comparisons was conducted to provide indirect evidence on the efficacy and safety of the available opioids in the study population. Two network meta-analyses (NMAs) were identified for this review. Different approaches and statistical models were adopted in the two NMAs; however, in both cases, a major limitation was the decision by the authors to combine all doses and formulations of a drug and treat them as a single intervention in the analysis. This is considered by the

CDR reviewer to be inappropriate from a clinical perspective. The Health Canada–approved product monograph for tapentadol ER states that tapentadol ER should only be used in patients for whom alternative treatment options are ineffective or not tolerated, or would otherwise be inadequate to provide sufficient management of pain (e.g., immediate-release opioids).[12] In addition the combination of immediate- and extended-release formulations, the NMAs provides no evidence specific to tapentadol ER, the study drug under review. Thus, the usefulness of the results of these analyses is compromised.

Potential Place in Therapy[2]

Nucynta ER has two mechanisms of action: it is a mu-opioid receptor agonist and norepinephrine reuptake inhibitor. The mu-opioid receptor agonist is similar to other opioids such as morphine or oxycodone, and it mediates the analgesic and adverse effects of morphine such as sedation, drowsiness, nausea, vomiting, and constipation. The colon contains a large population of mu-opioid receptors, and opioid-induced constipation can be a difficult clinical problem. In contrast to tapentadol, oxycodone is a mu-opioid receptor agonist that also may have kappa agonist activity, conferring an advantage to oxycodone for the management of visceral pain such as occurs in gallbladder and pancreatic disease.[10] Nucynta's mechanism of action is similar to that of tramadol, a weak mu-opioid receptor agonist and weak norepinephrine-serotonin reuptake inhibitor. The potency of tapentadol seems to be between tramadol and morphine.[11]. Aside from potency, another way to interpret weak opioids is by defining those that have a ceiling dose and would not be able to treat severe pain that requires higher doses.

Weak opioids available in Canada include codeine, tramadol, transdermal buprenorphine, and tapentadol. Codeine and tramadol have limited use in patients requiring daily long-term continuous opioid treatment due to their pharmacology; given that they require metabolism by the liver to active metabolites, their efficacy can be unpredictable. In contrast, tapentadol exerts its analgesic effects without a pharmacologically active metabolite.[12] Weak opioids are generally used for mild-to-moderate pain, or when it is unlikely that the patient will need to use high doses of opioids. Weak opioids are usually the first-line opioids for patients who are opioid naive. Similar to codeine and tramadol, Nucynta also has a ceiling dose. There is a perception that weak opioids are less addictive than strong opioids. Some physicians report only prescribing weak opioids for patients with chronic pain, and their rational is that they have concerns regarding potential long-term AEs, such as addiction and misuse.[13]

The fact that Nucynta has a ceiling dose can be seen as a disadvantage when the patient has severe pain and the dose of the opioid needs to be increased. In such cases, the prescriber will need to switch from Nucynta to a stronger opioid, such as hydromorphone, morphine, oxycodone, or fentanyl. In randomized trials, Nucynta has been compared with oxycodone ER, and this might suggest that Nucynta can be used as a strong opioid analgesic, even for cancer-related pain.[14]

The management of neuropathic pain usually requires polypharmacy with analgesics that have different mechanisms, and Nucynta offers the advantage of having a mu-opioid receptor agonist and norepinephrine reuptake inhibition mechanism in one single drug. The diagnosis of neuropathic pain is by history and physical exam. There is no need for special tests such as imaging or electrodiagnostic tests. Clinicians who are taught about neuropathic pain usually do not have difficulty identifying cases. However, for clinicians who

[2] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

do not have the knowledge or skills to make the diagnosis of neuropathic pain, there might be some confusion about which patients would benefit from Nucynta.

Nucynta may increase the risk of seizures compared with other opioids aside from tramadol. Like other opioids, it has the potential for misuse, diversion, addiction, may cause withdrawal symptoms if tapered abruptly, has risks of overdose and death, and may cause central nervous system depression and cognitive impairment that are important for driving.

Most drugs are metabolized by the cytochrome P450 system. The major pathway of metabolism of tapentadol is conjugation with glucuronic acid to produce glucoronides, which offers the large advantage of its metabolism not being mediated by the cytochrome P450 system. Therefore, there is very low risk of drug-to-drug interactions with Nucynta.

Conclusions

Based on the eight RCTs included in this systematic review, the comparative efficacy of tapentadol ER versus other long-acting opioids (oxycodone CR, oxycodone/naloxone PR, morphine SR or CR) is uncertain due to important limitations of the reviewed trials, including high and unbalanced study withdrawal and considerable imputation of missing data.

Based on the reviewed trials, tapentadol ER was associated with a lower frequency of treatment discontinuations than oxycodone CR or oxycodone/naloxone PR for non-cancer pain, most notably when the reason was AE. AEs in both the cancer and non-cancer pain trials, especially gastrointestinal AEs, were reported less frequently with tapentadol ER than with oxycodone CR, oxycodone/naloxone PR, morphine CR, or morphine SR. AEs and treatment discontinuations were likely not as affected by the numerous threats to internal validity as the other outcomes. However, it is unclear to what extent these benefits would be realized in clinical practice where patients may have more flexibility to adjust doses and clinicians can encourage their patients to acclimatize to the side effects of their treatment.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Six inputs were received from the following patient groups: The Chronic Pain Association of Canada (CPAC), the Canadian Arthritis Patient Alliance (CAPA), Arthritis Consumer Experts (ACE), the Halton/Hamilton Chronic Pain Support Group (HHCPSG), Action Atlantic Pain Society (AAPS), and Chronic Pain Support Group (CPSG) of the Sarnia-Lambton community in Ontario.

CPAC is an extensive patient group across Canada serving people with pain. Membership in CPAC is open largely to people with pain, their family members, and professionals. CAPA is a grassroots, patient-driven, independent, national education and advocacy organization with members and supporters across Canada. ACE is a national patient-led organization that provides science-based information, education, and support programs to people with all forms of arthritis. HHCPSG does not provide any medical services but supports persons living with chronic pain through monthly meetings. The meetings typically include a time for social networking, presentation on topics of interest and relevance to people in pain, and exercises and meditation. AAPS is a not-for-profit organization supporting approximately 20 chronic pain support groups with people in pain across the Atlantic provinces. The CPSG of the Sarnia-Lambton community allows people suffering from chronic pain to attend its monthly meeting.

CPAC received financial support from Purdue Pharma over the past two years with the amount ranging from $10,001 to $50,000. CAPA received financial support from Amgen, Janssen, Lilly, Manulife, Novartis, Pfizer (including Pfizer Hospira), Purdue, Roche, Sanofi, and UCB over the past two years. ACE declares no funding or grants-in-aid received from Paladin Labs Inc., the manufacturer of Nucynta. HHCPSG is funded exclusively by the Ontario Pain Foundation, which is an independent provincial not-for-profit organization that aims to advance education and awareness for the benefit of people living with debilitating pain. AAPS received funding from Canopy-Tweed, Merck, and Purdue Pharma over the past two years. No conflict of interest was disclosed in the preparation of the submission by the CPSG of Sarnia-Lambton. All patient groups indicated that their respective submission was not influenced by any outside party.

2. Condition-Related Information

The patient groups indicated that even though patients may not share the same illness, they share the same symptoms in most cases. Patients living with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis have indicated pain as a significant symptom of their disease. Pain has negative impacts on almost all aspect of the patient's day-to-day life, such as family relationships, social outings, workplace settings, and even the ability to carry out daily activities (i.e., getting out of bed, getting dressed, taking a bath, caring for children, making meals, doing household tasks while trying to remain employed). In addition, patients are sleep-deprived and the pain is associated with mental health issues. The patients feel depressed, isolated, and helpless and they lose hope. Suicide becomes more prevalent in this population compared with the general public. Patients' quality of life is greatly impaired. Some examples of quotes from patients are provided below:

"I lost my career several years ago due to inflammatory arthritis and chronic pain, and have difficulties with daily activities such as cooking, housework and recreational activities."

"Pain causes a person to withdraw."

Caregivers of patients living with pain have indicated that time management is a significant concern for them. When the patients are in pain, the caregivers have to help with many aspects of their daily activities. The caregivers also suffer from being helpless in trying to understand what it is like to live with pain.

3. Current Therapy-Related Information

The information was gathered through a call for patient input, interactions with patients suffering from pain (monthly meetings, survey, or emails), communications with professionals, discussions with scientific members of the patient groups, relationships with other patient groups, and ongoing research. The ACE submission noted that there were no respondents in their submission who met the manufacturer's requested reimbursement criteria (pain severe enough to required daily, continuous, long-term opioid treatment, and is opioid responsive, and for which alternative treatment options are inadequate), but four of them commented specifically on pain as a symptom of arthritis in previous submissions to CADTH.

Current non-pharmaceutical treatments for chronic pain include rehabilitative therapy, cognitive behavioural therapy, and surgery. CAPA identified the issues for patients in accessing non-pharmaceutical treatments such as physiotherapy and psychological treatment in the public system, and the significant costs associated with accessing such treatments privately. Based on patients' underling disease, they receive various pharmaceutical treatments, including opioids, disease-modifying antirheumatic drugs (i.e., methotrexate, phosphodiesterase 4 inhibitor, tumour necrosis factor inhibitor), and anesthetic agents (i.e., lidocaine infusions). One patient stated, "My pain is not well managed without my current medication regimen, and when pain management becomes poor, I get discouraged and have trouble staying active. This leads to more pain." According to CAPA, "For many patients opioids are an important part of their treatment regime. Despite being a contributing factor to the current opioid crisis, many patients use these drugs safely, appropriately and effectively." CPAC indicated that the use of opioids is often misunderstood, mainly because of the lack of understanding and education, as well as false information about the use of this medication.

Many patients who were taking medications to treat their pain experienced side effects of the drugs. Constipation is the most common side effect associated with the use of medication in the submissions by AAPS and HHCPSG. Other side effects were tiredness, drowsiness, nausea, stomach upset, kidney and liver damage, weight gain or loss, loss of appetite, anxiety, hyperactivity, feelings of being unwell, dizziness, headache, dry mouth, mood swings, brain fog, insomnia, irritability, and paranoia. One patient with psoriatic arthritis from the ACE group reported a serious side effect (demyelination of temporal lobes) related to her previous treatment with tumour necrosis factor inhibitor.

A number of challenges with respect to the current pain management options were identified by the patient groups. AAPS indicated that the majority of members in their support group are forced to live on very limited incomes, and many of them are jobless, retired earlier than expected, or unable to find gainful employment primarily due to the chronic pain. Medical training on pain management is very limited in Canada, and it is a challenge to find a doctor who will treat pain. In most cases, the patients have to wait for 18 to 24 months to see a pain specialist. Some patients stated the following problems: "some

drugs not on the drug benefit plan," "can't afford my medications," and "public transport does not go near my pharmacy."

4. Expectations About the Drug Being Reviewed

Of the patient groups provided the inputs, ACE, HHCPSG, and CPSG in Sarnia-Lambton indicated that none of the patients from their groups have experience using Nucynta to treat severe pain. It is unknown whether the patients in AAPS have received Nucynta therapy. The submission from CAPA included input from one patient who has received Nucynta. CPAC also included input from patients with experience in Nucynta, but the numbers of such patients were not specified.

One patient described their experience with Nucynta as follows: "Before starting Nucynta, I had tried several other opioids. All had intolerable side effects in terms of severe constipation. I had to take laxatives and other treatments for the constipation and this was a real problem for me. My doctor had told me that Nucynta has fewer G.I. side effects than other opioids and this has made the world of difference for me in terms of my ability to take this medication and stay active." The patient also highlighted the expense associated with accessing Nucynta through a private drug plan. The CPAC submission indicated that patients have experienced far fewer side effects with Nucynta than with some other medications, including non-opioid drugs. Although some patients have not tolerated Nucynta well, it seems to benefit most patients.

In general, all patient groups expect to see safer and more effective treatments for pain relief. They want new treatments that can relieve pain and improve function, are non-addictive and won't cause withdrawal, have long-lasting effects, have the fewest side effects, and can improve their quality of life. They also emphasize that the drug should be affordable and accessible for those who need it. CPAC suggests that Nucynta be approved, "as it has fewer gastrointestinal effects, has a lower abuse potential, and overall has a positive effect on a person with pain quality of life. Approving it also makes it more accessible to those covered under public sector insurance plans."

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE(R) ALL to present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 15, 2018
Alerts:	Weekly search updates until September 19, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
medall	Ovid database code; MEDLINE ALL; 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1. (tapentadol* or palexia* or nucynta* or r-331333 or H8A007M585 or 71204KII53 or bn-200 or bn200 or cg-5503 or cg5503 or hsdb-8309 or hsdb 8309).ti,ab,ot,hw,rn,nm,kf.
2. (cynta* or dol-proxyvon* or lopenta* or paincure* or tapal or tapcynta* or tapenta* or vorth-tp* or yantil*).ti,ab,ot,hw,nm,rn,kf.
3. or/1-2
4. 3 use medall
5. *tapentadol/
6. (tapentadol* or palexia* or nucynta* or H8A007M585 or 71204KII53 or bn-200 or bn200 or cg-5503 or cg5503 or hsdb-8309 or hsdb 8309).ti,ab,kw.
7. (cynta* or dol-proxyvon* or lopenta* or paincure* or tapal or tapcynta* or tapenta* or vorth-tp* or yantil*).ti,ab,kw.
8. or/5-7
9. 8 use oemezd
10. 4 or 9
11. conference abstract.pt. 12. 10 not 11 13. remove duplicates

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per Medline search.

Grey Literature

Dates for Search:	May 2018
Keywords:	Drug name
Limits:	None used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

Appendix 3: Excluded Studies

Table 56: Excluded Studies

Reference	Reason for Exclusion
Buynak R, Rappaport SA, Rod K, Arsenault P, Heisig F, Rauschkolb C, et al. Long-term Safety and Efficacy of Tapentadol Extended Release Following up to 2 Years of Treatment in Patients With Moderate to Severe, Chronic Pain: Results of an Open-label Extension Trial. Clin Ther. 2015 Nov 1;37(11):2420-38.	Extension study, will be summarized in a supplemental issue
Etropolski M, Kelly K, Okamoto A, Rauschkolb C. Comparable efficacy and superior gastrointestinal tolerability (nausea, vomiting, constipation) of tapentadol compared with oxycodone hydrochloride. Adv Ther. 2011 May;28(5):401-17.	Irrelevant intervention (tapentadol immediate release)
Moorthy S, Sudar CR, Surendher R, Manimekalai K. Comparison of the efficacy and safety of tramadol versus tapentadol in acute osteoarthritic knee pain: A randomized, controlled trial. Asian Journal of Pharmaceutical and Clinical Research. 2016;9(3):253-256.	Irrelevant intervention (tapentadol 50 mg twice daily, unspecified formulation)
Steigerwald I, Muller M, Davies A, Samper D, Sabatowski R, Baron R, et al. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: results of an open-label, phase 3b study. Curr Med Res Opin. 2012 Jun;28(6):911-36.	Not an RCT (single arm trial)
Ueberall MA, Mueller-Schwefe GH. Efficacy and tolerability balance of oxycodone/naloxone and tapentadol in chronic low back pain with a neuropathic component: a blinded end point analysis of randomly selected routine data from 12-week prospective open-label observations. J Pain Res. 2016;9:1001-1020.	Not an RCT (retrospective study)

Appendix 4: Detailed Outcome Data

Table 57: Sensitivity Analyses for Change in Pain Intensity From Baseline — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010			PAI-3009 Serrie 2017			PAI-3011 Buynak 2011		
	PL	TAP	OXY	PL	TAP	OXY	PL	TAP	OXY
NRS-11 pain intensity score, ITT set, BOCF	**N = 336**	**N = 344**	**N = 342**	**N = 336**	**N = 319**	**N = 331**	**N = 316**	**N = 312**	**N = 323**
Maintenance week 12									
LSM change	–1.7	–2.0	–1.2	–1.7	–1.7	–1.1	–1.3	–1.8	–1.5
LSMD vs. PL (SE)[a]	NA	–0.3 (0.2) *P* = 0.084	0.5 (0.2) *P* = 0.002	NA	0.0 (0.2) *P* = 0.95	0.6 (0.2) *P* < 0.001	NA	–0.6 (0.2) *P* = 0.002	–0.2 (0.2) *P* = 0.22
LSMD, TAP vs. OXY (SE)[a]	NA	–0.8 (0.2) *P* < 0.001		NA	–0.6 (0.2) *P* < 0.001		NA	–0.3 (0.2) *P* = 0.051	
Overall maintenance									
LSM change (SE)	–2.0	–2.3	–1.5	–1.8	–1.8	–1.2	–1.5	–2.1	–1.9
LSMD vs. PL (SE)[a]	NA	–0.3 (0.2) *P* = 0.05	0.5 (0.2) *P* = 0.001	NA	0.0 (0.2) *P* = 0.93	0.6 (0.2) *P* < 0.001	NA	–0.7 (0.2) *P* < 0.001	–0.4 (0.2) *P* = 0.023
LSMD, TAP vs. OXY (SE)[a]	NA	–0.9 (0.2) *P* < 0.001		NA	–0.6 (0.2) *P* < 0.001		NA	–0.3 (0.3) *P* = 0.11	
NRS-11 pain intensity score, PP set, LOCF	**N = 284**	**N = 298**	**N = 270**	**N = 296**	**N = 292**	**N = 288**	**N = 241**	**N = 249**	**N = 255**
Maintenance week 12									
LSM change	–2.3	–3.0	–2.7	–2.5	–2.7	–2.3	–2.2	–3.0	–3.0
LSMD vs. PL (SE)[a]	NA	–0.8 (0.2) *P* < 0.001	–0.4 (0.2) *P* = 0.061	NA	–0.2 (0.2) *P* = 0.41	0.2 (0.2) *P* = 0.31	NA	–0.9 (0.2) *P* < 0.001	–0.8 (0.2) *P* < 0.001
LSMD, TAP vs. OXY (SE)[a]	NA	–0.4 (0.2) *P* = 0.052		NA	–0.3 (0.2) *P* = 0.068		NA	–0.1 (0.2) *P* = 0.71	
Overall maintenance									
LSM change	–2.3	–3.0	–2.7	–2.3	–2.5	–2.2	–2.2	–3.0	–3.0
LSMD vs. PL (SE)[a]	NA	–0.7 (0.2) *P* < 0.001	–0.4 (0.2) *P* = 0.034	NA	–0.2 (0.2) *P* = 0.36	0.1 (0.2) *P* = 0.47	NA	–0.8 (0.2) *P* < 0.001	–0.8 (0.3) *P* < 0.001
LSMD, TAP vs. OXY (SE)[a]	NA	–0.3 (0.2) *P* = 0.092		NA	–0.3 (0.2) *P* = 0.10		NA	–0.0 (0.2) *P* = 0.98	

BOCF = baseline observation carried forward; ITT = intention-to-treat; LOCF = last observation carried forward; LSM = least squares mean; LSMD = least squares mean difference; NA = not applicable; NRS-11 = 11-point numeric rating scale; OXY = oxycodone controlled-release; PL = placebo; PP = per-protocol set; SE = standard error; TAP = tapentadol extended-release; vs. = versus.

[a] Analysis of covariance model adjusted for pooled site and baseline pain intensity.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 58: Change in Pain Intensity From Baseline by Prior Opioid Use — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 336	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
NRS-11 pain intensity score, no prior opioid use	N = 223	N = 235	N = 234	N = 281	N = 267	N = 284	N = 144	N = 136	N = 161
Mean baseline score (SD)	7.1 (1.3)	7.2 (1.4)	7.2 (1.3)	7.3 (1.1)	7.2 (1.1)	7.2 (1.1)	7.4 (1.3)	7.4 (1.4)	7.4 (1.2)
Maintenance week 12									
LSM change (SE)	–2.4	–3.0	–2.6	–2.3	–2.7	–2.0	–2.1	–3.2	–2.9
LSMD vs. PL (SE)[a]	NA	–0.7 (0.2) *P* = 0.003	–0.3 (0.2) *P* = 0.24	NA	–0.4 (0.2) *P* = 0.055	0.3 (0.2) *P* = 0.12	NA	–1.1 (0.3) *P* < 0.001	–0.8 (0.3) *P* = 0.008
LSMD, TAP vs. OXY (SE)[a]	NA	–0.4 (0.2) *P* = 0.067		NA	–0.7 (0.2) *P* < 0.001		NA	–0.3 (0.3) *P* = 0.35	
Overall maintenance									
LSM change (SE)	–2.3	–3.0	–2.6	–2.2	–2.5	–2.0	–2.2	–3.1	–2.9
LSMD vs. PL (SE)[a]	NA	–0.7 (0.2) *P* = 0.001	–0.3 (0.2) *P* = 0.14	NA	–0.4 (0.2) *P* = 0.04	0.2 (0.2) *P* = 0.21	NA	–1.0 (0.3) *P* = 0.001	–0.7 (0.3) *P* = 0.017
LSMD, TAP vs. OXY (SE)[a]	NA	–0.4 (0.2) *P* = 0.082		NA	–0.6 (0.2) *P* < 0.001		NA	–0.3 (0.3) *P* = 0.33	
NRS-11 pain intensity score, prior opioid use	N = 113	N = 109	N = 108	N = 55	N = 52	N = 47	N = 172	N = 176	N = 162
Mean baseline score (SD)	7.4 (1.3)	7.8 (1.2)	7.4 (1.4)	7.3 (1.3)	7.5 (1.2)	7.4 (1.1)	7.7 (1.3)	7.6 (1.3)	7.7 (1.2)
Maintenance week 12									
LSM change (SE)	–2.1	–3.0	–2.7	–2.5	–1.7	–2.5	–2.0	–2.7	–2.9
LSMD vs. PL (SE)[a]	NA	–0.9 (0.3) *P* = 0.012	–0.6 (0.3) *P* = 0.10	NA	0.8 (0.5) *P* = 0.12	–0.0 (0.5) *P* = 0.95	NA	–0.7 (0.3) *P* < 0.009	–1.0 (0.3) *P* < 0.001
LSMD, TAP vs. OXY (SE)[a]	NA	–0.3 (0.4) *P* = 0.39		NA	0.8 (0.5) *P* = 0.096		NA	0.3 (0.3) *P* = 0.32	
Overall maintenance									
LSM change (SE)	–2.1	–2.9	–2.7	–2.4	–1.6	–2.4	–2.0	–2.6	–3.0
LSMD vs. PL (SE)[a]	NA	–0.8 (0.3) *P* = 0.014	–0.5 (0.3) *P* = 0.10	NA	0.8 (0.5) *P* = 0.11	–0.0 (0.5) *P* = 0.94	NA	–0.6 (0.2) *P* = 0.015	–1.0 (0.3) *P* < 0.001
LSMD, TAP vs. OXY (SE)[a]	NA	–0.3 (0.3) *P* = 0.42		NA	0.8 (0.5) *P* = 0.082		NA	0.4 (0.3) *P* = 0.11	

ITT = intention-to-treat; LSM = least squares mean; LSMD = least squares mean difference; NA = not applicable; NRS-11 = 11-point numeric rating scale; OXY = oxycodone controlled-release; PL = placebo; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus.

Note: Last observation carried forward was used for imputing missing value in the main analysis.

Prior opioid use is defined as taking opioid analgesics during the three months prior to the screening visit.

[a] Analysis of covariance model adjusted for pooled site and baseline pain intensity.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 59: Change in Pain Intensity From Baseline by Baseline Pain Intensity Category — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 ITT Set			PAI-3009 Serrie 2017 ITT Set			PAI-3011 Buynak 2011 ITT Set		
	PL N = 336	TAP N = 344	OXY N = 342	PL N = 336	TAP N = 319	OXY N = 331	PL N = 316	TAP N = 312	OXY N = 323
NRS-11 pain intensity score, moderate	N = 61	N = 49	N = 58	N = 42	N = 35	N = 32	N = 40	N = 35	N = 33
Maintenance week 12									
LSM change (SE)	–1.4	–2.1	–1.9	–1.6	–2.3	–1.1	–0.6	–2.4	–2.0
LSMD vs. PL (SE)[a]	NA	–0.6 (0.5) *P* = 0.18	–0.5 (0.4) *P* = 0.24	NA	–0.7 (0.5) *P* = 0.19	0.4 (0.6) *P* = 0.42	NA	–1.8 (0.7) *P* = 0.009	–1.5 (0.6) *P* = 0.015
LSMD, TAP vs. OXY (SE)[a]	NA	–0.2 (0.5) *P* = 0.75		NA	–1.1 (0.5) *P* = 0.03		NA	–0.3 (0.7) *P* = 0.62	
Overall maintenance									
LSM change (SE)	–1.6	–1.9	–2.0	–1.4	–2.1	–1.1	–0.9	–2.3	–2.0
LSMD vs. PL (SE)[a]	NA	–0.3 (0.5) *P* = 0.46	–0.4 (0.4) *P* = 0.27	NA	–0.7 (0.5) *P* = 0.12	0.3 (0.5) *P* = 0.56	NA	–1.4 (0.6) *P* = 0.028	–1.2 (0.6) *P* = 0.039
LSMD, TAP vs. OXY (SE)[a]	NA	–0.1 (0.5) *P* = 0.82		NA	–1.0 (0.5) *P* 0.031		NA	–0.3 (0.7) *P* = 0.70	
NRS-11 pain intensity score, severe	N = 275	N = 293	N = 284	N = 294	N = 284	N = 299	N = 276	N = 277	N = 290
Maintenance week 12									
LSM change (SE)	–2.4	–3.0	–2.7	–2.5	–2.7	–2.3	–2.2	–3.1	–3.0
LSMD vs. PL (SE)[a]	NA	–0.6 (0.2) *P* = 0.002	–0.3 (0.2) *P* = 0.089	NA	–0.2 (0.2) *P* = 0.23	0.1 (0.2) *P* = 0.52	NA	–0.8 (0.2) *P* < 0.001	–0.8 (2) *P* < 0.001
LSMD, TAP vs. OXY (SE)[a]	NA	–0.3 (0.2) *P* = 0.15		NA	–0.4 (0.2) *P* = 0.064		NA	–0.0 (0.2) *P* = 0.94	
Overall maintenance									
LSM change (SE)	–2.4	–3.0	–2.7	–2.3	–2.5	–2.2	–2.3	–3.0	–3.0
LSMD vs. PL (SE)[a]	NA	–0.6 (0.2) *P* < 0.001	–0.4 (0.2) *P* = 0.057	NA	–0.2 (0.2) *P* = 0.18	0.1 (0.2) *P* = 0.74	NA	–0.7 (0.2) *P* < 0.001	–0.8 (0.2) *P* < 0.001
LSMD, TAP vs. OXY (SE)[a]	NA	–0.3 (0.2) *P* = 0.15		NA	–0.3 (0.2) *P* = 0.096		NA	0.1 (0.2) *P* = 0.67	

ITT = intention-to-treat; LSM = least squares mean; LSMD = least squares mean difference; NA = not applicable; NRS-11 = 11-point numeric rating scale; OXY = oxycodone controlled-release; PL = placebo; SE = standard error; TAP = tapentadol extended-release; vs. = versus.

Note: Last observation carried forward was used for imputing missing values.

[a] Analysis of covariance model adjusted for pooled site and baseline pain intensity.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Table 60: Change in Pain Intensity From Baseline by Pain Subsets — Back Pain with Neuropathic Component

	Baron 2016 Full Analysis Set	
	TAP	**OXN**
NRS-11 pain intensity score, painDETECT positive	N = 96	N = 96
Mean baseline score (SD)	7.7 (1.1)	7.7 (0.9)
End of maintenance	3.9 (2.7)	4.7 (2.6)
LSM change (SE)	–4.0 (0.29)	–3.0 (0.30)
LSMD, TAP vs. OXN (97.5% CI)[a]	–1.0 (–1.9 to –0.1) *P* < 0.001 for noninferiority *P* = 0.007 for superiority	
NRS-11 pain intensity score, painDETECT unclear	N = 33	N = 27
Mean baseline score (SD)	7.5 (1.0)	7.2 (1.0)
End of maintenance	4.1 (2.7)	4.9 (1.9)
Mean change (SD)	–3.3 (0.54)	–2.1 (0.56)
LSMD, TAP vs. OXN (97.5% CI)[a]	–1.2 (–2.9 to 0.6) *P* = 0.001 for noninferiority *P* = 0.066 for superiority	
NRS-11 pain intensity score, lumbar radiculopathy	N = 76	N = 73
Mean baseline score (SD)	7.5 (1.0)	7.6 (0.9)
End of maintenance	3.7 (2.5)	4.8 (2.4)
Mean change (SD)	–3.5 (0.34)	–2.1 (0.35)
LSMD, TAP vs. OXN (97.5% CI)[a]	–1.3 (–2.3 to –0.4) P < 0.001 for noninferiority *P* = 0.001 for superiority	

CI = confidence interval; LSM = least squares mean; LSMD = least squares mean difference; NRS-11 = 11-point numeric rating scale; OXN = oxycodone/naloxone prolonged-release; SD = standard deviation; SE = standard error; TAP = tapentadol extended-release; vs. = versus.

Note: Last observation carried forward was used for imputing missing values.

At each time point, patients rated their pain intensity during the past three days on the NRS-11.

[a] Analysis of covariance model adjusted for pooled site and baseline value.

Source: Baron et al. 2016.[19,20]

Table 61: Treatment Discontinuations by Prior Opioid Use — Osteoarthritis and Low Back Pain

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
	PL	**TAP**	**OXY**	**PL**	**TAP**	**OXY**	**PL**	**TAP**	**OXY**
No prior opioid use	N = 223	N = 235	N = 234	N = 281	N = 267	N = 284	N = 147	N = 140	N = 163
Completed treatment period, n (%)	145 (65)	137 (58)	73 (31)	186 (66)	157 (59)	100 (35)	84 (57)	85 (61)	61 (37)
Discontinued treatment during titration, n (%[a])	48 (22)	63 (27)	121 (52)	47 (17)	61 (23)	131 (46)	33 (22)	27 (19)	75 (46)
Patient choice	6 (3)	13 (5)	16 (7)	11 (4)	16 (6)	31 (11)	7 (5)	10 (7)	14 (9)
Lost to follow-up	NR	NR	NR	NR	NR	NR	5 (3)	0	0
Adverse event	9 (4)	31 (13)	94 (40)	14 (5)	30 (11)	91 (32)	2 (1)	10 (7)	46 (28)

	PAI-3008 Afilalo 2010 Safety Set			PAI-3009 Serrie 2017 Safety Set			PAI-3011 Buynak 2011 Safety Set		
	PL	TAP	OXY	PL	TAP	OXY	PL	TAP	OXY
Lack of efficacy	27 (12)	13 (6)	3 (1)	20 (7)	7 (3)	4 (1)	11 (8)	3 (2)	3 (2)
Non-compliance with study drug	3 (1)	0	3 (1)	0	4 (2)	2 (0.7)	6 (4)	3 (2)	7 (4)
Other	3 (1)	6 (3)	5 (2)	2 (0.7)	4 (2)	3 (1)	2 (1)	1 (0.7)	5 (3)
Discontinued treatment during maintenance, N (%[a])	30 (13.5)	35 (15)	40 (17)	48 (17)	49 (18)	53 (19)	30 (20)	28 (20)	27 (17)
Patient choice	7 (3)	13 (6)	10 (4)	14 (5)	16 (6)	15 (5)	7 (5)	7 (5)	11 (7)
Lost to follow-up							3 (2)	3 (2)	0
Adverse event	7 (3)	15 (6)	19 (8)	9 (3)	20 (8)	30 (11)	5 (3)	9 (6)	9 (6)
Lack of efficacy	10 (5)	1 (0.4)	3 (1)	13 (5)	7 (3)	6 (2)	7 (5)	1 (0.7)	0
Non-compliance with study drug	4 (2)	3 (1)	3 (1)	5 (2)	2 (0.7)	1 (0.4)	7 (5)	6 (4)	3 (2)
Other	2 (0.9)	3 (1)	5 (2)	7 (3)	4 (2)	1 (0.4)	1 (0.7)	2 (1)	4 (3)
Prior opioid use	N = 114	N = 109	N = 108	N = 56	N = 52	N = 47	N = 172	N = 178	N = 165
Completed treatment period, n (%)	62 (54)	60 (55)	48 (44)	35 (63)	29 (56)	21 (45)	77 (45)	87 (49)	81 (49)
Discontinued treatment during titration, n (%[a])	35 (31)	17 (16)	48 (44)	11 (20)	16 (31)	17 (36)	75 (44)	56 (32)	54 (33)
Patient choice	11 (10)	4 (4)	8 (7)	1 (2)	3 (6)	3 (6)	11 (6)	9 (5)	5 (3)
Lost to follow-up	1 (0.9)	1 (0.9)	0	0	1 (2)	0	3 (2)	4 (2)	2 (1)
Adverse event	4 (4)	6 (6)	30 (28)	2 (4)	8 (15)	12 (26)	6 (4)	24 (14)	41 (25)
Lack of efficacy	14 (12)	4 (4)	5 (5)	5 (9)	4 (8)	1 (2)	40 (23)	10 (6)	4 (2)
Non-compliance with study drug	1 (0.9)	1 (0.9)	5 (5)	0	0	1 (2)	6 (4)	6 (3)	2 (1)
Other	4 (4)	1 (0.9)	0	3 (5)	0	0	9 (5)	3 (2)	0
Discontinued treatment during maintenance, N (%[a])	17 (15)	32 (29)	12 (11)	10 (18)	7 (14)	9 (19)	20 (12)	35 (20)	30 (18)
Patient choice	4 (4)	8 (7)	1 (0.9)	NR	NR	NR	5 (3)	6 (3)	6 (4)
Lost to follow-up	0	1 (0.9)	0	NR	NR	NR	1 (0.6)	4 (2)	4 (2)
Adverse event	2 (2)	14 (13)	4 (4)	3 (5)	2 (4)	8 (17)	2 (1)	10 (6)	10 (6)
Death	0	0	1 (0.9)	NR	NR	NR	NR	NR	NR
Lack of efficacy	5 (4)	4 (4)	2 (2)	5 (9)	3 (6)	1 (2)	8 (5)	4 (2)	2 (1)
Non-compliance with study drug	0	2 (2)	1 (0.9)	0	1 (2)	0	1 (0.6)	6 (3)	2 (1)
Other	6 (5)	3 (3)	3 (3)	2 (4)	1 (2)	0	3 (2)	5 (3)	6 (4)

NR = not reported; OXY = oxycodone controlled-release; PL = placebo; TAP = tapentadol extended-release.

Note: Prior opioid use is defined as taking opioid analgesics during the three months prior to the screening visit.

Source: Clinical study reports for PAI-3008,[15] PAI-3009,[16] and PAI-3011.[17]

Appendix 5: Validity of Outcome Measures

Aim

The purpose of this section is to provide an overview of the characteristics, validity, and clinically important differences of the scales measured in trials included in the CADTH Common Drug Review (CDR) systematic review. These include:

- pain intensity on an 11-point numerical rating scale (NRS)
- Brief Pain Inventory (BPI)
- Western Ontario and McMaster Questionnaire (WOMAC)
- sleep questionnaire or sleep diary
- Short Form – 36 items (SF-36)
- EuroQol 5-Dimensions questionnaire (EQ-5D) or EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L)
- Patient Global Impression of Change (PGIC)
- Clinical Opiate Withdrawal Scale (COWS)
- Subjective Opiate Withdrawal Scale (SOWS)
- Patient Assessment of Constipation Symptoms (PAC-SYM)
- Neuropathic Pain Symptom Inventory (NPSI)
- Hospital Anxiety and Depression Scale (HADS).

Findings

Table 62: Summary of Validity and Minimal Clinically Importance Difference for Outcomes

Instrument	Type	Evidence of Validity	MCID	References
11-point Pain NRS	A self-rated instrument for pain intensity assessment	Yes	Range from 1.1 to 2.2 for various conditions	Mintken 2009[48] Cleland 2008[47] Young 2010[49]
BPI	A validated 11-item instrument for assessing pain intensity and pain interference	Yes	Unknown	Song 2016[52] Atkinson 2010[51]
WOMAC	A self-administered, validated disease-specific questionnaire for evaluation of osteoarthritis	Yes	0.51 to 1.33 for worsening; 0.67 to 0.75 for improvement	Strand 2007 [62] Angst 2001[66]
Sleep questionnaire	A self-reported questionnaire for sleep evaluation in patients with various conditions	No	Unknown	Haythornthwaite 1991[73]
SF-36	A generic health status questionnaire	Yes	For summery components: 2.5 to 5 points; For BP subscale: MCID for worsening of 7.2 and MCID for improvement of 7.8	Hays 2009[60] Samsa 1999[61] Strand 2008[62] Mortenson 2017[74]
EQ-5D	A generic health status questionnaire	Yes	0.033 to 0.074 for general population	Brooks 1996[55] Health Policy 1990[56] Sinnott 2007[58]

Instrument	Type	Evidence of Validity	MCID	References
PGIC	A 7-point numerical scale used for global improvement with treatment	Yes	Not identified	Dworkin 2005[75]
COWS	Clinician administered, 11-item instrument used to assess the signs and symptoms associated with opioid withdrawal	Yes	Not identified	Wesson 2003[76] Tompkins 2009[69] Altintoprak 2015[68]
SOWS	16-item self-administered instrument used to rate the intensity and presence of opiate withdrawal symptoms	Unknown	Not identified	Handelsman 1987[77]
PAC-SYM	12-item patient self-administered instrument that measures the severity of constipation-related symptoms	Yes	–0.52 to –0.63	Slappendel 2006[78] Yiannakou 2017[67]
NPSI	A self-reported instrument to evaluate the properties of neuropathic pain	Yes	Unknown	Baron 2016[20] Crawford 2008[54]
HADS	Self-rated instrument to assess anxiety and depression in medically compromised patients	Yes	Unknown	Baron 2016[19,20] Bjelland 2002[79]

BP = bodily pain; BPI = Brief Pain Inventory; COWS = Clinical Opiate Withdrawal Scale; EQ-5D = EuroQol 5-Dimensions questionnaire; HADS = Hospital Anxiety and Depression Scale; MCID = minimal clinically important difference; NPSI = Neuropathic Pain Symptom Inventory; NRS = Numerical Rating Scale; PAC-SYM = Patient Assessment of Constipation Symptoms; PGIC = Patient Global Impression of Change; SF-36 = Short Form – 36 items; SOWS = Subjective Opiate Withdrawal Scale; WOMAC = Western Ontario and McMaster Questionnaire.

11-point Pain Numerical Rating Scale

The 11-point pain NRS is a self-reported, commonly used tool to assess patient's pain intensity. The scores of NRS range from 0 to 10, where a score of 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine." Overall, scores of 1 to 3 are considered mild pain, 4 to 6 are considered moderate pain, and 7 to 10 are considered severe pain.[51 80] Previous studies indicated that the NRS was valid, reliable, and responsive outcome measure in patients with various musculoskeletal conditions such as neck pain and cervical radiculopathy. In a study of 137 patients with neck pain, the test-retest reliability calculated with intra class correlation coefficient (ICC) was 0.76.[47] In another study of 101 patients with shoulder pain, similar test-retest reliability was reported, with an ICC of 0.74.[48] Good correlation was found between the pain scores derived from the 11-point NRS and other rating scales for pain, with the correlation coefficients ranging between 0.90 and 1.00.[81] In one study that enrolled 165 patients with cervical radiculopathy, the test-retest reliability was lower compared with other conditions (ICC of 0.59); construct validity of the 11-point NRS was determined when significant changes ($P < 0.001$) in disability, function, and pain were found between the "stable" clinically improved group and the "larger" clinically improved groups by comparing the patients' baseline and follow-up scores; responsiveness of the 11-point NRS was measured with area under the curve (AUC) and an AUC value 0.72 was reported for the larger improved group (AUC of 0.50 means the measure has no diagnostic accuracy beyond chance; AUC of 1 means perfect accuracy; AUC greater than 0.70 is considered to be satisfactory).[49] The pain NRS is recommended by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) as a core outcome measure in clinical trials of chronic pain treatments.[75]

The MCIDs of 11-point NRS in patients with chronic pain have been identified, ranging from 1.1 to 2.2; 2 points in patients with low back pain,[47] 1.3 points in patients with neck pain,[47] 2.2 points in patients with cervical radiculopathy,[49] and 1.1 to 2.17 points in patients with shoulder pain.[48,50]

Brief Pain Inventory

The BPI is a questionnaire designed to provide information on pain intensity (the sensory dimension, four items) and the degree to which pain interferes with functioning in daily living (the reactive dimension, seven items). It is recommended by the IMMPACT as a core outcome measure of pain. Four items assess patient's pain intensity: 1) pain at its worst in the last 24 hours, 2) pain at its least in the last 24 hours, 3) average pain, and 4) pain right now, using a 0 to 10 numeric rating scale, with "0" representing "no pain" and "10" representing "pain as bad as you can imagine." For the seven items assessing pain interference with functioning, patients are asked to rate how their pain interferes with seven life domains, including general activity, mood, walking ability, normal work, relations with others, sleep, and enjoyment of life, on a similar type of numeric rating scale. The anchor points in each item of the interference scale are "0" (not interfered) and "10" (completely interfered). The scores for the two BPI subscales (pain intensity and pain interference) range from 0 to 10 and are calculated using the mean of their corresponding items' scores. The total score of BPI is the mean of the two subscale scores. A high score represents a high pain intensity or pain interference. The BPI also contains supplemental items that allow a patient to indicate treatments or medications they are receiving to treat their pain, the percentage of relief obtained in the past 24 hours from the treatments or medications, and the anatomical location of their pain on a body diagram.[51,52] Although originally developed for evaluation of cancer pain (breast, prostate, colon, rectum, or gynecologic cancer), it has also been shown to be a reliable (e.g., internal consistency and test-retest reliability) and valid (e.g., construct, convergent, and discriminative validity) instrument for evaluation of non-malignant chronic pain (e.g., low back pain, osteoarthritis [OA], rheumatoid arthritis or multiple sclerosis) across various languages, and is also commonly used for non-malignant pain.[51,52]

An overall minimal clinically important difference (MCID) of BPI has not been identified from the literature, although a 2-point change was suggested as a reasonable estimate for the MCID of the BPI worst pain item.[53]

Western Ontario and McMaster Questionnaire

The WOMAC is a self-administered questionnaire assessing hip and knee OA. It is a valid, reliable and responsive measure of outcome in knee OA and has been widely used in clinical and interventional settings. The WOMAC consists of 24 items divided into three subscales:[16,82]

- pain (5 items): during walking, using stairs, in bed, sitting or lying, and standing upright
- stiffness (2 items): after first waking and later in the day
- physical function (17 items): using stairs, rising from sitting, standing, bending, walking, getting in or out of a car, shopping, putting on or taking off socks, rising from bed, lying in bed, getting in or out of the bath, sitting, getting on or off the toilet, heavy domestic duties, light domestic duties.

The Likert version of the WOMAC is rated on an ordinal scale of 0 to 4, where 0 means the lowest level of symptoms or physical disability. Each subscale is summated to a maximum

score of 20, 8, and 68, respectively; providing a maximum global score of 96 (sum of the three subscales).[63]

In a study of patients with hip and knee OA and underwent comprehensive inpatient rehabilitation, the MCID for WOMAC global and subscale scores ranged from 0.51 to 1.33 for worsening and 0.67 to 0.75 for improvement.[66] The WOMAC 3.1 version with a 5-point Likert format was used in studies PAI-3008 and PAI-3009. It was administered once during the titration and three times during the maintenance treatment periods, including end of treatment. A global score is calculated by summing the scores for the three subscales and using coefficients as follows: 0.42 × pain subscale + 0.21 × stiffness subscale + 0.37 × physical function subscale. An MCID for this global score was not identified by CDR.

Sleep Questionnaire/Sleep Diary

This four-item self-reported sleep questionnaire evaluated sleep latency, time slept, number of awakenings, and sleep quality experienced by the patient during the preceding night, via a sleep diary. The items and responses were developed based on a validated instrument reported by Haythornthwaite et al.[73] The adapted version of the sleep questionnaire was used in studies PAI-3007, PAI-3008, PAI-3009, PAI-3011, and Baron 2016. It was unclear whether this has been validated. Sleep was assessed once a week during the entire double-blind treatment period of the included studies.

An MCID of the sleep questionnaire was not identified from the literature.

Short Form-36

The SF-36 is a 36-item, general health status instrument that has been used extensively in clinical trials in many disease areas.[59] It consists of eight health domains — physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health.[83] For each of the eight categories, a subscale score can be calculated. The SF-36 also provides two component summaries, the physical component summaries (PCS) and the mental component summary (MCS), derived from aggregating the eight domains according to a scoring algorithm. The PCS and MCS scores range from zero to 100 with higher scores indicating better health status. The summary scales are scored using norm-based methods, with regression weights and constants derived from the general US population. Both the PCS and MCS scales are transformed to have a mean of 50 and a standard deviation (SD) of 10 in the general US population. Therefore, all scores above or below 50 are considered above or below average for the general US population. The two-item BP subscale of the SF-36 questionnaire has been validated in a wide range of populations.[84] One item assesses pain interference on a scale of 1 to 5, with response options range from “not at all” to “extremely.” The second item assesses pain severity on a scale of 1 to 6, with response options range from “none” to “very severe.”

The MCID for either the PCS or MCS of the SF-36 is typically between 2.5 points and 5 points.[60-62] For the bodily pain subscale, the scores range from 0 to 100, and an MCID for worsening of 7.2 and MCID for improvement of 7.8 were reported for patients with osteoarthritis of the lower extremities in a previous study.[74]

EQ-5D

The EQ-5D is a generic health-related quality of life instrument that may be applied to a wide range of health conditions and treatments.[55,56] The first of two parts of the EuroQol 5-Dimensions 3-Levels (EQ-5D-3L) is a descriptive system that classifies respondents (aged

≥12 years) into one of 243 distinct health states based on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-3L has three possible levels (1, 2, or 3) for each domain, representing "no problems," "some problems," and "extreme problems," respectively. The original UK scoring algorithm of the EQ-5D-3L was described by Dolan et al. in 1997.[57] Respondents are asked to choose one level that reflects their own health state for each of the five dimensions. The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., US or UK). The lowest possible overall score for the 3L version (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., –0.59 for the UK algorithm and –0.109 for the US algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states of "dead" and "perfect health," respectively. Reported MCIDs for the 3L version of the scale have ranged from 0.033 to 0.074.[58] The second part is a 20 cm visual analogue scale (EQ-VAS) that has endpoints labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents are asked to rate their health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their health on that day. The MCID for the EQ-5D-3L VAS among patients with chronic pain was not identified by CDR.

The EQ-5D produces three types of data for each respondent:

- A profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
- A population preference–weighted health index score based on the descriptive system.
- A self-reported assessment of health status based on the EQ-VAS.

Patient's Global Impression of Change

PGIC is a widely used, validated outcome measure for clinical pain trials.[85,86] It is a 7-point numerical scale that is assessed by patients who indicate perceived change by completing the statement "Since I began trial treatment, my overall status is ____." There are 1 of 7 possible responses: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7).[16,17] In a data set of 2,724 patients who received pregabalin for diabetic neuropathy, postherpetic neuralgia, chronic low back pain, fibromyalgia, and OA from 10 placebo-controlled clinical trials, the 11-point pain NRS and PGIC were used as determinants of a clinically important difference and the relationship between the 11-point NRS and PGIC was explored. A consistent relationship between the change in 11-point pain NRS and the PGIC was demonstrated regardless of study, disease type, age, sex, study result, or treatment group.[86] The PGIC questionnaire is recommended for use in chronic pain clinical trials by IMMPACT as a core outcome measure of global improvement with treatment.[87]

Clinical Opiate Withdrawal Scale

The COWS is an instrument used by a clinician to assess the signs and symptoms associated with opioid withdrawal in a patient presenting with substance abuse disorder.[76] It can be administered in an office, clinic, or hospital setting and is quick to administer (generally with a few minutes).[69,76] It was originally published in a buprenorphine treatment training manual.[69,76] The COWS can also be used to track opioid withdrawal and differentiate it from opioid toxicity through serial measurements.[69] It is comprised of and

rates 11 common signs and symptoms of opioid withdrawal, including resting pulse rate (beats per minutes), sweating (over past half an hour and not accounted for by room temperature or activity), restlessness (during assessment), pupil size (during assessment), aching bones or joints (only additional component attributed to withdrawal is scored), runny nose or tearing (not accounted for by cold or allergies), gastrointestinal upset (over last half an hour), tremor (observing outstretched hands), yawning (during assessment), anxiety or irritability (during assessment), and gooseflesh skin (during assessment).[76] Each symptom is scored on a scale ranging from 0 to 4 or 0 to 5, with higher scores indicating more severe symptoms. The total score is created by summing the scores on the 11 items and ranges from 0 to 47. Overall scores can be interpreted as follows: 5 to 12 (mild); 13 to 24 (moderate); 25 to 36 (moderately severe); greater than 36 (severe withdrawal); although these groupings have not been validated.[69,76] The overall score may be used to assess the physical level of opioid dependence.[76]

Tompkins et al.[69] obtained measurements with the COWS, the previously validated Clinical Institute Narcotic Assessment (CINA) scale, and VAS self-report items (e.g., bad drug effect, feeling sick) in order to examine the validity and reliability of the COWS in a sample of 46 out-of-treatment people who were opioid dependent and had been randomized to complete naloxone and placebo challenges. In the naloxone challenge, COWS and CINA scores were similar in terms of magnitude and the time course when they occurred. A positive correlation between the peak COWS and CINA was evident ($r = 0.66$; $P < 0.0001$) in addition to a strong positive correlation between the peak scores ($r = 0.85$; $P < 0.001$) in the naloxone challenges. The aforementioned provides evidence of concurrent validity between the two instruments.[69]

When analyzing the internal consistency of the COWS, an overall Cronbach's alpha of 0.78 indicated good reliability.[69] In addition, content validity was evident as there was only a small amount of inter-item correlation observed between most of the individual COWS items. The only significant correlation that was observed was between the anxiety or irritability and restlessness items (0.67) and yawning and runny nose or tearing items (0.54).[69] The COWS differentiates between mild opiate withdrawal and its absence.[69] The COWS has also been validated and found reliable when translated into other languages.[68]

No MCID for the COWS was identified in patients with chronic pain who were discontinuing opioid therapy.

Subjective Opiate Withdrawal Scale

The SOWS is a patient-completed instrument that is used to rate the intensity and presence of opiate withdrawal symptoms.[77] It is comprised of 16 items that reflect common symptoms associated with opiate withdrawal; namely psychic, musculoskeletal, gastrointestinal, motor, and autonomic issues. Each symptom is rated on a scale of 0 to 4; 0 (not at all), 1 (a little), 2 (moderately), 3 (quite a bit), and 4 (extremely). Ratings are based on how patients are feeling when they are completing the instrument. The total SOWS score is the sum of the individual item scores and ranges from 0 to 64, with a higher score indicating greater withdrawal severity.[77]

In order to assess the SOWS validity and reliability, Handelsman et al.[77] examined male patients in or entering treatment for substance abuse who were abusing only opioids or opioids and another substance. In addition to the SOWS, the investigators also administered the previously validated Addiction Research Centre Inventory – Weak Opiate Withdrawal Scale (ARCI-WOWS) to the same cohort. Validity was assessed by

administering the two instruments before and after pharmacological interventions (methadone and naloxone) that were likely to significantly alter the opiate withdrawal level. Statistically significant decreases in the before and after total SOWS and the ARCI-WOWS scores were observed; however, those patients with concomitant opioid and another substance abuse had more variability in their SOWS scores.[77] SOWS scores significantly increased after receiving a naloxone challenge; however, this change was not significant in the ARCI-WOWS.

In order to examine the test-retest reliability of the SOWS, Handelsman et al.[77] administered the SOWS and the ARCI-WOWS on two occasions (one week separating the administration of the tests) in patients who were expected to maintain stable levels of opiate withdrawal symptoms. The ICCs were moderate for the SOWS (ICC: 0.60) and strong for the ACRI-WOWS (ICC: 0.85); however, the ARCI-WOW displayed a higher degree of test–re-test reliability over one week.[77] The SOWS is responsive; however, its validity and reliability have not yet been established. All of the aforementioned results indicate that the SOWS (and the ARCI-WOW) is sensitive to changes in opiate withdrawal symptom severity that occur spontaneously and in response to naloxone.[77]

No MCID for the SOWS was identified in patients with chronic pain who were discontinuing opioid therapy.

Patient Assessment of Constipation Symptoms

The PAC-SYM is a validated measure for assessment of the severity of constipation-related symptoms in patients using opioids for the control of chronic pain.[78] This tool was designed for measuring the efficacy of treatments for constipation relief, but was used in this study as part of the safety evaluation. The PAC-SYM is a 12-item patient self-administered instrument that measures the severity of constipation-related symptoms over a two-week period. Responses are rated on a 5-point scale ranging from 0 (absence of symptom) to 4 (very severe symptoms). The PAC-SYM contains three subscales: stool symptoms (five items), abdominal symptoms (four items), and rectal symptoms (three items). The PAC-SYM overall score is an average score of all the items.

The MCIDs of PAC-SYM range from -0.52 to –0.63 in the literature for patients with chronic constipation.[67]

Neuropathic Pain Symptom Inventory

The NPSI is a self-reported, validated questionnaire that includes 10 items (on different pain sensations, e.g., burning, squeezing, electric-shock, etc.) used to evaluate the properties of neuropathic pain. Each item is scored on an 11-point NRS (0 meaning no symptom and 10 meaning worst symptom), with higher scores indicating more severe neuropathic pain symptoms.[20,54] Validation of NPSI was performed in 176 consecutive patients with neuropathic pain of peripheral (n = 120) or central (n = 56) origin, recruited in five pain centres in France and Belgium. The procedure included: (i) assessment of the test-retest reliability of each item, (ii) determination of the factorial structure of the questionnaire and analysis of convergent and divergent validities (i.e., construct validity), and (iii) evaluation of the ability of the NPSI to detect the effects of treatment (i.e., sensitivity to change). The psychometric properties of the NPSI suggested that it might be used to characterize subgroups of neuropathic pain patients and verify whether they respond differentially to various pharmacological agents or other therapeutic interventions.[88] The questionnaire was developed to assess more specifically the different components of

neuropathic pain syndromes, such as spontaneous ongoing and paroxysmal pain, evoked pain, paresthesia and dysesthesia.[54] The NPSI also includes a measure of the number of pain attacks during the previous 24 hours.[20] The recall period for the NPSI was 24 hours. A total intensity score is calculated as the sum of the scores of the 10 items, with the range of 0 to 100.[88]

An MCID of NPSI was not identified in the literature for patient with chronic pain.

Hospital Anxiety and Depression Scale

The HADS is a validated instrument used to assess symptoms of anxiety and depression.[19,79,89]

It includes 14 questions, each of which was answered by patients using a 4-point scale (0 to 3: 0 indicating absence, 3 indicating extreme presence; and higher scores indicating more severe anxiety or depression symptoms). An anxiety subscale score (possible score of 0 to 21) was calculated by combining seven items from the HADS, and a depression subscale score (possible score of 0 to 21) was calculated by combining the remaining seven items.[19] For both subscales, scores of less than 7 indicate non-cases, 8 to 10 indicate mild condition, 11 to 14 indicate moderate condition, and 15 to 21 indicate severe condition. The HADS is useful for initial diagnosis and to track progression (or resolution) of psychological symptoms. The test-retest reliability was determined to be ranged from adequate to excellent in patients with coronary heart disease or spinal injury. Criterion/construct validity were demonstrated by examining the correlations between the HADS and other measures of depressions and anxiety.[90]

An MCID for HADS in patients with chronic pain was not identified from the literature.

Conclusion

A number of instruments were adopted in the included studies to evaluate general health of the study participants, pain intensity, sleep, patient response, anxiety, and depression, as well as adverse events (including signs and symptoms associated with opioid withdrawal); however, limitations exist in the use of these instruments. Some instruments haven't been validated in patients with chronic pain. MCIDs are not always available to help determine the clinical relevance of a change in the health status.

Appendix 6: Summary of Other Studies

Objective

To summarize the safety and efficacy results from one open-label extensions trial. The following summary is based on the published data.

Trial Description

Patients who had completed Study PAI-3008, Study PAI-3011, Study PAI-3007, or a seven-week phase IIIb, randomized, double-blind, crossover study between tapentadol immediate-release and tapentadol extended-release (ER) for chronic moderate-to-severe low back pain (LBP) were eligible for the extension study.[91] Patients who were expected to require major surgery during the study and those who had a clinically significant disease or a condition in addition to osteoarthritis or LBP that could affect efficacy or safety assessment were excluded from the study. After screening and titrating tapentadol ER (up to four weeks) to an optimal dose, patients received tapentadol ER (100 mg to 250 mg twice daily) during the 48-week maintenance period after finishing treatment in the preceding studies. Titration was not required for patients who were previously treated with tapentadol ER in the one-year study (PAI-3007), and they continuously received the drug at the same dose for up to two years in total. Rescue medication of acetaminophen was allowed during the extension phase. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors were permitted if they were prescribed for a reason other than pain. Benzodiazepines, mood stabilizers, anti-Parkinsonian drugs, and anticonvulsants were permitted for patients who were on a controlled, stable dose for at least 30 days before screening. Non-pharmaceutical adjunctive therapies, such as acupuncture and transcutaneous electrical nerve stimulation, were allowed during the study for those who had been on regular therapy for at least 14 days.

Efficacy outcome measures in this extension study included change in pain intensity (measured with the 11-point numeric rating scale [NRS]), health status outcomes (measured with the Patient Global Impression of Change, EuroQol 5-Dimensions, and Short Form – 36 items questionnaires). Safety was evaluated in terms of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs). Adverse events (AEs) associated with the treatment with opioids were examined using the Patient Assessment of Constipation Symptoms, Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale, and a sleep questionnaire. Analyses of safety were conducted in the safety population, which included all patients who received at least one dose of tapentadol ER during the study. Analyses of efficacy were conducted in the intention-to-treat population that included all patients in the safety population, except for five patients at a site that had major audit findings identified before database lock. Patients were grouped according to prior treatment groups: 1) tapentadol ER for up to 15 weeks, 2) tapentadol ER for one year, 3) oxycodone controlled-release (CR) for 15 weeks, 4) oxycodone CR for one year, and 5) placebo.

In statistical analysis, baseline values were defined as the values from the last available assessment of the preceding study that were recorded before or on the day of the first dose of open-label tapentadol ER in the extension study. Pain intensity scores and changes from baseline in pain intensity were summarized by using descriptive statistics at each time point and at study end point. Last observation carried forward was used for imputing missing pain

intensity scores at study end point. There was no information provided for handling missing data of other efficacy and safety outcome measures. A total of 1,082 patients were planned to be eligible for the extension study, based on the planned number of patients to be randomized in each study and an estimated discontinuation rate for the four preceding studies (40% during the first month of study treatment and 10% every month thereafter). The incidence of AEs, SAEs, and withdrawal due to AEs were summarized for the overall treatment period. A separate analysis of efficacy and safety results was performed for patients who had received tapentadol ER for up to two years.

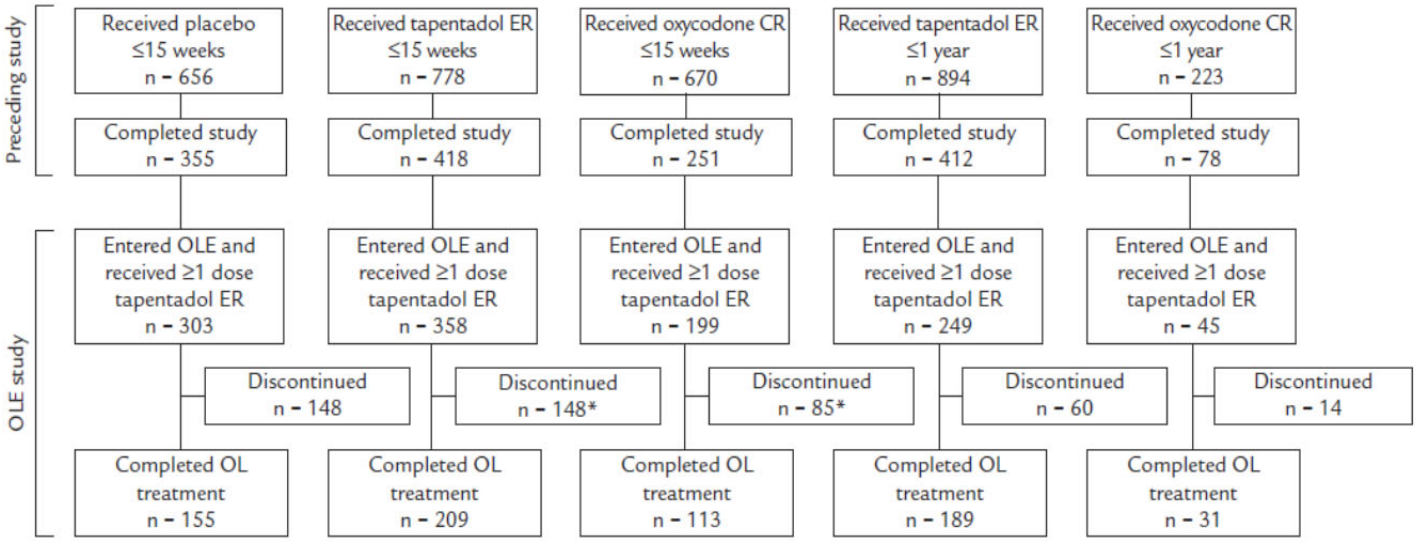
Results

A total of 1,154 patients were enrolled in this extension study and received at least one dose of tapentadol ER: 358 had received tapentadol ER for up to 15 weeks, 249 had received tapentadol ER for one year, 199 had received oxycodone CR for 15 weeks, 45 had received oxycodone CR for one year, and 303 had received placebo. There was no description of the proportion of patients enrolled from their original studies. At baseline, the mean age of study participants was 54.3 (standard deviation [SD]: 11.43) years, 42.1% were male and 78.9% were white; 46.1% of the patients had a diagnosis of osteoarthritis in knee or hip, while 53.9% had LBP; 50.1% had mild baseline pain intensity, when “mild” was defined as baseline pain intensity score < 4. During the study, 38.7% of patients received a concomitant non-opioid medication: 39.4% for tapentadol ER ≤ 15 weeks, 47.0% for tapentadol ER one year, 31.2% for oxycodone CR ≤ 15 weeks, 37.8% for oxycodone CR one year, and 36.3% for placebo.

Patient Disposition

Of the 1,152 patients (two patients did not have end-of-treatment reason for discontinuation and were not included in the efficacy analyses) in the extension study, 697 (60.5%) completed the treatment. The numbers of patients who discontinued the treatment in each treatment groups were: 148 (41.5%) for tapentadol ER ≤ 15 weeks, 60 (24.1%) for tapentadol ER one year, 85 (42.9%) for oxycodone CR ≤ 15 weeks, 14 (31.1%) for oxycodone CR one year, and 148 (48.8%) for placebo (Figure 2). The most common reason for early withdrawal was AEs (11.2%, 6.4%, 15.7%, 17.8%, and 18.2%, respectively). The proportions of patients who withdrew due to lack of efficacy were 3.9%, 2.0%, 1.5%, 2.2%, and 4.6%, respectively. The duration of treatment in each treatment group (mean ± SD) were: 258.8 ± 133.8 days, 301.3 ± 92.6 days, 243.5 ± 146.5 days, 266.2 ± 147.9 days, and 233.3 ± 146.1 days, respectively.

Figure 2: Patient Disposition in the Extension Study



CR = controlled release; ER = extended release; OL = open label; OLE = open-label extension.

Source: Permission obtained from the publisher to use Figure 1 from Long-term Safety and Efficacy of Tapentadol Extended-Release Following up to 2 Years of Treatment in Patients With Moderate to Severe, Chronic Pain: Results of an Open-label Extension Trial by Buynak R, Rappaport SA, Rod K, Arsenault P, Heisig F, Rauschkolb C, and Etropolski M. 2015.[91]

Efficacy

In the intention-to-treat population, the pain intensity score (mean ± SD) measured with the 11-point NRS remained stable throughout the study. In the overall population, the mean pain intensity score was 3.87 ± 2.38 at baseline and 3.65 ± 2.42 at study end point; in the five groups divided according to their prior treatment, the mean changes of pain intensity score (mean ± standard error) from baseline to study end point were 0 ± 0.11, 0.26 ± 0.15, –0.19 ± 0.15, 0.12 ± 0.28 and –0.89 ± 0.14, respectively (Table 63).

Across the five groups of patients divided based on their prior treatment, the percentages of patients reporting improvements in the Patient Global Impression of Change were 86.3%, 92.8%, 87.0%, 78.0%, and 78.0% for the groups of tapentadol ER ≤ 15 weeks, tapentadol ER one year, oxycodone CR ≤ 15 weeks, oxycodone CR one year, and placebo, respectively (Table 63).

The improvement in health-related quality of life in the study population was measured with the EuroQol 5-Dimensions and the Short Form – 36 items questionnaires. The mean changes in all domains in these instruments from baseline to study end point were stated to be small. Actual data were not reported in the study.

Safety

The most common TEAEs (> 10%) reported in this extension study were headache (13.1%), nausea (11.8%), and constipation (11.1%). In the five groups divided according to their prior treatment (tapentadol ER ≤ 15 weeks, tapentadol ER one year, oxycodone CR ≤ 15 weeks, oxycodone CR one year, and placebo), the incidences of headache were 17.3%, 5.6%, 13.1%, 2.2%, and 15.8%, respectively; the incidences of nausea were 12.6%, 3.2%,

11.6%, 8.9%, and 18.5%, respectively; the incidences of constipation were 10.6%, 6.8%, 10.6%, 2.2%, and 16.8%, respectively; the incidences of withdrawal syndrome were 2.8%, 0.8%, 4.5%, 8.9%, and 3.0%, respectively.

The proportion of patients reporting AEs was lowest among the patients who had previously received tapentadol ER or oxycodone CR in the long-term (one-year) study.

SAEs were reported for 7.3% (84 out of 1,154) of patients and the incidence of SAEs ranged from 4.5% to 8.8% across all groups of patients divided according to their prior treatment. Three deaths were reported, including one cardiac arrest, one myocardial infarction, and a completed suicide. It's unknown in which group these deaths occurred (Table 63).

The incidence of WDAEs occurred in 12% (139 out of 1,154) of patients in the extension study. The most common TEAEs leading to discontinuation were nausea (1.4%, 16 out of 1,154) and dizziness (1.3%, 15 out of 1,154) (Table 63).

Results of the COWS assessments performed two to four days after abrupt discontinuation of the study drug (at the end of the study or after early withdrawal from the study), 88.8% of patients had no opiate withdrawal (total score or 0 to 4), 10.7% had mild withdrawal (total score of 5 to 12), and 0.5% had moderate withdrawal (total score of 13 to 24). No severe withdrawals (total score of 25 to 48) were reported. The percentage of patients who had no opiate withdrawal was higher in the tapentadol ER ≤ 15 weeks group and the oxycodone CR one-year group (Table 63). If COWS was performed more than five days after abrupt discontinuation of the study drug, 90.7% had no opiate withdrawal, 8.7% had mild withdrawal, and 0.6% had moderate withdrawal. The mean Subjective Opiate Withdrawal Scale total scores for patients who did not take opioids after study discontinuation were similar across the five treatment groups and ranged from 4.5 to 9.3. Detailed data were not reported in the published article.

In the overall population, changes from baseline to study end point in the overall PAC-SYM score (mean ± standard error) was 0 ± 0.02. The changes in each prior treatment groups were: 0 ± 0.03, 0 ± 0.02, –0.2 ± 0.04, 0.3 ± 0.14, and 0.1 ± 0.03, respectively.

Table 63: Efficacy and Safety Results From the One-Year Extension Trial

OL Extension Studies					
	Tapentadol ER ≤ 15 weeks N = 358	**Tapentadol ER 1 year N = 249**	**Oxycodone CR ≤ 15 weeks N = 199**	**Oxycodone CR 1 year N = 45**	**Placebo N = 303**
Efficacy					
Change from baseline in pain intensity score, mean (SE)					
	0 (0.112)	0.26 (0.15)	–0.19 (0.15)	0.12 (0.28)	–0.89 (0.140)
% of improvement in PGIC, n/N (%)					
	289/335 (86.3)	207/223 (92.8)	154/177 (87.0)	32/41 (78.0)	240/283 (84.8)
Safety					
SAEs, n (%)					
overall 84/1154 (7.3)	Ranged from 4.5% to 8.8% across all treatment groups. No details on the percentage of SAE for each group.				
WDAEs, n (%)					
overall 130/1154 (12)	39 (10.9)	14 (5.6)	26 (13.1)	7 (15.6)	53 (17.5)

OL Extension Studies					
	Tapentadol ER ≤ 15 weeks N = 358	Tapentadol ER 1 year N = 249	Oxycodone CR ≤ 15 weeks N = 199	Oxycodone CR 1 year N = 45	Placebo N = 303
COWS 2 to 4 days after the last intake of study drug, %[a]					
No	93.0	84.4	87.9	100	86.9
Mild	7.0	13.5	12.1	0	13.1
Moderate	0	2.1	0	0	0
Moderately severe and severe	0	0	0	0	0
Change from baseline to study end point in PAC-SYM scores, mean (SE)					
Overall score	0 ± 0.03	0 ± 0.02	-0.2 ± 0.04	-0.3 ± 0.14	0.1 ± 0.03

COWS = Clinical Opioid Withdrawal Scale; CR = controlled release; ER = extended release; PAC-SYM = Patient Assessment of Constipation Symptoms; PGIC = Patient Global Impression of Change; SAE = serious adverse event; SE = standard error; WDAE = withdrawal due to adverse event.

[a] Based on results in 384 patients.

Source: Buynak et al.2015.[91]

Critical Appraisal

The main limitations of the extension study were the open-label nature of the study (which can potentially bias the reporting of patient-reported outcome measures such as the COWS or AEs) and the lack of a control group. The study did not report how many patients from the original study went into the extension phase. According to their characteristics at entry of the extension phase, their mean pain intensity score was 3.9 on the 11-point pain NRS, and 50% of them were classified as with mild condition by the investigators. Among the patients who had previously received tapentadol ER or oxycodone CR, those who experienced benefit and tolerated these treatments well may have been more likely to enter the long-term extension. The proportion of patients who discontinued the studies early ranged from 24% to 49%. The reasons for early discontinuation were unclear. No data on illicit opioid use during the trial were reported. Health-related quality of life data were not adequately reported. These methodological issues should be considered when making conclusions with respect to the efficacy and safety of tapentadol ER in patients with chronic pain.

Summary

One open-label extension study reported data from a total of 1,154 patients who completed treatments with tapentadol ER (up to 15 weeks or one year), oxycodone CR (up to 15 weeks or one year), or placebo in four previously conducted randomized controlled trials, and were followed for up to one year. At the end of the study, the pain intensity remained stable through the maintenance therapy. There were no new safety signals were apparent. In general, findings from this extension study were consistent with the safety and tolerability profile that has been established in the previous randomized controlled trial for tapentadol ER. However, due to the limitations of the extension phase (large proportion of dropouts, open-label study design, and insufficient data reporting), the reported results for the long-term efficacy may be overly optimistic.

Appendix 7: Summary of Indirect Comparisons

Background

The randomized controlled trials (RCTs) in the CADTH Common Drug Review (CDR) systematic review include ones that were designed to compare the efficacy and safety of tapentadol extended-release (ER) with oxycodone controlled-release (CR), oxycodone/naloxone combination, and morphine CR, but not other long-acting opioids for chronic pain. The aim of this section was to provide an overview and critical appraisal of the indirect evidence available for the assessment of the comparative efficacy and harms of tapentadol ER relative to opioids available in Canada in patients with chronic pain.

Methods

One network meta-analysis (NMA) by Riemsma et al. was included in the manufacturer's pharmacoeconomic evaluation.[92] In addition, CDR conducted an independent literature search for published indirect treatment comparison that compared tapentadol with other available opioids when used for the treatment of chronic pain. One additional NMA was identified from the CDR literature search.[93]

Description of Network Meta-Analysis Identified

The inclusion criteria for each of the NMAs are summarized in Table 64 below. In the Riemsma review, WHO step 3 opioids were eligible regardless of dose and duration, but only oral and transdermal routes of administration were included; in addition, enriched design studies were excluded.

Table 64: Criteria for Study Inclusion

	Riemsma et al.	Meng et al.
Population	Adults suffering from cancer or non-cancer chronic pain	Adults with cancer or non-cancer chronic pain, to treat with an opioid drug
Interventions	WHO step 3 opioids (oral or transdermal only)	Opioid drug either alone or in combination with NMDA-receptor antagonist
Comparisons	Comparisons were made between the above-mentioned regimens	Comparisons were made between the above-mentioned regimens
Outcomes	• Pain relief • PGIC • HRQ0L • Sleep • AEs • Treatment discontinuation due to AE	• AEs • Incidence of constipation • Trial withdrawal rate • Patient satisfaction
Study design	RCT	

AE = adverse event; HRQoL = health-related quality of life; NMDA = N-methyl D-aspartic acid; PGIC = Patient's Global Impression of Change; RCT = randomized controlled trial.

Review and Appraisal of Indirect Treatment Comparisons

Review of the Riemsma Review[92]

Objectives and Rationale for Riemsma Review

The aim of this systematic review was to determine the evidence base for current recommendations concerning opioids and to determine the relative safety and clinical effectiveness of tapentadol and other strong opioids for the treatment of chronic, severe pain in adults, using an NMA approach.

Methods for Riemsma Review

Study Eligibility and Selection Process

The NMA was based on a systematic review of the literature that included both electronic and manual search components. Multiple databases were searched from 1980 up to November 2010. There was no language limit on the electronic database searches.

It is unclear whether the selection criteria were defined a priori. The main inclusion criteria for the systematic review were RCTs that recruited adult patients (aged 18 or older) with chronic pain (pain lasting three months or longer) who were treated with step 3 (on the WHO pain ladder) opioids, regardless of dose and duration. Only oral or transdermal routes of administration were included. To be eligible, the studies were required to report at least one of the following outcomes: pain relief, Patient Global Impression of Change (PGIC), Health-related quality of life (HRQoL), or safety. Study selection was accomplished through two levels of screening by two independent researchers. Any disagreements were resolved through discussion and consensus.

Data Extraction

Data were extracted by one reviewer, and verified by a second reviewer. Any disagreements were resolved by consensus.

Comparators

Oral or transdermal WHO step 3 opioids were of interest for inclusion in the NMA. These included tapentadol immediate-release or ER, oxycodone, buprenorphine, hydromorphone, morphine, fentanyl, oxymorphone, oxycodone + morphine, oxycodone + naltrexone. All treatment dosages for the relevant comparators identified through the systematic literature review were considered for inclusion in the NMA.

Outcomes

The main end points of interest included in the systematic review were stated to be:

- pain relief: measured with mean change from baseline in pain intensity scores or number of patients achieving 30% pain relief
- PGIC: the number of patients that reported “very much improved” or “much improved”
- HRQoL: measured with the Short Form – 36 items (SF-36) or EuroQol 5-Dimensions (EQ-5D) questionnaires
- safety: overall adverse events (AEs), discontinuation due to AEs.

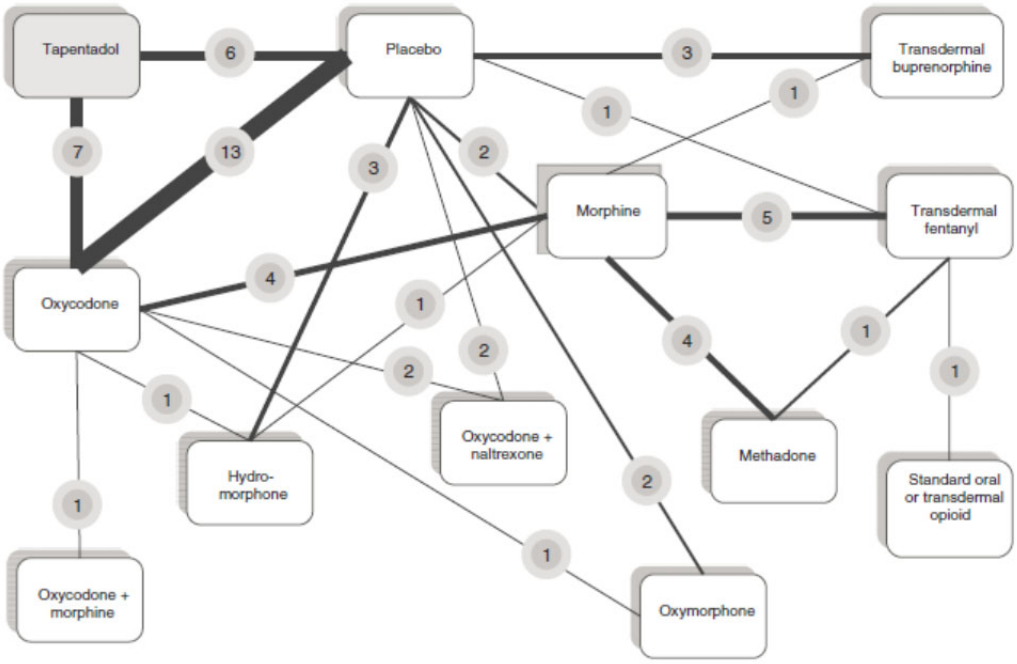
The time points of these outcome measures were not specified in the NMA, while the length of the follow-up period in the included studies ranged from approximately seven days to 24 months, with the majority of the length of follow-up being less than one month (43%) and three-to-five months (26%).

Quality Assessment of Included Studies

All included RCTs were evaluated for risk of bias using the Cochrane Collaboration checklist and the authors indicated that the results of the evaluation were used to put into perspective the outcome of the individual trials used in the network analysis; however, no more details were provided. Quality assessment was performed independently by two reviewers. Any disagreements were resolved by consensus.

Evidence Network

Figure 3: Network of Available Comparisons for Moderate-to-Severe Pain



Source: Permission obtained from the publisher to use Figure 3 from Systematic review of tapentadol in chronic severe pain by Riemsma R, Forbes C, Harker J, Worthy G, Misso K, Schäfer M, Kleijnen J, and Stürzebecher S. 2011.[92]

Indirect Comparison Methods

Standard meta-analyses were employed to assess the direct evidence on the treatment effect of the study drugs. Dichotomous data and continuous data were analyzed by calculating the relative risk and corresponding 95% confidence intervals (CIs) for each trial, or the mean difference between groups and the corresponding 95% CIs, respectively. Since heterogeneity was possible, random-effect models was adopted for calculation of the relative risks or mean differences. Heterogeneity was assessed by visual observation of forest plots and measuring I^2.

NMAs were used to compare more than two treatments in the same analysis. With NMAs it is possible to perform direct and indirect comparisons in one analysis. A few assumptions were made for the NMA: 1) when standard deviations (SD) were missing and could not be construed from CI, SDs were imputed using data from similar trials; 2) different doses and formulations (immediate- and long-acting formulations) of the same drug were treated as one intervention.

An approach based on an ordinary regression model in which all available information (combing all information from direct and indirect comparisons) is pooled with respect to the difference in effect of two or more treatments was employed in the Riemsma study.

For dichotomous data, such as the number of patients achieving 30% pain relief or serious adverse events (SAEs), a data set consisting of two to four (depending on the number of treatment arms in a particular trial) by two (representing response of yes/no for the outcome of interest) contingency tables for each trial was constructed. Relevant covariates, such as age, study duration, types of pain, or drug dose, were added to the data set. If the covariate was a continuous value (e.g., age or dose), the mean values were entered. Then a logistic regression analysis was performed with outcome of interest as the dependent variable and the different treatment options as independent variables. This started with placebo treatment as the reference group followed by identical analyses where various interventions (e.g., tapentadol, morphine, oxycodone, or hydromorphone) served as a reference group to which the other treatments were compared. A dummy variable for each trial was included to preserve randomization within each trial, and to adjust for differences in risk profiles and study setup between trials. Stratified analyses were proposed to assess whether covariates influenced the relative treatment effect; however, these analyses were not performed due to insufficient data within the network.

For continuous data such as the mean change in pain intensity, data were extracted as mean and SDs. Standardized mean differences were calculated using a 100-point standardized scale where the original scales differed. A multiple linear regression analysis was performed (using individual patient values derived from the mean and SDs, assuming a normal distribution for each patient outcome), which included a dummy variable for each trial to allow for comparisons between the different treatments after allowing for differences between the trials.

Analyses were conducted in patients with severe pain and moderate-to-severe pain. The severity of pain was not defined in the NMA, but was based on the definitions in the individual trials.

The authors indicated that subgroup analyses based on treatment duration were conducted; however, results of subgroup analyses were not presented in the published article.

Results

In total, 42 trials of patients with chronic pain were identified for the NMA. Among them, four included patients with “at least severe” pain and eight included patients with “moderate-to-severe” pain but reported separate data specific for the subgroup of patients with severe pain. These 12 trials were included in the analysis of “severe pain.” All 42 trials were included in the analysis of “moderate-to-severe pain.” The interventions in trials of severe pain were tapentadol, oxycodone, transdermal buprenorphine patch, morphine, methadone, and placebo. The interventions in trials of moderate-to-severe pain were tapentadol (doses

ranged from 189 mg to 500 mg per day), oxycodone (doses ranged from 10 mg to 120 mg per day), transdermal buprenorphine patch (doses ranged from 5 mcg to 70 mcg per hour), morphine (doses ranged from 30 mg to 540 mg per day), methadone (doses ranged from 18 mg to 25 mg per day), transdermal fentanyl (doses ranged from 25 mcg to 100 mcg per hour), hydromorphone (doses ranged from 4 mg to 108 mg per day), oxymorphone (doses ranged from 10 mg to 50 mg per day), oxycodone + morphine (dose not reported), oxycodone + naltrexone (doses ranged from 9 mg to 10 mg per day + 2 mcg to 4 mcg per day), and placebo. Various formulations and dose regimens of the study medications were included and contained in a single node for each medication. The time points of outcome measures were not reported in this review.

The authors reported that the overall, risk of bias of the included RCTs was low, especially for those where full articles or clinical study reports were available. The authors indicated that the main reasons for poor quality of the trials were due to poor reporting of the methods of randomization. Two out of 42 trials were published as abstracts. The tapentadol trials were generally considered at low risk of bias by the authors.

Severe Pain

Twelve RCTs with patients with severe pain were identified. Among them, efficacy and safety of tapentadol were compared with oxycodone or placebo in eight trials, and were included in data synthesis: six for tapentadol prolonged-release/ER; two for tapentadol immediate-release. Two RCTs compared transdermal buprenorphine patches with placebo, one compared morphine with placebo, and one compared morphine with methadone. Nine of them included patients with non-cancer chronic pain, one included neuropathic pain patients, one included patients with cancer and non–cancer-related chronic pain, and one included cancer pain patients only.

Indirect comparison was not feasible for patients with severe pain, due to the major differences between the trials in terms of populations, dose regimens, length of follow-up and definition/measurement of pain intensity. Only results of direct comparisons were reported. Based on seven trials, tapentadol showed a greater reduction in pain intensity compared with oxycodone (mean difference –2.64, 95% CI –4.84 to –0.44). Tapentadol was also superior to oxycodone in the proportion of patients achieving a 30% or a 50% reduction in the pain intensity scores (30% pain reduction — relative risk [RR]: 0.68; 95% CI, 0.59 to 0.77; 50% pain reduction — RR: 0.75; 95% CI, 0.64 to 0.89). There were no statistically significant difference between tapentadol and oxycodone for the incidence of SAEs based on four trials (RR: 0.52; 95% CI, 0.15 to 1.74). The measures of heterogeneity (I^2) were not reported.

Moderate-to-Severe Pain

In total, 42 trials of patients with moderate-to-severe pain were identified. Eight trials of tapentadol with various formulations and dose regimens and compared with oxycodone or placebo were included in the analyses. However, results exclusive for tapentadol ER were not available given that immediate- and extended-release formulations were combined in the analyses. Other step 3 opioids included in the network comparing with placebo were transdermal buprenorphine patches (three trials), transdermal fentanyl (one trial), morphine (two trials), oxycodone (13 trials), oxycodone plus naltrexone (one trial), and oxymorphone (one trial). Oxycodone was compared with hydromorphone, morphine, oxymorphone, and in combination with naltrexone. Morphine was compared with oxycodone, methadone, transdermal fentanyl, and transdermal buprenorphine patches. Twenty-seven trials included

patients with non-cancer chronic pain, 12 included cancer pain patients only, two included neuropathic pain patients, and one included patients with cancer and non-cancer pain.

Results of Direct Comparison: Based on seven trials, direct comparisons between tapentadol and oxycodone for pain intensity showed a greater reduction from baseline for tapentadol (mean difference: –2.45; 95% CI, –4.04 to –0.86). Results of a 30% and a 50% reduction in pain intensity score also favoured tapentadol when compared with oxycodone (30% pain reduction — RR: 0.72; 95% CI, 0.59 to 0.88; 50% pain reduction — RR: 0.74; 95%, CI 0.59 to 0.94). In addition, more patients treated with tapentadol reported "very much improved" or "much improved" using PGIC compared with those treated with oxycodone (RR: 0.90; 95% CI, 0.81 to 1.00), based on seven trials. In terms of HRQoL, results of SF-36 general health status index and the EQ-5D health status index both showed statistically significant effects of tapentadol over oxycodone (EQ-5D: mean difference: 0.06; 95% CI, 0.01 to 0.11; SF-36: mean difference: 1.76, 95% CI, 0.53 to 3.00. It is unclear whether these mean differences were change from baseline or measurements at study end point). Patients treated with tapentadol had a lower risk of SAEs compared with oxycodone (RR: 0.53; 95% CI, 0.28 to 1.00). The incidence of treatment discontinuation due to AEs were statistically significantly lower in the tapentadol groups compared with oxycodone groups (RR: 0.58; 95% CI, 0.47 to 0.71).

Results of Indirect Comparison: Five out of eight tapentadol trials (62.5%) had a duration of longer than 10 weeks; this percentage was 55% for oxycodone trials, 25% for buprenorphine trials, and less than 20% for morphine, fentanyl, and oxymorphone trials. The proportion of patients with prior experience with opioid also varied across trials; e.g., ranged from 15.7% to 53.4% in the tapentadol trials. No sensitivity analyses were reported that explored these effects. Results of indirect comparison presented in the published Riemsma review were generated using fixed-effect models. It is unclear how many trials contributed to the analyses of the following outcome measures. In addition, there were no network diagrams provided in the published article for each of the outcome measures.

Pain Intensity

Tapentadol showed a greater reduction of pain intensity from baseline than morphine (mean difference –3.93; 95% CI, –6.86 to –1.00), oxycodone (mean difference –2.03; 95% CI, –3.34 to –0.72), hydromorphone (mean difference –8.00; 95% CI, –11.59 to –4.41) and placebo (mean difference –6.13; 95% CI, –7.51 to –4.75). All other comparisons showed non-significant differences in pain intensity; none of the other interventions were significantly superior to tapentadol in terms of pain intensity. Results of the number of patients with a 30% reduction in pain intensity favoured tapentadol when compared with oxycodone (odds ratio [OR]: 0.58; 95% CI, 0.49 to 0.69) or hydromorphone (OR: 0.59; 95% CI, 0.37 to 0.95). Similarly, results of the number of patients with a 50% reduction in pain intensity favoured tapentadol when compared with other interventions (data not presented in the published article).

Patient's Global Impression of Change

The numbers of patients who reported "very much improved" or "much improved" scores for PGIC were higher for tapentadol when compared with oxycodone (OR: 0.81; 95% CI, 0.71 to 0.93) and placebo (OR: 0.48; 95% CI, 0.41 to 0.56).

Health-Related Quality of Life

Tapentadol was superior to oxycodone (mean difference: 1.73; 95% CI, 0.05 to 3.41) for quality of life (instruments not specified, assuming the use of a 100-point standardized scale), but inferior to transdermal fentanyl (mean difference: –12.09; 95% CI, –16.81 to –7.37) and oxymorphone (mean difference: –45.20; 95% CI, –51.16 to –39.24).

Serious Adverse Events

No statistically significant differences were detected in the comparisons between tapentadol and other opioids. It is unclear how many trials contributed to the analysis of SAEs.

Treatment Discontinuation Due to Adverse Events

Treatment with tapentadol was related to more withdrawals due to AEs than placebo (OR: 0.33; 95% CI, 0.27 to 0.40). However, all other comparators reported more withdrawals due to AEs than tapentadol; significant differences were with morphine (OR: 2.03; 95% CI, 1.42 to 2.90), oxycodone (OR: 2.31; 95% CI, 2.01 to 2.65), transdermal fentanyl (OR: 1.82; 95% CI, 1.21 to 2.74), oxymorphone (OR: 4.27; 95% CI, 2.82 to 6.47), and hydromorphone (OR: 2.38; 95% CI, 1.73 to 3.26).

Critical Appraisal

In the Riemsma review, the analyses were based on a systematic review of the literature to identify all relevant studies. The literature search was comprehensive but outdated (up to 2010). The methods for study selection and data extraction were suitable. Risk of bias of all individual studies was assessed using the Cochrane Collaboration checklist, and was low in general by the authors. However, from the systematic review we know that high and unbalanced study discontinuation in the reviewed tapentadol trials is expected to bias results. Thus, it is unclear why the authors determined there was low risk of bias in the included trials for the NMA. The outcome measures assessed in the NMA were appropriate and consistent with the key efficacy and safety assessments included in the CDR review. However, tapentadol is not compared with weak opioids (e.g., codeine or tramadol).

One of the potential limitations of the NMA body of evidence was that some important patient characteristics (such as prior opioid experience and use of rescue medication) were not reported. Hence, potential sources of heterogeneity with respect to the baseline characteristics and other important factors across the included studies were unable to be assessed comprehensively. In addition, the small network size (in some cases there was only one trial that provided information per treatment, so there was a lack of power to consider covariates in the models) and the differences among the trials made it challenging to establish reliable results. Stratified analyses were planned but not actually performed in this review, due to the insufficient number of studies within the network.

The indirect comparisons were carried out using a regression model approach, where the authors claimed that this was a valid method, straightforward generalization of the fixed-effect meta-analysis, and the randomization can be preserved. Additional benefits of using this approach were suggested as: three or more treatment arms can be included; the similarity of the studies and possible causes for heterogeneity can be investigated (details not provided in the article, though); avoiding overweighting small studies as all random-effect models do (ensure that each patient, irrespective of the size of the study he/she participated in, contributes in the same way to estimating the coefficients); no additional assumptions needed for the zero cell arms, allowing checking the assumptions needed to model the effect parameters, in particular whether the effect parameters can be assumed to

follow a normal distribution. In this review, significant heterogeneity was found across the included trials, such as study duration, formulations and dosages of the study drugs, and patient's prior opioid experience. According to the methods described in the article, the study means for the change from baseline in pain intensity were deconstructed to create individual patient data. But the authors did not explain how they came up with the estimated adjusted outcome for the line-by-line individual patient data ("*For each participant the adjusted outcome was estimated, assuming a normal distribution*"), and the generation of estimated outcomes for individual patients were not adequately described, and the formula for correcting these outcomes is not derived or cited, and therefore we cannot draw any conclusions from the results from the change from baseline in pain intensity derived from these data. Results of the direct comparisons were generated using random-effect models, while results generated using fixed-effect models were reported for the indirect comparisons. While the authors indicated that a fixed-effect model was appropriate using this regression model-based approach in their indirect comparisons, the reasons for model selection were not elaborated. The underlying assumption of a fixed-effect analysis is that there is no study-level variability in the effect estimates, which may not have been valid in the Riemsma NMA. There are also concerns with how the continuous end point data were imputed, such as pain intensity and quality of life. The authors stated that for each participant the data entries could be imputed by assuming normal distributions of such continuous data, and the methods for correction (for slight deviation from normal distribution) was provided, but they did not justify or indicate whether they had or could not examine those assumptions.

Comparisons of the results from direct and indirect estimates were possible for some of the outcomes, such as change in pain intensity from baseline, and a 30% or a 50% reduction in pain intensity. Both results favoured tapentadol when compared with oxycodone.

Data of NMAs were insufficiently reported; for example, the individual network diagram for each of the reported outcome was not provided, and a description on the number of trials contributing to the analysis of a particular outcome was lacking.

Other issues raised in this NMA included: all doses and formulations were combined in the analyses without providing a clinical justification or a planned exploration of the potential impact on data analysis (although this may not be feasible due to limited data); all durations of follow-up were combined in the analyses without providing a clinical justification; and no results of subgroup analysis was reported although the authors indicated that subgroup analysis based on study duration was performed. The authors' decision to consider all doses and formulations of a drug as a single intervention is considered by the CDR reviewer to be inappropriate and a major limitation, as patient response (both in terms of efficacy and adverse events) may be expected to differ between immediate-release and long-acting formulations. In addition, the analysis does not address the needs for this CDR review (i.e., efficacy and safety specific to tapentadol ER in relation to other long-acting opioids).

The study was funded by the industry.

Review of Meng Et Al.[93]

Objectives and Rationale for Meng Review

To evaluate the tolerability of opioid analgesia by performing an NMA of RCTs investigating the effects of opioids for the management of chronic pain.

Methods for Meng Review

The NMA was based on a systematic review of the literature, which included both electronic and manual search components. Multiple databases were searched from the inception date of respective databases and June 2016. Two reviewers independently screened the literature. Eligibility criteria for this study are presented in Table 64. Overall, RCTs recruiting patients with chronic pain (cancer or non-cancer) to treat with an opioid drug were included if at least one of the following endpoints were reported: incidence of AEs, incidence of constipation, trial withdrawal, or patient satisfaction. Bayesian NMAs were used to assess indirect comparisons. The study was not sponsored by the industry.

Data Extraction

Data extraction was performed by two reviews independently.

Comparators

Opioid drugs either alone or in combination with N-methyl-D-aspartate-receptor antagonist.

Outcomes

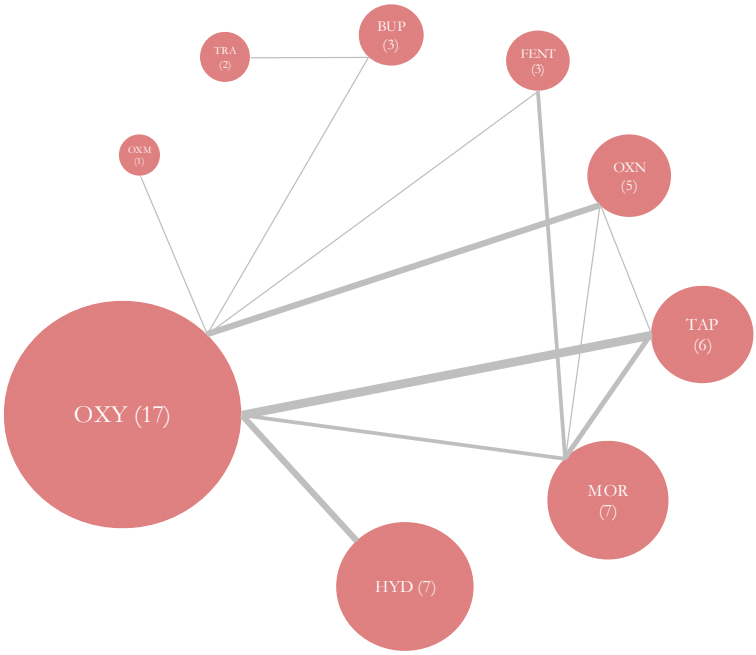
Study end points included incidence of AEs, incidence of constipation, trial withdrawal rate, and patient satisfaction with treatment. The incidence of AEs was the primary end point of this review, while the rest of the outcome measures were secondary outcomes.

Quality Assessment

Quality of the included trials was examined using the Cochrane Collaboration's tool for the assessment of the risk of bias.

Evidence Network

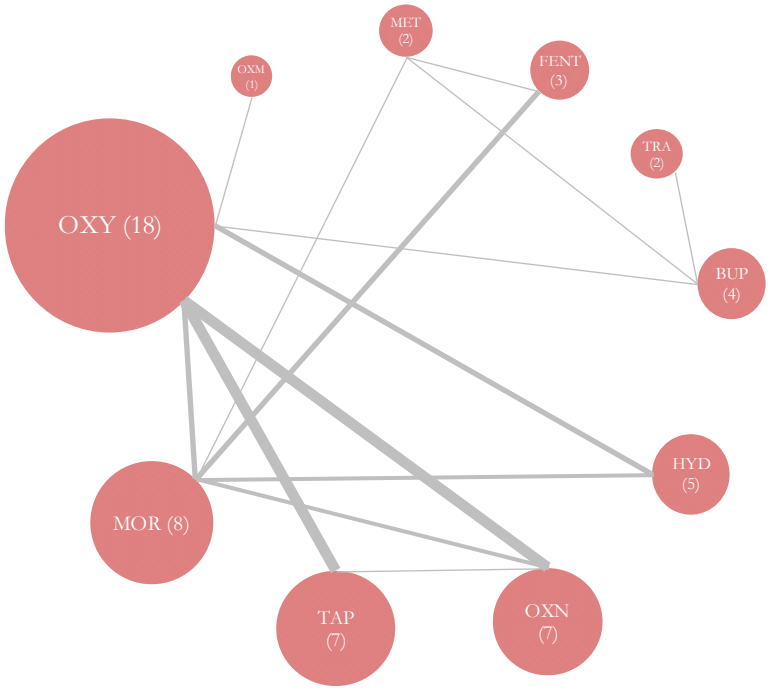
Figure 4: Network Diagram of the Incidence of Adverse Events Network Meta-Analysis



BUP = buprenorphine; FENT = fentanyl; HYD = hydromorphone; MOR = morphine; OXM = oxymorphone; OXN = oxycodone-naloxone; OXY = oxycodone; TAP = tapentadol; TRA = tramadol.

Source: Figure S1a of Tolerability of Opioid Analgesia for Chronic Pain: A Network Meta-Analysis by Meng Z, Yu J, Acuff M, Luo C, Wang S, Yu L, and Huang R[93] is licensed under https://creativecommons.org/licenses/by/4.0/.

Figure 5: Network Diagram of Trial Withdrawal Rate Network Meta-Analysis



BUP = buprenorphine; FENT = fentanyl; HYD = hydromorphone; MET = methadone; MOR = morphine; OXM = oxymorphone; OXN = oxycodone-naloxone; OXY = oxycodone; TAP = tapentadol; TRA = tramadol.

Meta-Analysis and Indirect Comparison for Meng Review

The Bayesian random-effect Poisson regression-based probabilistic model was adopted in the NMA. Odds ratios were estimated using total number of events and accumulated patients/patient-weeks. Prior distribution for treatment effects was non-informative. The model involved calculations on 50,000 iterations with 20,000 iterations as burn-in. Statistical heterogeneity across the included trials was examined from between-trial variance of the posterior distribution. Conventional meta-analyses were performed by using the numeric values of the study end points to achieve individual and overall odds ratios between the study drugs.

Results of Meng Review

In total, 32 RCTs investigating 10 opioid drugs met the eligibility criteria. The included opioids were buprenorphine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxycodone-naloxone, oxymorphone, tapentadol, and tramadol. Overall, the trials were of moderate-to-high methodology quality. The authors indicated that there was no significant inconsistency between direct and indirect evidence for any of the study end points (data not shown).

Incidence of Adverse Events

Results of the direct comparison suggested that treatment with tapentadol was associated with fewer AEs (point estimate of OR from a random-effect model: 0.81; 95% CI, 0.73 to 0.90; I^2: 36%) compared with other opioids (oxycodone, tramadol, oxycodone-naloxone, fentanyl, and morphine). In the indirect comparison, based on the data from nine drugs in 25 trials, the incidence of AEs was lower in the tapentadol group compared with the other opioids: the ORs (95% credible interval [CrI]) were 0.84 (0.68 to 1.05) for tapentadol versus oxycodone-naloxone, 0.85 (0.54 to 1.36) for tapentadol versus tramadol, 0.79 (0.69 to 0.92) for tapentadol versus oxycodone, 0.77 (0.55 to 1.06) for tapentadol versus fentanyl, 0.77 (0.59 to 1.00) for tapentadol versus morphine, 0.76 (0.61 to 0.97) for tapentadol versus hydromorphone, 0.74 (0.51 to 1.10) for tapentadol versus buprenorphine, and 0.55 (0.37 to 0.83) for tapentadol versus oxymorphone. OR < 1 indicates favourable results for tapentadol.

Incidence of Constipation

Results of the direct comparison suggested that treatment with tapentadol was associated with fewer constipations (point estimate of OR from a random-effect model: 0.56; 95% CI, 0.44 to 0.70; I^2: 54%) compared with other opioids (oxycodone, tramadol, oxycodone/naloxone, fentanyl, and morphine). In the indirect comparison, based on the data from nine drugs in 25 trials, the incidence of constipation was lower in the tapentadol group compared with the other opioids: the ORs (95% CrI) were 0.90 (0.60 to 1.26) for tapentadol versus oxycodone-naloxone, 0.69 (0.37 to 1.24) for tapentadol versus fentanyl, 0.68 (0.21 to 2.23) for tapentadol versus tramadol, 0.52 (0.33 to 0.76) for tapentadol versus morphine, 0.51 (0.38 to 0.64) for tapentadol versus oxycodone, 0.50 (0.19 to 1.26) for tapentadol versus buprenorphine, 0.45 (0.22 to 0.87) for tapentadol versus oxymorphone, and 0.40 (0.25 to 0.59) for tapentadol versus hydromorphone. OR < 1 indicates favourable results for tapentadol.

Trial Withdrawal Rate

Results of the direct comparison suggested that treatment with tapentadol was associated with lower trial withdrawal rate (point estimate of OR from a random-effect model: 0.64; 95% CI, 0.47 to 0.88; I^2: 84%) compared with other opioids (oxycodone/naloxone, fentanyl, oxycodone, hydromorphone, and buprenorphine). In the indirect comparison, based on the data from 10 drugs in 27 trials, the trial withdrawal rate was lower in the tapentadol group compared with the other opioids: the ORs (95% CrI) were 0.58 (0.34 to 0.98) for tapentadol versus oxycodone-naloxone, 0.59 (0.24 to 1.51) for tapentadol versus fentanyl, 0.51 (0.25 to 1.00) for tapentadol versus hydromorphone, 0.50 (0.34 to 0.75) for tapentadol versus oxycodone, 0.41 (0.15 to 1.15) for tapentadol versus buprenorphine, 0.41 (0.13 to 1.30) for tapentadol versus methadone, 0.36 (0.10 to 1.33) for tapentadol versus tramadol, 0.39 (0.21 to 0.75) for tapentadol versus morphine, and 0.26 (0.08 to 0.83) for tapentadol versus oxymorphone. OR < 1 indicates favourable results for tapentadol.

Patient Satisfaction

Results of the direct comparison suggested that treatment with oxycodone-naloxone was associated with higher patient satisfaction rate (point estimate of OR from a random-effect model: 1.70; 95% CI, 1.46 to 1.98; I^2: 0%) compared with other opioids (fentanyl, tapentadol, morphine, hydromorphone, and buprenorphine). The OR for comparison between tapentadol and other opioids was 1.10 (95% CI, 0.96 to 1.25). In the indirect

comparison, based on the data from eight drugs in 15 trials, the patient satisfaction rate was higher in the oxycodone-naloxone group compared with the other opioids: the ORs (95% CrI) were 0.1.87 (0.67 to 5.31) for oxycodone-naloxone versus fentanyl, 3.44 (2.04 to 6.32) for oxycodone-naloxone versus tapentadol, 4.21 (2.76 to 7.03) for oxycodone-naloxone versus oxycodone, 4.40 (2.09 to 10.11) for oxycodone-naloxone versus buprenorphine, 4.51 (2.92 to 7.34) for oxycodone-naloxone versus morphine, 4.60 (2.68 to 8.02) for oxycodone-naloxone versus hydromorphone, and 5.44 (2.15 to 15.13) for oxycodone-naloxone versus tramadol. OR > 1 indicates favourable results for tapentadol.

Critical Appraisal of Meng Review

The analysis was based on a systematic review of the literature to identify all relevant studies. While the primary outcome measure of this review was safety, only data retrieved from RCTs may be a limitation because, in general, efficacy outcomes are the primary outcome of interest in an RCT, and safety data tend to be insufficiently reported. The methods for study selection and data extraction were appropriate. Validity of all individual studies was assessed. The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian random-effect analysis models). The outcome measures assessed in the NMA were appropriate and consistent with the key safety assessments included in the CDR review. Patient's baseline characteristics were reported in the article.

Limitations of this review include the focus on safety assessment (without distinction as to the severity of the AE), while the key efficacy outcomes, such as pain intensity, were not evaluated in this review. As with the Riemsma study, the decision to consider all doses and formulations of a drug as a single intervention is considered by the CDR reviewer to be inappropriate from a clinical perspective and a major limitation of the analysis. The analysis does not address the needs for this CDR review (i.e., efficacy and safety specific to tapentadol ER in relation to other long-acting opioids).

Conclusion

Due to the lack of sufficient head-to-head trials on data for tapentadol and other opioids for chronic pain management, NMAs were searched to provide indirect evidence on the efficacy and safety of the available opioids in the study population. Two NMAs were identified for this review. Different approaches and statistical models were adopted in the two NMAs; however, in both cases a major limitation was the decision by the authors to combine all doses and formulations of a drug and treat them as a single intervention in the analysis. This is considered by the CDR reviewer to be inappropriate from a clinical perspective and provides no evidence specific to tapentadol ER, the study drug under review. Thus, the usefulness of the results of these analyses are compromised.

Appendix 8: Summary of Additional Harms

Introduction

The aim of this supplemental issue is to summarize comparative studies of harms not observed in a randomized controlled trial setting. Studies comparing outcome measures related to opioid misuse, overdose, or diversion between tapentadol extended-release (ER) and relevant opioids were included.

Summary of Studies

From the main systematic search, 17 studies were selected for full-text screening and four studies were included. Details of the studies are provided in Table 65.

Three retrospective cross-sectional studies were included: one funded by Janssen Scientific Affairs comparing prevalence of self-reported abuse between tapentadol and other opioid analgesics (Butler 2015[94]), one comparing incidence of diversion and street price between tapentadol and other opioid analgesics (Dart 2016[95]), and the third comparing prevalence of abuse and diversion between tapentadol and other opioid analgesics (Vosburg 2018[96]).

One retrospective cohort study was included and it compared clinical outcomes and naloxone use following toxic ingestion between tapentadol and tramadol (Tsutaoka 2015[97]).

Table 65: Details of Included Studies on Additional Harms

		Butler 2015	Dart 2016	Vosburg 2018	Tsutaoka 2015
Designs and Populations	**Study design**	Retrospective cross-sectional study	Retrospective cross-sectional study	Retrospective cross-sectional study	Retrospective cohort study
	Locations	US	US	US	US
	Sample size (N)	113,914	38,388 diversion cases		8,783 cases
	Data source(s)	NAVIPPRO ASI-MV surveillance system (624 facilities in 38 states) IMS Health for prescription volume data	RADARS System (260 drug diversion investigators in 49 states) StreetRx for prices paid for licit or illicit drugs IMS Health for prescription volume data	Poison Center, Drug Diversion, and Treatment Center Programs Combined data streams from the RADARS System IMS Health for prescription volume data	National Poison Data System of the American Association of Poison Control Centers
	Study period	January 2011 to September 2012	October 2011 to September 2014	October 2011 to June 2016	June 2009 to December 2011
Drugs	**Exposure**	Tapentadol ER and IR, combined and individually	Tapentadol ER and IR individually	Tapentadol ER and IR combined	Tapentadol ingestion alone, followed by a known toxic medical outcome
	Comparator(s)	Oxymorphone, hydromorphone, hydrocodone, morphine, fentanyl, oxycodone, tramadol, and buprenorphine	Oxycodone, hydromorphone IR and ER, oxymorphone, morphine IR and ER, and methadone	Tramadol, hydrocodone, morphine, oxycodone, hydromorphone, and oxymorphone	Tramadol ingestion alone, followed by a known toxic medical outcome

		Butler 2015	Dart 2016	Vosburg 2018	Tsutaoka 2015
Outcomes	**Outcome measures**	Prevalence of self-reported abuse during the previous 30 days, both unadjusted and adjusted for prescription volume during the study period	• Incidence (estimated in the general population) of drug diversion cases (resulting in written complaint or report), both unadjusted and adjusted for prescription volume during the study period • Median street price	• Prevalence of intentional abuse (poison centres) • Prevalence of drug diversion • Prevalence of self-reported abuse during the previous 30 days • The above, both unadjusted and adjusted for prescription volume during the study period	• Percentage of patients with mild, moderate, or severe medical outcomes • Clinical effects • Naloxone use

ASI-MV = Addiction Severity Index-Multimedia Version; ER = extended release; IR = immediate release; NAVIPPRO = National Addictions Vigilance Intervention and Prevention Program; RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance.

Source: Butler et al. 2015,[94] Dart et al. 2016,[95] Tsutaoka 2015 et al.,[97] Vosburg et al. 2018.[96]

Methods

Butler 2015

This retrospective cross-sectional study examined the relative prevalence of self-reported abuse of tapentadol and eight specific comparators (immediate release [IR], ER, or long-acting formulations of tramadol, oxymorphone, hydromorphone, hydrocodone, morphine, fentanyl, and oxycodone) using data from a large, national sample of patients (113,914 adults) assessed for substance use problems in the US. Abuse was determined through self-report during the Addiction Severity Index-Multimedia Version interview. Substance abuse was assessed through response to substance-specific questions about alternate routes of administration, source of the substance, and use of the substance not as prescribed for pain. Prevalence and prescription-adjusted prevalence of past 30-day abuse of tapentadol as a compound, as well as its IR and ER formulations individually, with the comparators were measured. Generalized estimating equation Poisson regression models accounting for within-subject correlation (as respondents were classified per drug) were used to estimate probability of abuse and estimates of prevalence controlled for gender, age category, race, and geographic region.

Dart 2016

This retrospective cross-sectional study examined diversion rates and street prices of tapentadol IR and ER compared with other opioids (oxycodone, hydromorphone IR and ER, oxymorphone, morphine IR and ER, and methadone). The Researched Abuse, Diversion and Addiction-Related Surveillance's (RADARS) Drug Diversion Program monitors the number of cases opened by drug diversion investigators throughout the US and StreetRx uses online crowdsourcing to estimate the street price of controlled substances. Drug diversion rates were calculated per population and per prescriptions dispensed.

Vosburg 2018

This retrospective cross-sectional study examined relative prevalence of intentional abuse, drug diversion, and self-reported abuse of tapentadol and six comparators. Data from the RADARS System, which provides post-marketing surveillance data regarding prescription

medication abuse, misuse, and diversion to various stakeholders was used.[96] The following RADARS System data streams were used: Poison Center Program, Drug Diversion Program, and Treatment Center Programs Combined. Any formulations of tapentadol were examined, including IR, ER, or unknown formulations. Self-reported abuse included endorsements in a self-administered questionnaire of past month use to get high with a drug of interest. There were no results specific for tapentadol ER reported. Rates of abuse and diversion of tapentadol-containing products were compared with products containing oxycodone, hydrocodone, oxymorphone, hydromorphone, morphine, and tramadol, using the following three denominators: population, total number of prescriptions dispensed, and total number of dosage units dispensed. Event rates were calculated by dividing the sum of events by the sum of one of the denominators.

Tsutaoka 2015

This retrospective cohort study examined the clinical outcomes following potentially toxic exposures of tapentadol and tramadol. There were no distinctions made based on ER and IR formulations. Patients with sole ingestion of one of the drugs and a known outcome were included. Clinical effects, medical outcomes (mild or other), and use of naloxone were compared using Fisher's exact test with the Bonferroni correction used for multiple comparisons.

Limitations

The limitations common to all of the studies are that they were retrospective and observational. There was no randomization to the different interventions and only one of the four studies (Butler 2015) attempted to adjust for potential confounders aside from prescription volume per intervention. It is unclear whether the analyses were pre-specified in a protocol. Self-reported substance abuse in patients assessed for substance abuse treatment, exposure, or intended substance abuse reported to poison centres, and reported cases of diversion may not capture the full range of substance abuse or misuse or diversion activities that occur. Also, the credibility of self-reported substance abuse and cases reported as intentional abuse at poison centres is unclear.

The results may not be generalizable to tapentadol ER and other opioids in the Canadian setting as all of the studies used data from the US population, and the Vosburg and Tsutaoka studies combined results for both the ER and IR formulations of tapentadol. Furthermore, it is possible that the results for all of the studies contained a mixture of cases with the older tapentadol formulation (known as Nucynta Controlled-Release in Canada) and the newer formulation (Nucynta Extended-Release in Canada). Given that the newer formulation was intended to have abuse deterrent properties, this may be an important distinction for the substance abuse and diversion outcomes.

Results

Butler 2015

Tapentadol ER had the lowest estimate of prevalence of abuse of all the comparators and was statistically significantly different than the comparators, except for hydromorphone ER. The unadjusted prevalence as a proportion of the total assessments (possible range of 0 to 1) was 0.000140 (95% confidence interval [CI], 0.000057 to 0.000343) with relative risks versus tapentadol ER ranging from 1.10 for hydromorphone ER to 315.45 for oxycodone

ER. The prescription-adjusted prevalence of tapentadol ER abuse was 0.000024 (95% CI, 0.000010 to 0.000060). Relative risks versus tapentadol ER were 1.92 for hydromorphone ER, 1.96 for fentanyl ER, 2.31 for tramadol ER, 3.1 for morphine ER, 7.6 for buprenorphine in combination, 12.5 for oxycodone ER, and 15.8 for buprenorphine alone.

Dart 2016

From the fourth quarter in 2011 to the third quarter in 2014, there were seven cases of tapentadol ER diversion, 56 cases of tapentadol IR diversion, and 38,325 cases of diversion of the pooled comparators. The average quarterly rate of tapentadol ER diversion was 0.001 (95% CI, 0 to 0.001) compared with 1.495 (95% CI, 1.366, 1.637) for the pooled comparators per 100,000 population and 0.016 (95% CI, 0.007 to 0.034) compared with 0.172 (95% CI, 0.158 to 0.187) for the pooled comparators per 1,000 prescriptions dispensed.

Median street price in US dollars per milligram was 0.10 (interquartile range [IQR], 0.06 to 0.15) for tapentadol ER (N = 12) and 1.00 (IQR, 0.60 to 2.00) for the other opioids pooled (N = 11,539).

Vosburg 2018

Using data from poison centres, the average quarterly rate of intentional abuse of tapentadol per 1,000,000 people was 0.015 (95% CI, 0.012 to 0.019), which was the lowest among the comparators. Rate ratios versus tapentadol were 8.9 for hydromorphone, 17.8 for morphine, 33.7 for tramadol, and 84.3 for oxycodone.

The average quarterly rate of intentional abuse of tapentadol per 10,000 prescriptions dispensed was 0.207 (95% CI, 0.166 to 0.255). Rate ratios versus tapentadol were 0.77 for tramadol, 1.36 for oxycodone, 1.81 for morphine, and 2.58 for hydromorphone.

The average quarterly rate of intentional abuse of tapentadol per 100,000 dosage units dispensed was 0.028 (95% CI, 0.023 to 0.035). Rate ratios versus tapentadol were 0.77 for tramadol, 1.28 for oxycodone, 1.86 for morphine, and 2.2 for hydromorphone.

The average quarterly rate of diversion per 1,000,000 people was lowest out of all the comparators when population, regardless of whether 1,000,000 population (0.029 [95% CI, 0.022 to 0.038]), 10,000 prescriptions dispensed (0.334 [95% CI, 0.254, 0.432]), or 100,000 dosage units dispensed (0.045 [95% CI, 0.034 to 0.058]) was used as the denominator. Of the relevant comparators, oxycodone and hydromorphone had the highest rates of diversion per 1,000,000 population (rate ratios of 316.9 and 45.4 versus tapentadol), 10,000 prescriptions dispensed (rate ratios of 6.3 and 16.2 versus tapentadol), and 100,000 dosage units dispensed (rate ratios of 6.1 and 13.9 versus tapentadol). Tapentadol and tramadol were similar in terms of diversion per prescription dispensed and per dosage units dispensed.

Using data from treatment centre programs, the average quarterly rate of past month self-reported tapentadol abuse was 0.245 (95% CI, 0.228 to 0263) per 1,000,000 population, 3.162 (95% CI, 2.939 to 2.298) per 10,000 prescriptions dispensed, and 0.436 (95% CI, 0.405 to 0.468) per 100,000 dosage units dispensed. Rate ratios per 1,000,000 population versus tapentadol were 3.5 for tramadol, 23.2 for hydromorphone, 23.5 for morphine, and 53.0 for oxycodone. Rate ratios per 10,000 prescriptions dispensed versus tapentadol were 0.08 for tramadol, 0.83 for oxycodone, 2.44 for morphine, and 6.72 for hydromorphone.

Rate ratios per 100,000 dosage units dispensed versus tapentadol were 0.08 for tramadol, 0.77 for oxycodone, 2.49 for morphine, and 5.67 for hydromorphone.

Tsutaoka 2015

Most exposures occurred in adults for both tapentadol and tramadol (82% for tapentadol and 64% for tramadol) and there was a higher proportion of exposures in children under six years of age for tramadol (21%) compared with tapentadol (14%). In patients over 19 year of age, the most common reasons for tapentadol exposure were suspected suicide (32%) and therapeutic error (25%), while the most common reasons for tramadol exposure were suspected suicide (43%) and intentional misuse (16%).

Results for medical outcomes and naloxone use are presented in Table 66. Ingestion of tapentadol was associated with a higher risk for severe medical outcomes (risk ratio: 1.24 [95% CI, 1.04 to 1.48]) and higher risk of naloxone use (risk ratio: 3.80 [95% CI, 2.96 to 4.88]) compared with ingestion of tramadol. Compared with tramadol, tapentadol ingestion was also associated with statistically significantly higher rates of respiratory depression (relative risk of 5.56), coma (4.16), drowsiness or lethargy (1.38), slurred speech (3.51), hallucination or delusion (7.25), and confusion (2.54). Tramadol ingestion was associated with higher rates of seizures (relative risk of 7.94) and vomiting (1.96).

Table 66: Summary of Results for Tsutaoka 2014

	Tapentadol N = 217	Tramadol N = 8,566
Effect category, n (%)		
No effect	60 (28)	3,195 (37)
Minor effect	76 (35)	2,787 (33)
Moderate effect	69 (32)	2,160 (25)
Major effect	11 (5)	414 (5)
Death	1 (0.5)	10 (0.1)
Risk ratio for severe outcome (moderate or major effect or death), tapentadol vs. tramadol (95% CI)	1.24 (1.04 to 1.48)	
Naloxone use, n (%)	52 (24)	540 (6)
Risk ratio for naloxone use, tapentadol vs. tramadol (95% CI)	3.80 (2.96 to 4.88)	

CI = confidence interval; vs. = versus.

Source: Tsutaoka et al. 2014.[97]

Summary

Four retrospective studies conducted in the US of tapentadol abuse, diversion, and medical outcomes following misuse compared with other opioids were summarized. Tapentadol abuse and diversion were reported less often than all comparator opioids.

In a study using data from patients assessed for substance use problems from 2011 to 2012 in the National Addictions Vigilance Intervention and Prevention Program, tapentadol ER was found to have the lowest prevalence of self-reported abuse per population and per prescriptions dispensed of all the ER opioids, which included fentanyl ER, tramadol ER, morphine ER, buprenorphine in combination, oxycodone ER, and buprenorphine alone. In a study using data from 2011 to 2016 from RADARS, tapentadol (IR and ER combined) had the lowest unadjusted rate of intentional abuse reported from poison control centres out of all the opioids, which included tramadol, oxycodone, morphine, and hydromorphone.

However, when adjusted for prescriptions and dosage units dispensed, rates of intentional abuse became higher than those of tramadol. Self-reported abuse assessed from treatment centre programs was also lowest for tapentadol when unadjusted. Again, the relevant comparators were tramadol, oxycodone, morphine, and hydromorphone. When adjusted by prescription volume, rates of self-reported abuse of tapentadol were higher than for tramadol and oxycodone.

Results from two studies indicated that tapentadol was rarely sold illicitly in the US. In one study, diversion rates of tapentadol were lower than for other opioids pooled together and in the second study, diversion rates of tapentadol were the lowest among the opioids (including morphine, oxycodone, and hydromorphone) and similar to those of tramadol.

In poison control centre cases of tapentadol and tramadol ingestion, medical effects that were moderate or more severe and naloxone use were more likely with tapentadol ingestion. Tapentadol ingestion was associated with higher rates of respiratory depression, coma, drowsiness or lethargy, slurred speech, hallucination or delusion, and confusion while tramadol ingestion was associated with higher rates of seizures and vomiting.

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