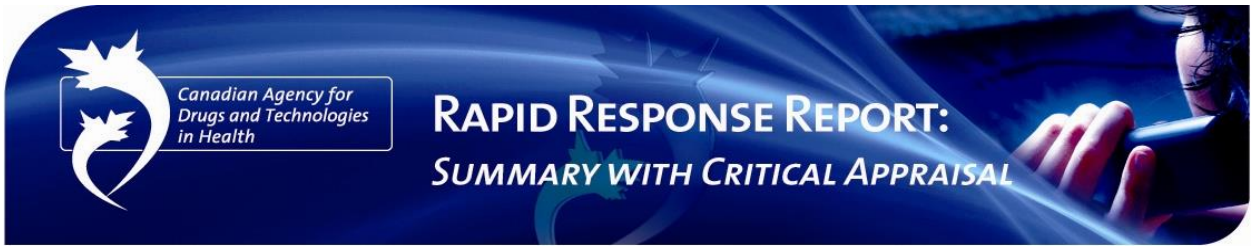

TITLE: Long-acting Opioids for Chronic Non-cancer Pain: A Review of the Clinical Efficacy and Safety

DATE: 27 August 2015

CONTEXT AND POLICY ISSUES

Chronic non-cancer pain (CNCP) of neuropathic or proprioceptive origin is a source of substantial morbidity, although prevalence estimates vary according to definitions and study methods. The Canadian Pain Society estimates that one in five adults suffers from chronic pain, which increases with age to a prevalence as high as 65% to 80% amongst seniors.[1] Also, the Canadian Guideline for Safe and Effective use of Opioids for CNCP quotes prevalence figures of 27% of community-living seniors and 38% of those in long-term care.[2] Chronic pain following major surgery, including joint replacement, occurs in an estimated 10% to 50% of patients, with severe pain in 2% to 10%.[1] Neuropathic pain occurs in an estimated 8.2% of diabetics, which in the Canadian population translates to a prevalence of one million people affected.[2] Low back pain (15% of the population in an American survey), and osteoarthritis (3 million Canadians) are two common causes of chronic pain.[2] Chronic pain is associated with poor quality of life, decreased work performance and capacity, and greatly increased risk of depression and suicide.[1,2]

Opioid analgesics are used widely in the treatment of chronic pain.[2] The majority of evidence, however, is from studies on short term use,[3] and opioids are associated with individual adverse events of sedation, cognitive slowing, respiratory depression, overdose, and substance dependence.[3] Upward trends of prescription of opioids have been associated with increased reports of opioid-related deaths, addiction, and drug diversion.[2-4] It, therefore, is important that opioid prescription be tailored appropriately to need.

Long-acting opioids have been recommended for the management of chronic pain to improve compliance.[2] A 2011 descriptive systematic Drug Class Review (Carson 2011)[5] identified 10 trials from fair to poor quality that compared long-acting opioids with each other, but concluded that there was insufficient evidence to suggest that any one was superior. The authors found no significant difference in measures of pain relief or function in trials of long-acting opioids with the exception of two poor-quality open-label trials.[5] This rapid response report reviews recent

research comparing long-acting opioids, such as morphine, hydromorphone, oxycodone, and fentanyl, in adults with chronic non-cancer pain.

RESEARCH QUESTION

What is the comparative efficacy and safety of long-acting opioids in adults with chronic non-cancer pain?

KEY FINDINGS

One systematic review of long-term (>3 months) treatment and one extension study of an earlier randomized controlled trial comparing two opioids were identified. There is insufficient evidence assessing long-acting opioids, and insufficient evidence to discriminate between the four long-acting opioids in terms of efficacy and safety.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1st, 2011 and July 29, 2015.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with chronic non-cancer pain
Intervention	Morphine, long-acting, oral Hydromorphone, long-acting, oral Oxycodone, long-acting, oral Fentanyl, long-acting, transdermal
Comparator	Morphine, long-acting, oral Hydromorphone, long-acting, oral Oxycodone, long-acting, oral Fentanyl, long-acting, transdermal
Outcomes	Efficacy outcomes for the management of CNCP: • Pain relief (≥ 30% reduction in pain intensity is considered clinically significant) • Functional outcomes Safety outcomes: • Incidence of adverse events • Dropout rates due to adverse events or lack of pain relief

Study Designs	Health technology assessments (HTAs), Systematic reviews (SRs) Meta-analyses (MAs), Randomized controlled trials (RCTs)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, they did not report long-acting opioids separately from other forms, or were published prior to 2011.

Critical Appraisal of Individual Studies

The included systematic review was critically appraised using AMSTAR.[6] The extension study was appraised for blinding, patient attrition, comparability of groups at baseline and comparability to the original RCT population. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 442 citations were identified in the literature search. Following screening of titles and abstracts, 433 citations were excluded and nine potentially relevant reports from the electronic search were retrieved for full-text review. Eight potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 15 publications were excluded for various reasons, while two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Details of the study characteristics are tabulated in Appendix 2.

Study Design

One SR on the use of long-term opioids in chronic pain included a research question on the comparative effectiveness of long-term opioids (Key question 3c). Of a total of five studies found, two were relevant to this review.[7] One of these has already been included in a previous review.[5]

One 28-week multicentre extension study (n=112) of a 24-week RCT[8] of hydromorphone extended release (ER) versus oxycodone controlled release (CR).[9]

Country of Origin

The systematic review was conducted in US, using world literature in English.[7] The extension study was conducted in Europe.[9]

Patient Population

The SR included five studies comparing long-term opioid treatments with each other for the treatment of various types of chronic pain (pain lasting >3 months) in adults (aged >18 years).[7] The authors defined long-term use as use on most days for three months or more. Eligible studies that did not report treatment duration could be included if they involved long-acting opioids.

The extension study included patients ≥18 years, with chronic non-cancer pain (i.e. pain occurring ≥20 days per month for >3 months) requiring continuous opioid treatment.[9]

Interventions and Comparators

The SR included long- and short-acting opioids used as long-term therapy that was defined as opioids used on most days over ≥3 months. For the question relevant to this review (Key Question 3c), one long acting opioid was compared with another long-acting opioid.

The extension study compared once-daily hydromorphone ER (flexible dosing to a maximum of 32 mg per day) with twice-daily oxycodone CR (flexible dosing to a maximum of 80 mg per day).[9]

Outcomes

The SR[7] sought evidence for effectiveness in terms of pain, function, and quality of life, and doses of opioids used. The harms outcomes measured were: overdose; opioid use disorder; addiction; abuse and misuse; other opioid-related harms, including gastrointestinal, falls, fractures, motor vehicle accidents; endocrinological harms; infections; cardiovascular events; cognitive harms; and psychological harms.[7]

The primary outcome measured for the extension study was the change in the Brief Pain Inventory (BPI) item “pain right now” from Baseline to Weeks 38 and 52, which measures pain on a 10-point scale with lower values representing less pain.[9] Secondary outcome measured were “pain at its worst”, “pain relief”, and pain interference items of the BPI, global assessments of efficacy, tolerability and convenience, sleep, and quality of life according to the Short Form-36, and adverse effects.[9]

Summary of Critical Appraisal

Details of the critical appraisal of the SR are tabulated in Appendix 3.

The SR[7] was well-conducted, with no significant sources of bias. It was limited to the English language literature. The research questions were determined by an advisory committee, and a protocol was prepared and published in advance. The literature search was designed by a librarian and encompassed multiple clinical databases and hand-searching of citation lists of retrieved references. Lists of included and excluded studies were provided, and the scientific quality of the studies was assessed using validated instruments. For the question of interest, the literature was sparse and the synthesis was narrative. The strength of evidence was formally assessed and used in formulating conclusions.

The extension study[9] was an extension of an open-label RCT,[8] and included around 20% of the patients in the original study. A further 17% of patients receiving hydromorphone ER and 10% of patients receiving oxycodone CR discontinued before the end of the extension study. Thus, the study is considered at high risk of bias. Patients in the extension study were described as comparable at baseline, but only the demographics were reported. Safety does not appear to have been reported for all patients. In addition, the subset of patients who entered the extension study generally had lower pain scores and greater improvement in pain and function during the 24-week RCT, and may therefore not have been representative of the study population as a whole.

Summary of Findings

Details of the summary of findings are tabulated in Appendix 4.

Systematic review

For Key Question 3c, which asked "what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?" the reviewers retrieved three randomized head-to-head trials, and two cohort studies. Of the three RCTs, one was relevant to this rapid response report, as it compared transdermal fentanyl with sustained release morphine in patients with chronic low back pain (Allan 2005). The other two studies involved comparators were not included in this report. Overall, the authors found no difference in trial outcomes relating to pain or function, with low strength of evidence and no RCT evidence for adverse outcomes relating to risk of overdose, addiction, abuse, or misuse.

The cohort study was published in 2007, and compared outcomes for transdermal fentanyl, methadone, morphine ER, and oxycodone ER. It found some evidence of difference in rates of abuse-related adverse events, but outcomes were not specific for opioid-related adverse events. The reviewers considered the strength of evidence low and the results inconclusive.

Extension study of randomized controlled trial

Fifty patients in the hydromorphone ER group and 47 patients in the oxycodone CR group completed the extension study. More patients in the hydromorphone ER group discontinued due to adverse events (4 patients versus 1 patient) or withdrew for other reasons (6 patients versus 4 patients).[9,10]

Based on the BPI scale, the change from baseline to Week 38 was -3.0 (0.3) and -2.9 (0.3), and the change from baseline to Week 52 was -2.9 (0.3) and -2.8 (0.3), for hydromorphone ER and oxycodone CR respectively. A clinically meaningful difference is 30%. Secondary efficacy measures of "pain at its worst", "pain at its least", "pain interference", and functional scales of "general activity", "walking activity", "normal work activity", and "sleep" all show similar improvement in both groups. The baseline for the activity measures was higher for the patients receiving oxycodone CR.

Adverse events were reported for 84% of patients receiving hydromorphone ER and 91% of those receiving oxycodone CR.[9] It is unclear from the denominator whether safety was reported for all patients exposed. The values are equal to the numbers who completed the study rather than those who started, but the table includes subjects who withdrew due to adverse events.

More patients receiving hydromorphone ER had adverse events leading to withdrawal (4 patients versus 1 patient), and more patients receiving hydromorphone ER had serious adverse events (6 patients versus 4 patients). Given the number of subjects in each group (hydromorphone ER 50 and oxycodone CR 47), it is difficult to assess differences in individual adverse events.

Limitations

There is insufficient evidence specifically addressing the efficacy and safety of older long-acting opioids, as opposed to more recently introduced agents (e.g., tapentadol).[5] Available studies were generally of low quality and short duration, for treatment intended for a chronic condition. A review included in this rapid response of long-term (>3 months) opioid therapy retrieved five studies comparing long-acting opioids with each other.[7]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Despite the quantity of research on the efficacy and safety of opioids, there is relatively scant evidence assessing long-acting opioids. These findings were similar to those of Carson 2011, who retrieved ten studies in total, but found that most of their individual outcomes of interest were measured in one to three trials. There is still insufficient evidence to discriminate between the different long-acting opioids in terms of efficacy and safety.

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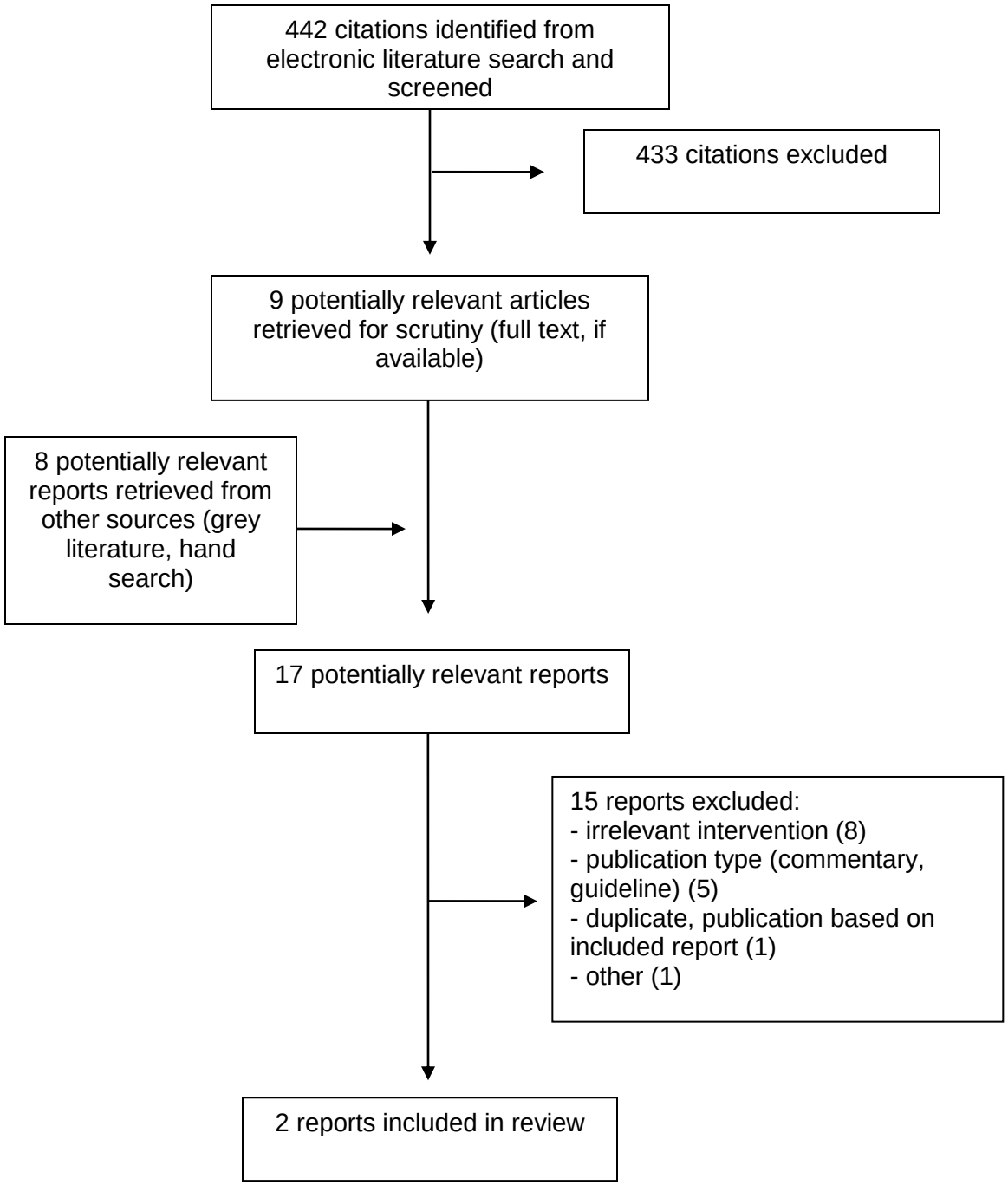
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A2-1: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparat-or(s)	Clinical Outcomes, Length of Follow-Up
Pacific Northwest Evidence-based Practice Centre 2014[7] US (AHRQ)	For specific question of interest (Key Question 3c). 3 RCTs, cohort 2 studies.	Studies of long-term opioid treatment in adults (aged >18 years) with various types of chronic pain (pain lasting >3 months) including acute exacerbations.	Key Question 3c: long-acting opioids used as long-term therapy (defined as opioids used on most days over ≥3 months)	As for intervention	Effectiveness: pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression), and doses. Harms: Overdose, opioid use disorder, addiction, abuse, and misuse; other opioid-related harms (including gastrointestinal, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms, e.g., depression).

AHRQ = Agency for Healthcare Research and Quality; RCT = randomized controlled trial

Table A2-2: Characteristics of Included Clinical Studies

First Author, Pub. Year, Country,	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Richarz 2013[9] Czech Republic, Germany, Poland, Slovakia	28-week extension study of open-label RCT (24 weeks), Binsfeld 2010.[8]	Adults ≥18 years, with chronic non-cancer pain (pain occurring ≥20 days/month for >3 months) requiring continuous opioid treatment. Completed 24 week RCT.	Once-daily hydromorphone extended release, flexible dosing to maximum 32 mg/dy.	Twice-daily oxycodone controlled-release, flexible dosing to a maximum of 80 mg/day.	Primary: BPI item "pain right now". Secondary: BPI "pain at its worst", "pain relief", pain interference, global assessments efficacy, tolerability and convenience, sleep, SF-36, adverse effects.

BPI = Brief Pain Inventory; RCT = randomized controlled trial; SF-36 = Short Form 36.

APPENDIX 3: Critical Appraisal of Included Publications

Table A3-1: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[6]

Strengths	Limitations
Pacific Northwest Evidence-based Practice Centre 2014[7]	
• An "a priori" design was provided, and a protocol was prepared and published in advance. • There was duplicate study selection and data extraction. • A comprehensive literature search was performed. • The status of publication was used as an inclusion criterion. • A list of studies (included and excluded) was provided. • The characteristics of the included studies were provided. • The scientific quality of the included studies was assessed and documented. • The scientific quality of the included studies was used appropriately in formulating conclusions. • The methods used to combine the finding of studies were appropriate. • The likelihood of publication bias was assessed. • Any conflict of interest was stated.	• Search was limited to the English language literature.

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A4-1: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Pacific Northwest Evidence-based Practice Centre 2014[7]	
For Key Question 3c. "In patients with chronic pain, what is the comparative effectiveness of different long- acting opioids on outcomes related to pain, function, and quality of life; and risk of overdose, addiction, abuse, or misuse?" Three RCTs, two of which contained a comparator not relevant to this review, and one of which was included in a previous report. Two cohort studies, one of which included a comparator not relevant to this review. **Hartung, 2007**. Retrospective cohort study. Patients with cancer or non-cancer pain and ≥1 new 28-day prescription of transdermal fentanyl, methadone, sustained release morphine, sustained release oxycodone. Based on administrative data, n=5,684. Quality: fair. Adjusted for opioid dose, co-morbidities, concomitant medications, other confounders. All patients: Death, adjusted HR Morphine ER versus: transdermal fentanyl 0.71 (95% CI 0.46 to 1.08), oxycodone ER 0.71 (95% CI 0.54 to 0.94). Chronic non-cancer pain: ED visit or hospitalization for opioid-related AE, adjusted HR Morphine ER versus oxycodone ER 0.45 (95% CI 0.26 to 0.77). Others non-significant. Authors note large, statistically significant differences in baseline characteristics between patients in groups.	Excerpted from Table A. Summary of Evidence. (pES-16.)[7]

Key question outcome	Strength of evidence grade	Conclusion
Pain and function	Low	No difference between various long-acting opioids
Assessment of risk of overdose, addiction, abuse, or misuse	Insufficient	No studies were designed to assess risk of overdose, addiction, abuse, or misuse
Overdose (as indicated by all-cause mortality)	Low	One cohort study found methadone to be associated with lower all-cause mortality risk than sustained-release morphine in a propensity adjusted analysis
Abuse and related outcomes	Insufficient	Another cohort study found some differences between long-acting opioids in rates of adverse outcomes related to abuse, but outcomes were nonspecific for opioid-related adverse events, precluding reliable conclusions

Table A4-1: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions

Richarz 2013[9]

	HM ER N=60	OC CR N=52
Mean BPI 'pain right now' (primary endpoint)		
Baseline (SEM)	6.8 (0.2)	6.9 (0.2)
Week 52 (SEM)	3.9 (0.3)	4.1 (0.3)
Mean change (SEM)	-2.9 (0.3)	-2.8 (0.3)
Mean BPI 'pain at its worst'		
Baseline (SEM)	8.1 (0.2)	8.1 (0.2)
Week 52 (SEM)	5.3 (0.2)	5.7 (0.3)
Mean BPI 'pain at its least'		
Baseline (SEM)	4.5 (0.2)	4.8 (0.3)
Week 52 (SEM)	2.6 (0.2)	2.4 (0.2)
Mean BPI 'pain interference'		
Baseline (SEM)	6.6 (0.2)	7.0 (0.3)
Week 52 (SEM)	4.2 (0.3)	4.4 (0.3)
Mean BPI 'pain interference with general activity'		
Baseline[a] (range)	7.1 (6.9 to 7.3)	7.5 (7.2 to 7.8)
Week 52[a] (range)	4.6 (4.3 to 4.8)	4.9 (4.6 to 5.1)
Mean BPI 'pain interference with walking ability'		
Baseline[a] (range)	6.7 (5.4 to 7.0)	7.0 (6.8 to 7.2)
Week 52[a] (range)	4.3 (4.0 to 4.5)	4.5 (4.2 to 4.7)
Mean BPI 'pain interference with normal work activity'		
Baseline[a] (range)	6.8 (6.6 to 7.1)	7.4 (7.1 to 7.6)
Week 52[a] (range)	4.0 (3.7 to 4.2)	4.2 (3.8 to 4.4)

[a] Values extracted from plot.
BPI = Brief Pain Inventory; HM ER = hydromorphone extended release; OC CR = oxycodone controlled release; SEM = standard error of the mean

Safety:

	HM ER N=50[a]	OC CR N=47[a]
All adverse events, n (%)	42 (84)	43 (91)
Serious adverse events	6 (12)	4 (8.5)
AEs leading to withdrawal	4 (8.0)	1 (2.1)
Common adverse events n (%)		
Nasopharyngitis	1 (2.0)	3 (6.4)
Vertigo	1 (2.0)	3 (6.4)
Weight decreased	3 (6.0)	1 (2.1)
Anorexia	3 (6.0)	0 (0)
Drug withdrawal syndrome	0 (0)	3 (6.4)
Hypertension	3 (6.0)	0 (0)
Nausea	1 (2.0)	2 (4.3)

[a] It is unclear from the paper which group of subjects these represent. The numbers, from which the percentages are calculated, are equal to the numbers who completed the study, but the table includes subjects who withdrew due to adverse events.
HM ER = hydromorphone extended release; OC CR = oxycodone controlled release

- "Overall, the results of this long-term, 28-week extension phase indicate that OROS hydromorphone ER and oxycodone CR are effective and well tolerated in patients with chronic non-cancer pain. Changes in efficacy endpoints from baseline to Week 38 and to Week 52 were generally comparable to the changes from baseline to the endpoint of the core phase, indicating a consistent analgesic effect. The long-term safety, efficacy, and convenience of OROS hydromorphone ER may afford a rational treatment option in appropriate patients." (p38)[9]

AE = adverse event; CI = confidence interval; CR = controlled release; HR = hazard ratio