

TITLE: Opioid Trial Periods for Management of Chronic Non-Cancer Pain: A Review of Clinical Effectiveness, Guidelines and Recommendations

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CONTEXT AND POLICY ISSUES

While opioid analgesics are widely used to treat chronic pain associated with cancer and end of life, controversy exists regarding the use of chronic opioid therapy (COT) for treating chronic non-cancer pain (CNCP).¹ According to the International Association for the Study of Pain, chronic pain is defined as pain that persists beyond the normal tissue healing time of three months.¹ CNCP affects approximately 25% of Canadians,^{2,3} and is often associated with common conditions including back pain, osteoarthritis, fibromyalgia, and headaches.¹ While some physicians are reluctant to prescribe opioids for CNCP due to the risk of harms, there was a 50% increase in Canadian prescriptions between 2000 and 2004.⁴ Increased prescribing is associated with increased misuse, abuse, injury and overdose-related deaths among opioid users.⁴ A national study found that most Canadians who inject opioids are now injecting prescription opioids, such as morphine (51%), and hydromorphone (50%), rather than street-derived heroin.⁵ A National Opioid Use Guideline Group (NOUGG) was formed in 2007 to provide evidence-based guidance on COT for CNCP.⁴ The Canadian guideline is intended to inform physicians about starting trials of opioid therapy for patients with CNCP and guide monitoring of long-term therapy.⁴

A trial of opioid therapy includes initiation, titration, and maintenance phases.⁶ Initiation involves selecting an appropriate opioid and dose based on a comprehensive patient assessment.⁶ During titration, the dosage is adjusted to maximize pain relief while minimizing unmanageable side effects. When the daily dose stabilizes, the patient has entered the maintenance phase. If pain gets worse after a period of stable maintenance, it may indicate disease progression, increased activity, tolerance, or an increased sensitivity to pain. If no response is found despite increasing the dosage, the opioid is discontinued.⁶

This review summarizes the clinical effectiveness, and guidelines and recommendations regarding opioid trial periods for the management of CNCP to determine the optimal duration.

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RESEARCH QUESTIONS

1. What is the clinical effectiveness of opioid trial periods for the management of chronic non-cancer pain?
2. What are the evidence-based guidelines and recommendations regarding opioid trial periods for the management of chronic non-cancer pain?

KEY MESSAGE

One non-randomized study and two guidelines suggest that opioid trial periods may be effective in managing CNCP. When conducting a trial of opioid therapy, it is recommended to start with a low dosage, increase the dosage gradually over time, and monitor opioid effectiveness until an optimal dose is reached.

METHODS

Literature Search Strategy

A focused search (with main concepts appearing in title or major subject heading) was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and May 8, 2012.

Selection Criteria and Methods

One reviewer screened citations to identify health technology assessments, systematic reviews, meta-analyses, randomized and non-randomized studies, and guidelines regarding trial periods with opioids for the management of CNCP. Potentially relevant articles were ordered based on titles and abstracts, where available. One reviewer considered full-text articles for inclusion according to the selection criteria listed in Table 1.

Table 1. Selection Criteria

Population	Patients with chronic non-cancer pain (CNCP)
Intervention	Opioids (morphine and oxycodone)
Comparator	Different trial treatment periods
Outcomes	Pain management, switching, dose escalation, trial duration
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCT), non-randomized studies, and guidelines

Exclusion Criteria

Articles were excluded if they did not satisfy the selection criteria, if they had incomplete methods, were included in a selected systematic review, were narrative reviews or case reports, or provided no opioid trial duration.

Critical Appraisal of Individual Studies

A critical appraisal of the included studies was performed based on study design. Non-randomized studies were assessed for quality using the Down's and Black instrument.⁷ Instead of calculating numeric scores, the strengths and limitations of the studies were described. Clinical practice guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 653 citations. Upon screening titles and abstracts, 10 potentially relevant articles were retrieved for full-text review. One potentially relevant report was retrieved from grey literature and hand searching. Of the 11 potentially relevant reports, eight contained irrelevant outcomes. Three publications were included in this review. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Clinical Effectiveness and Recommendations on Opioid Trial Periods for CNCP

Summary of Study Characteristics

The clinical effectiveness and evidence-based recommendations regarding opioid trial periods for the management of CNCP were reported in one non-randomized study⁸ and two guidelines.^{2,6} A United States post hoc analysis of data from an open label study evaluating analgesic tolerance in patients on oxymorphone extended release (OxymER) reported on titration/dose stabilization.⁸ The NOUGG² and Veteran's Affairs (VA) and the Department of Defense (DoD)⁶ report recommendations for using opioid therapy to manage CNCP. All reports in this review were published in 2010.^{2,6,8} While the NOUGG recommendations were published in Canada,² the VA and DoD⁶ recommendations and the non-randomized study⁸ were from the United States.

A summary of the study characteristics, critical appraisal and study findings for non-randomized studies can be found in Appendices 2, 3 and 4, respectively. Also, grading of recommendations and levels of evidence, guidelines and recommendations on opioid trial periods, and critical appraisal of guidelines are summarized in Appendices 5, 6, and 7 respectively. Finally, a summary of the clinical evidence and evidence-based recommendations regarding opioid trial periods for the management of CNCP can be found in Table 2.

1. Clinical Effectiveness of Opioid Trial Periods for CNCP

Non-Randomized Study

A post hoc analysis of a one year open label extension study examined the development of analgesic tolerance in 153 hip and knee osteoarthritis patients on OxymER.⁸ Primary analyses were limited to 62 patients who completed the study because of missing data for non-completers. No significant differences were noted between the age or baseline pain intensity ratings for completers versus non-completers. Patients had a mean age of 60 years and 71% were female. Subjects took 20 mg tablets of OxymER during the study, and dose adjustments were made in response to inadequate pain relief or unacceptable side effects. OxymER dose was calculated by pill counts at monthly visits and pain intensity was assessed at each visit using a visual analog scale.⁸

Summary of Critical Appraisal

Non-Randomized Study

The research objective, patient characteristics, intervention, outcomes and findings were described explicitly in the post hoc analysis of the open label study.⁸ There is potential for selection bias and information bias because assessors were not blinded, and patients were not randomized to treatment during the open label extension study. The primary analyses were limited to study completers because of a large amount of missing data for non-completers, so the study population may not be representative of the entire population from which they were recruited. The analysis did not include non-completers because 1563 data points were missing for non-completers. Last observation carried forward (LOCF) was used to account for missing data for completers of the study where 38 data points were missing. Pain assessments were infrequent, dose choices were limited and adverse events were not reported.⁸

Summary of Findings

Non-Randomized Study

The post hoc analysis of an open label extension study showed that most of the titration/dose stabilization changes occurred within the first 10 weeks of study. Significant increases in dose were noted from weeks 1 to 2 and 2 to 6 ($p < 0.05$).⁸ At week 6, doses stabilized suggesting that titration was complete. Following titration, 28% of patients experienced any dose changes. There was a lack of opioid tolerance in most osteoarthritis patients who completed the study.⁸ Results showed that pain ratings did not differ over time following titration and that completers had no change in dose following the titration period.⁸

2. Guidelines and Recommendations Regarding Opioid Trial Periods for CNCP

Summary of Study Characteristics

Two guidelines reported evidence-based recommendations regarding opioid trial periods for the management of CNCP.^{2,6} The Canadian NOUGG developed a national guideline for safe and effective opioid use for CNCP based on evidence and expert opinion consensus.² The guideline was intended to help physicians to decide when to initiate appropriate trials of opioid therapy for CNCP patients, and how to monitor long-term therapy, to detect and respond to

opioid misuse.² Twenty-four practice recommendations were finalized in the areas of deciding to initiate opioid therapy, conducting an opioid trial, monitoring long-term opioid therapy, treating populations with long-term opioid therapy, and managing opioid misuse and addiction in CNCP patients.² Final recommendations were based on 184 studies that met inclusion criteria, following a comprehensive literature search.²

The VA and DoD guideline was developed to identify critical decision points in the management of CNCP and to update the evidence base of the 2003 guideline.⁶ The guideline is intended to promote evidence-based management of patients with CNCP.⁶ Recommendations were provided regarding assessing potential candidates for therapy, determining the appropriateness of opioid therapy, starting the opioid trial, assessing patients for response, adjusting therapy, consultation, follow-up, discontinuation of therapy and management of special populations.⁶

Summary of Critical Appraisal

The NOUGG and VA and DoD provided evidence-based recommendations.^{2,6} The evidence-base for the Canadian review was limited to a single meta-analysis with a literature search for updates since 2006.² The VA and DoD guideline was based on a comprehensive literature but was limited to English language articles.⁶ The criteria whereby studies were included and assessed for quality were reported in both guidelines, however observational studies were not assessed for quality in the Canadian guideline.^{2,6} Both guidelines were independently funded and reported implementation plans and tools for use.^{2,6}

Summary of Findings

The United States guideline recommends that a trial of opioids be conducted for chronic pain when other analgesic approaches are not sufficient.⁶ NOUGG guidelines also recommend that the most appropriate opioid for trial therapy be selected using a stepped approach lending consideration to safety.² In most patients, trials with several medications may occur as no single agent is superior according to the guideline.⁶ When conducting an opioid trial, it is recommended to start with a low dose and to increase the dose gradually while monitoring opioid effectiveness until the optimal dose is reached.² For mild to moderate pain, codeine or tramadol were first line therapy followed by morphine, oxycodone or hydromorphone as second line agents.² For severe pain, morphine, oxycodone or hydromorphone were first line therapy followed by fentanyl, and lastly, methadone.² Starting doses, suggested dose increments and intervals for increase are summarized in table 2. United States guidelines recommend following up with patients no longer than two to four weeks after dosage or treatment adjustments.⁶ Small increments are appropriate for elderly or frail patients, those with low opioid tolerance and unsatisfactory pain relief in the presence of adverse effects.⁶ Larger increments may be used for patients with severe, uncontrolled pain or likely high levels of opioid tolerance. Rotating opioids may improve long-term efficacy.⁶

Table 2. Summary of the Clinical Effectiveness, Guidelines and Recommendations

Intervention	Evidence	Results
Opioid Trial Period		Clinical Effectiveness or Recommendation
Opioid Trial	1 guideline ⁶	<ul style="list-style-type: none"> • Most patients may require trials with several medications and opioid rotation may improve long-term efficacy • During titration, follow up with the patient no longer than 2 to 4 weeks after dose adjustments
OxymER	1 non-randomized study ⁸	<ul style="list-style-type: none"> • Pain stabilized after 2 weeks • Titration/dose stabilization changes occurred within the first 10 weeks • 28% of patients required dose increases after titration
IR Morphine	1 guideline ²	<ul style="list-style-type: none"> • Initial dose: 5-10 mg q 4 h as needed, max 40 mg/d • Minimum time interval for increase: 7 days • Suggested increase: 5-10 mg
CR Morphine	1 guideline ²	<ul style="list-style-type: none"> • Initial dose: 10-30 mg q, 12 h as needed • Minimum time interval for increase: 2 days, 14 days recommended • Suggested increase: NA
IR Oxycodone	1 guideline ²	<ul style="list-style-type: none"> • Initial dose: 5-10 mg q, 6 h as needed ; max 30 mg/day • Minimum time interval for increase: 7 days • Suggested increase: 5 mg/day
CR Oxycodone	1 guideline ²	<ul style="list-style-type: none"> • Initial dose: 10-20 mg q, 12 h; max 30 mg/day • Minimum time interval for increase: 2 days, 14 days recommended • Suggested increase: 10 mg/day
IR Hydromorphone	1 guideline ²	<ul style="list-style-type: none"> • Initial dose: 1-2 mg q, 4-6 h as needed; max 8 mg/day • Minimum time interval for increase: 7 days • Suggested increase: 1-2 mg/day
CR Hydromorphone	1 guideline ²	<ul style="list-style-type: none"> • Initial dose: 3 mg q, 12 h; max 9 mg/day • Minimum time interval for increase: 2 days , 14 recommended • Suggested increase: 2-4 mg/day

CR: controlled release; IR: immediate release; NA: not applicable; OxymER: oxymorphone extended-release

Limitations

The evidence included in this review has inherent limitations that restrict its usefulness in drawing conclusions about the comparative clinical effectiveness and recommendations on opioid trial periods for the management of CNCP. While one non-randomized study reported a lack of opioid tolerance in osteoarthritis patients, the study population may not represent the population (n=153) recruited as a whole because analyses were limited to 62 completers.⁸ Recommendations regarding opioid trials for the management of CNCP were limited to a Canadian guideline founded on one meta-analysis with update and an American guideline founded on a literature search limited to the English language.^{2,6} These recommendations seem to be generalizable to CNCP patients of interest for this review.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One non-randomized study and two guidelines suggest that opioid trial periods may be effective in managing CNCP.⁸ For mild to moderate pain, codeine or tramadol are recommended as first-line treatments, and morphine, oxycodone or hydromorphone as second-line therapies.² For severe pain, morphine, oxycodone, or hydromorphone are recommended as first-line therapies followed by fentanyl as a second line agent and lastly, methadone.² When conducting a trial of opioid therapy, it is recommended to start with a low dosage, increase the dosage gradually over time, and monitor opioid effectiveness until an optimal dose is reached.² During titration, it is recommended that patients be followed up no longer than 2 to 4 weeks after dosage modifications or treatment adjustments.⁶ Smaller increments in dosage are appropriate for elderly patients, those with low opioid tolerance, and patients with unsatisfactory pain relief in the presence of adverse events.⁶ Larger dose increments may be used in patients with severe uncontrolled pain or a high level opioid tolerance.⁶ Most titration/dose stabilization changes occur within the first 10 weeks of therapy according to a non-randomized study.⁸ Opioid rotation may improve long-term efficacy.⁶ Tools are available to facilitate incorporating recommendations on opioid trials for the management of CNCP into clinical practice.^{2,6}

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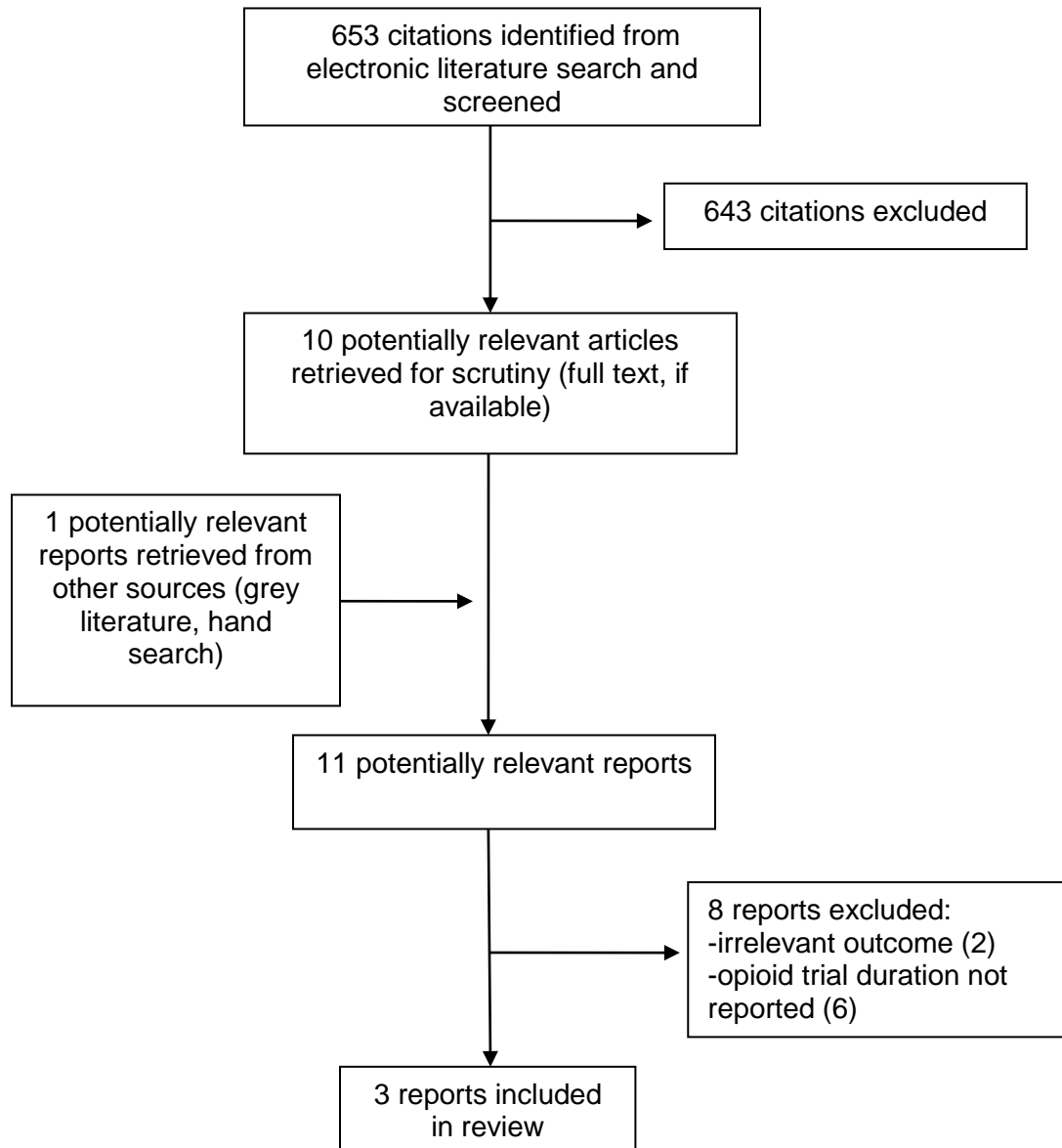
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References

1. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain*. 2009 Feb;10(2):113-30.
2. National Opioid Use Guideline Group (NOUGG). Canadian guideline for safe and effective use of opioids for chronic non-cancer pain. Version 4.6. Hamilton (ON): National Opioid Use Guideline Group (NOUGG); 2010 Apr 30.
3. Allen M. Self-reported practices in opioid management of chronic non-cancer pain: a survey of Canadian family physicians [Thesis on the Internet]. Halifax (NS): Dalhousie University; 2011 Apr. [cited 2012 May 25]. Available from: <http://dalspace.library.dal.ca/bitstream/handle/10222/13333/Allen,%20Michael,%20MSc,%20CHE,%20April%202011.pdf?sequence=1>
4. Furlan AD, Reardon Dip R, Weppler C. Opioids for chronic noncancer pain: a new Canadian practice guideline. *CMAJ*. 2010 Jun [cited 2012 May 25];182(9):923-30. Available from: <http://www.cmaj.ca/content/182/9/923>
5. Kahan M, Mailis-Gagnon A, Wilson L, Srivastava A. Canadian guideline for safe and effective use of opioids for chronic noncancer pain: clinical summary for family physicians. Part 1: general population. *Can Fam Physician* [Internet]. 2011 Nov [cited 2012 May 14];57(11):1257-66. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3215602/pdf/0571257.pdf>
6. The Management of Opioid Therapy for Chronic Pain Working Group. Clinical practice guideline: management of opioid therapy for chronic pain [Internet]. Version 2.0. Washington (DC): Department of Veterans Affairs, Department of Defense; 2010 May. [cited 2012 May 25]. Available from: http://www.healthquality.va.gov/COT_312_Full-er.pdf
7. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health* [Internet]. 1998 Jun [cited 2012 May 25];52(6):377-84. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf>
8. Harden RN, Gagnon CM, Graciosa J, Gould EM. Negligible analgesic tolerance seen with extended release oxymorphone: a post hoc analysis of open-label longitudinal data. *Pain Med*. 2010 Aug;11(8):1198-208.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Study Characteristics for Non-Randomized Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator	Clinical Outcomes Measured
Clinical Effectiveness					
<i>Non-Randomized Study</i>					
Harden ⁸ 2010 United States	Post-hoc analysis of a 1 yr MC, OL extension study where patients titrated as needed following a DB RCT (n=153)	Adults with hip and knee osteoarthritis (age: 60 yr; 71% F)	Oxymorphone extended release (OxymER) (20 mg; divided doses 8 am, 8 pm)	NA	OxymER doses (pill counts), pain intensity on visual analog scale

DB: double blind; ER: extended release; F: female; MC: multicentre; NA: not applicable; OL: open-label; RCT: randomized controlled trial

APPENDIX 3: Summary of Critical Appraisal for Non-Randomized Studies

First Author, Publication Year	Strengths	Limitations
Clinical Effectiveness of Opioid Trial Periods for CNCP		
<i>Non-Randomized Study</i>		
Harden ⁸ 2010	<ul style="list-style-type: none"> • Objective, patient characteristics, intervention, outcomes and findings were explicit. 	<ul style="list-style-type: none"> • This is an analysis of an OL extension study, so assessors were not blinded and patients were not randomized to treatment. • Time selected for titration was critical to the analysis but variable. Titration was defined to end at week 10, if week 16 was used, 87% of patients did not need dose escalations. Authors state that “there is no consensus in the literature as to what constitutes a reasonable average clinical time for titration for any opioid but say it is clear there should be an initial period of dose escalation leading to dose stabilization (pg 1204).”⁸ • Study population may not represent the entire population from which they were recruited as analyses were limited to study completers (n=62 of 153), because a significant amount of data (1,563 missing data points) were missing from non-completers (n=91). • Did not include non-completers but using last observation carried forward defeats ability to answer the question and creates the appearance of no tolerance in the subset that does drop out. • Infrequent pain assessments and limited dose choices. • Adverse events were not reported.

CNCP: chronic non-cancer pain; OL: open label

APPENDIX 4: Summary of Findings for Non-Randomized Studies

First Author, Publication Year	Main Study Findings	Authors' Conclusions
Clinical Effectiveness of Opioid Trial Periods for CNCP		
<i>Non-Randomized Study</i>		
Harden ⁸ 2010	<ul style="list-style-type: none"> • There were significant dose increases from weeks 1 to 2 and 2 to 6 ($p < 0.05$).⁸ • Doses stabilized at 6 weeks suggesting titration was complete.⁸ • Doses and pain ratings were stable when titration phase was excluded from analysis ($p = 0.751$; $p = 0.056$, respectively).⁸ • 28% of patients had dose changes following titration.⁸ • Majority of patients (72%) did not need further dose escalation following titration. By week 16, 22, 28, 34, 40, 46 and 52, 82%, 85%, 90%, 92%, 95%, 97% and 98% of patients reached stability.⁸ • While there was a significantly greater dose at week 52 compared with week 10 ($p = 0.010$), the increase in dose became insignificant after excluding 4 subjects who required two dose increases ($p = 0.103$).⁸ 	<ul style="list-style-type: none"> • “Results show that most of the titration/dose stabilization changes occurred within the first 10 weeks (pg 1198).”⁸ • “A minority (28%) of subjects required dosage increases after this titration period.(pg 1198).”⁸ • “Pain reports stabilized statistically after 2 weeks (pg 1198).”⁸ • “Findings suggest a lack of opioid tolerance in the majority (72%) of osteoarthritis patients who completes the study following a defined titration period on Oxymer (pg 1198).”⁸

CNCP: chronic non-cancer pain; ER: extended release

APPENDIX 5: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute, Publication Year, Country	Recommendation	Level of Evidence
<p>NOUGG² 2010 Canada</p>	<p>“I: Evidence from RCTs II-1: Evidence from controlled trials without randomization II-2: Evidence from cohort or case-control analytic studies, preferably from one than one centre or research group II-3: Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies III: Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees” (pg 19)²</p>	<p>“A: Recommendations are supported by evidence from RCTs. B: Recommendations are supported by:</p> <ul style="list-style-type: none"> • evidence from controlled trials without randomization, or, • evidence from cohort or case-control analytic studies, preferably from more than one centre or research group, or • evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments. <p>C: Recommendations are supported by consensus opinion of the National Advisory Panel.” (pg 19)²</p>
<p>VA/DoD⁶ 2010 Unites States</p>	<p>“I; Evidence obtained from at least one properly designed RCT. II-1: Evidence obtained from well-designed controlled trials without randomization. II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group. II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.” (pg 6)⁶</p>	<p>“A: A strong recommendation that clinicians provide the intervention to eligible patients. Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm. B: A recommendation that clinicians provide (the service) to eligible patients. At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harms. C: No recommendation for or against the routine provision of the intervention is made. At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation. D: Recommendation is made against routinely providing the intervention to asymptomatic patients. At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits. I: The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.” (pg 6)⁶</p>

NOUGG: National Opioid Use Guideline Group; VA/VoD: Veterans Affairs and Department of Defense

APPENDIX 6: Summary of Critical Appraisal of Guidelines Using AGREE

Guideline Society or Institute, Publication Year	Strengths	Limitations
NOUGG ² 2010	<ul style="list-style-type: none"> • Recommendations are evidence based • Inclusion/exclusion criteria were defined • Appraisal using Jadad • Executive summary tool • Project funded independently from industry through the Federation of Medical Regulatory Authorities of Canada and Canadian Institute of Health Research (CIHR) • Implementation plan • Updating plan 	<ul style="list-style-type: none"> • Literature search limited to a meta-analysis by Furlan with updates since 2006 • Observational studies were not assessed for quality due to lack of resources
VA/DoD ⁶ 2010	<ul style="list-style-type: none"> • Recommendations are evidence based • Strength of recommendation based on the quality of the evidence assessed using USPSTF criteria • Inclusions/exclusion criteria were defined • Algorithms and tools for implementation • Government funded 	<ul style="list-style-type: none"> • Literature search limited to the English language • Inclusion/exclusion criteria and quality assessment not reported

NOUGG: National Opioid Use Guideline Group; USPSTF: United States Preventive Services Task Force; VA/VoD: Veterans Affairs and Department of Defense

APPENDIX 7: Guidelines and Recommendations on Opioid Trial Periods for CNCP

Guideline Society or Institute, Publication Year	Recommendations
<p>NOUGG² 2010</p>	<p>Conducting an Opioid Trial:</p> <ol style="list-style-type: none"> 1. “During an opioid trial, select the most appropriate opioid for trial therapy using a stepped approach, and consider safety [Grade C].” (pg 5)² 2. “When conducting a trial of opioid therapy, start with a low dosage, increase dosage gradually and monitor opioid effectiveness until optimal dose is attained [Grade C].” (pg 5)² <ul style="list-style-type: none"> • “ Mild-to-moderate Pain: 1st line codeine or tramadol, 2nd line morphine, oxycodone or hydromorphone • Severe Pain: 1st line morphine, oxycodone or hydromorphone, 2nd line fentanyl, 3rd line methadone (pg 27) • Opioid effectiveness is determined by improved function or >30% reduction in pain intensity. During an opioid trial, schedule patient visits frequently (e.g., 2-4 weeks) to assess for changes in pain intensity and function. (pg 33) • Titration ends when the optimal dose is attained or the trial is considered a “failed trial” because the patient experiences insufficient analgesia after 2 or 3 dose increases and/or unacceptable AE and/or medical complications or there are indications of misuse or addiction. (pg 34) • IR Morphine: Initial dose: 5-10 mg q 4 h as needed, max 40 mg/d; minimum time interval for increase: 7 days; suggested increase: 5-10 mg • CR Morphine: Initial dose: 10-30 mg q 12 h; minimum time interval for increase: 2 days, 14 recommended; suggested increase: 5-10 mg/day • IR Oxycodone: Initial dose: 5-10 mg q 6 h as needed, max 30 mg/d; minimum time interval for increase: 7 days; suggested increase: 5 mg/day • CR Oxycodone: Initial dose: 10-20 mg q 12 h; minimum time interval for increase: 2 days, 14 recommended; suggested increase: 10 mg/day • IR Hydromorphone: Initial dose: 1-2 mg q 4-6 h as needed, max 8 mg/d; minimum time interval for increase: 7 days; suggested increase: 1-2 mg • CR Hydromorphone: Initial dose: 3 mg q 12 h, max 9 mg/d; minimum time interval for increase: 2 days, 14 recommended; suggested increase: 2-4 mg” (pg 35)² 3. “CNCP can be managed effectively in most patients with dosages at or below 200 mg/day or morphine or equivalent (Grade A). Consideration of a higher dose requires careful reassessment of pain and risk for misuse and frequent monitoring with evidence of improved patient outcomes [Grade C].”(pg 5)² 4. “When initiating a trial of opioid therapy for patients at higher risk for misuse, prescribe only for well-defined somatic or neuropathic pain conditions [Grade A], start with lower doses and titrate in small-dose increments [Grade B], and monitor closely for signs of aberrant drug-related behaviors [Grade C].” (pg 5)²
<p>VA/DoD⁶ 2010</p>	<p>Candidate for Trial of Opioid Therapy:</p> <ol style="list-style-type: none"> 1. “A trial of opioid for chronic pain when other analgesic approaches are insufficient [Class III, Level I].” (pg 40)⁶ 2. “No single agent is superior, in most patients, trials with several medications

Guideline Society or Institute, Publication Year	Recommendations
	<p>may be required; rotation among opioids may improve long-term efficacy [Class II, Level B].” (pg 40)⁶</p> <ol style="list-style-type: none"> 3. An opioid trial for either nociceptive or neuropathic pain [Class I, Level A].” (pg 40)⁶ 4. “Long-acting agents are effective for continuous, chronic pain [Class I, Level A].” (pg 40)⁶ 5. Start with agent and dose that have been effective in past [Class III, Level I].” (pg 40)⁶ <ul style="list-style-type: none"> • “During titration, follow up with the patient in no longer than 2 to 4 weeks after dosage modifications, or other treatment adjustments basing the frequency of follow-up on the clinical situation. • If necessary, the daily dose may be increased by 25% to 100% at a time. Smaller increments are appropriate for elderly or frail patients, those with low opioid tolerance, and patients with unsatisfactory pain relief in the presence of adverse effects. Larger increments may be used in patients with severe uncontrolled pain or likely high level of opioid tolerance. If the new dose is well tolerated but ineffective, additional increases in dose can be considered.” (pg 44)⁶

CNCP: chronic non-cancer pain; CR: controlled release; IR: immediate release; NOUGG: National Opioid Use Guideline Group; VA/VoD: Veterans Affairs and Department of Defense