The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain

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Table of Contents

Summary of recommendations

Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain

Recommendation 1: When considering therapy for patients with chronic non-cancer pain

Strong Recommendation

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Recommendation 2: For patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy

Weak Recommendation

We suggest adding a trial of opioids rather than continued therapy without opioids.

By a trial of opioids, we mean initiation, titration, and monitoring of response, with discontinuation of opioids if important improvement in pain or function is not achieved. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses. The mental illnesses identified in studies as risk factors for adverse outcomes were generally anxiety and depression, including ICD-9 definitions, as well as "psychiatric diagnosis", "mood disorder", and post-traumatic stress disorder.

Recommendation 3: For patients with chronic noncancer pain with an active substance use disorder

Strong Recommendation AGAINST

We recommend against the use of opioids

Clinicians should facilitate treatment of the underlying substance use disorders, if not yet addressed. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Recommendation 4: For patients with chronic noncancer pain with an active psychiatric disorder whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest stabilizing the the psychiatric disorder before a trial of opioids is considered

Recommendation 5: For patients with chronic noncancer pain with a history of substance use disorder, whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest continuing nonopioid therapy rather than a trial of opioids

The studies that identified a history of substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Recommendations 6 and 7: For patients with chronic noncancer pain who are beginning long term opioid therapy

Strong Recommendation

Recommendation 6: We recommend restricting the prescribed dose to less 90mg morphine equivalents daily rather than no upper limit or a higher limit on dosing

Some patients may gain important benefit at a dose of more than 90mg morphine equivalents daily. Referral to a colleague for a second opinion regarding the possibility of increasing the dose to more than 90mg morphine equivalents daily may therefore be warranted in some individuals.

Weak Recommendation

Recommendation 7: For patients with chronic noncancer pain who are beginning opioid therapy, we suggest restricting the prescribed dose to less than 50mg morphine equivalents daily.

The weak recommendation to restrict the prescribed dose to less than 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose higher than 50mg in order to potentially achieve improved pain control.

Rotation and Tapering of Opioids, for Patients with Chronic Noncancer Pain

Recommendation 8: For patients with chronic noncancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects

Weak Recommendation

We suggest rotation to other opioids rather than keeping the opioid the same

Rotation in such patients may be done in parallel with, and as a way of facilitating, dose reduction

Recommendation 9: For patients with chronic noncancer pain who are currently using 90mg morphine equivalents of opioids per day or more

Weak Recommendation

We suggest tapering opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy.

Some patients are likely to experience significant increase in pain or decrease in function that persists for more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Recommendation 10: For patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering

Strong Recommendation

We recommend a formal multidisciplinary program.

Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration that includes several health professionals whom physicians can access according to their availability (possibilities include, but are not limited to, a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist).

1 - Scope of the Guideline and How To Use the Guideline

Scope of the Guideline

What this guideline addresses
The purpose of this clinical practice guideline is to provide guidance on the use of opioids to manage chronic non-cancer pain for adults (18 years of age or older). Chronic non-cancer pain, for purposes of this guideline, includes any painful condition that persists for ≥3 months that is not associated with a diagnosis of cancer.

The target audience of this guideline are those who prescribe opioids for the management of chronic non-cancer pain or create policy regarding this issue, including but not limited to:

- Primary care physicians
- Specialists who manage patients with chronic non-cancer pain
- Nurse practitioners
- Regulatory agencies and other policy makers

Secondary audiences for this guideline include:

- Patients living with chronic non-cancer pain
- Pharmacists
- Other health care professionals who manage patients with chronic non-cancer pain

What this guideline does not address
This guideline does not address the use of opioids to manage the following:

- Cancer-related pain
- Opioid addiction or opioid use disorder
- Acute or sub-acute pain (pain lasting less than 3 months)
- Pain or suffering associated with end-of-life care

Funding
This guideline was an investigator-initiated study, supported by grants from the Canadian Institutes of Health Research and Health Canada. Health Canada personnel provided non-binding feedback during the preparation of the guideline. The funders had no other role in the design or conduct of the study; collection, analysis, and interpretation of the data; or preparation, review, or approval of the guideline. Final decisions regarding the protocol and issues that arose during the guideline development process were solely the responsibility of the Guideline Steering Committee.

How to use and understand these guidelines
These guidelines provide prescribers and patients with a basis for decisions about using opioids to manage chronic non-cancer pain. Prescribers, patients, and other stakeholders, in particular regulatory agents or the courts, should not view these guidelines as absolute. No guideline can account for the unique features of patients and their clinical circumstances, and this guideline is not meant to replace clinical judgement.

Statements about qualifying remarks and values and preferences are integral parts of the recommendations meant to facilitate accurate interpretation of the Guideline. These should never be omitted when quoting or translating recommendations from these guidelines.

Understanding strength of recommendations
Recommendations in this guideline are, according to standards for trustworthy guidelines and the GRADE system, categorized as **strong or weak recommendations**. *[84] [127]*

Strong recommendations indicate that all or almost all fully informed patients would choose the recommended course of action, and indicate to clinicians that the recommendation is appropriate for all or almost all individuals. Strong recommendations represent candidates for quality of care criteria or performance indicators.

Weak recommendations indicate that the majority of informed patients would choose the suggested course of action, but an appreciable minority would not. With weak recommendations, clinicians should recognize that different choices will be appropriate for individual patients, and should assist patients to arrive at a decision consistent with their values and preferences. Weak recommendations should not be used as a basis for Standards of Practice (other than to mandate shared decision-making).

The guideline also contains best practice statements and clinical expert guidance, which are distinct from formally GRADEd recommendations. Good practice statements represent common sense practice, are supported by indirect evidence, and associated with large net benefit. Clinical expert guidance provides direction in areas for which there is either no published evidence, or insufficient evidence to

justify a formal recommendation, and does not have the force of either GRADEd recommendations or good practice statements.

2 - Background and methods

Background

Chronic non-cancer pain comprises any painful condition that persists for three months or longer and is not associated with malignancy. According to seven national surveys conducted between 1994 and 2008, 15-19% of Canadian adults experience chronic non-cancer pain. *[178]*The prevalence of chronic non-cancer pain increases with age, and is significantly higher among women and those with lower education. *[178] [170]* Although chronic non-cancer pain is defined as lasting longer than three months, in most cases the duration is much longer. For example, one study found that as many as 54% of Canadians reporting chronic non-cancer pain suffered from pain for more than 10 years, while up to 25% suffered for more than 20 years. *[188]*

Chronic non-cancer pain interferes with activities of daily living and has a marked negative impact on quality of life and physical functioning. *[103] [145] [218] [48] [196]*Disability secondary to chronic non-cancer pain is associated with significant lost work and decreased work effectiveness. *[25] [209] [189] [175]* Due to lost productivity and increased health care expenses, chronic non-cancer pain is associated with large costs. *[105]* In Ontario, the incremental annual cost to manage chronic pain is $1,742 per person. *[98]* In Canada, total cost estimates associated with managing chronic non-cancer pain, including direct and indirect expenses, total $43 billion per year. *[138] [9]*Chronic pain not caused by cancer is the primary cause of health care resource consumption and disability among working age adults. *[137]*

Clinicians have increased their prescribing of opioids for chronic non-cancer pain, particularly in North America. Dispensing of prescription opioids in Canada has increased steadily since 2000, from 10,209 defined daily doses per million population per day in 2001 to 2003 to 30,540 in 2012 to 2014. *[106] [107]*High-dose opioid dispensing (defined as a daily dose exceeding 200mg morphine equivalents) has also increased, from 781 units per 1000 population in 2006 to 961 per 1000 population in 2011. *[76]* Canada has the second highest rate of opioid prescribing in the world when measured using defined daily doses, and the highest rate overall when considering morphine equivalents dispensed.

Some investigators have concluded that these trends have occurred without any significant change in the underlying population prevalence of chronic non-cancer pain and without new evidence for the efficacy of long-term opioid therapy. *[198]* These increases may be explained, in part, by aggressive marketing of opioids and efforts to encourage clinicians to become more proactive in identifying and treating chronic pain. *[155] [38] [112] [211]*

Opioid prescribing for chronic non-cancer pain varies widely among Canadian physicians. A study of drug prescribing behaviors in Ontario in 2006, found that family physicians in the highest quintile (n = 1,978) had an average opioid-prescribing rate of 931.5 per 1000 eligible patients during the study year, a rate 55 times higher than physicians in the lowermost quintile (n = 1,977), who had an average opioid prescribing rate of 16.7 per 1000 eligible patients. *[51]*

The use of opioids for chronic non-cancer pain is accompanied by significant risks. In Ontario, annual admissions to publicly funded treatment programs for opioid-related problems doubled between 2004 and 2013, from 8,799 to 18,232. *[148] [61]* The number of annual opioid related deaths in Ontario (excluding deaths due to heroin) rose from 127 in 1991 to 540 in 2010, and have continued to increase. *[52] [76] [223]* Overall, 1 of every 550 patients started on opioid therapy in Ontario died of opioid-related causes a median of 2.6 years from his or her first opioid prescription; the proportion was as high as 1 in 32 among patients receiving 200mg morphine equivalent dose (MED) per day or higher. *[113]*

Canadian physicians and medical regulators have recognized a growing need for guidance regarding the prescribing of opioids for chronic non-cancer pain. In late 2007, under the umbrella of the Federation of Medical Regulatory Authorities of Canada (FMRAC), provincial and territorial medical regulatory authorities formed the collaborative National Opioid Use Guideline Group (NOUGG) to oversee development of a clinical practice guideline: the Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain.

In 2010, the National Opioid Use Guideline Group offered recommendations for safe and effective use of opioids. *[150]* Critics have, however, remarked that many of the recommendations were less specific than would have been ideal. Moreover, almost all recommendations supported the prescribing of opioids, while little guidance was offered about when not to prescribe. An interventional time-series analysis in Ontario, Canada, from 2003 to 2014, found moderate reductions in opioid prescribing among Ontario Public Drug Program beneficiaries, although there were no changes in rates of opioid-related overdose and high-dose opioid prescribing and opioid-related hospital visits continued to increase. *[57]*

In 2014, the Canadian Federal Government expanded the focus of the National Anti-Drug Strategy from illicit drugs to include measures to address prescription drug misuse. Health Canada subsequently funded researchers at the Michael G. DeGroote National Pain Centre at McMaster University to update and revise the 2010 Canadian guideline for prescribing opioids in chronic non-cancer pain patients. The project team for the 2017 guideline included researchers with expertise in chronic non-cancer pain, opioids, systematic reviews and guideline development who engaged constructively with patients, pain specialists, and regulators to create evidence-based guidelines to support decision-making across Canada. This updated Guideline incorporates all new evidence published subsequent to the literature search used to inform the 2010 Guideline, and adheres to standards for trustworthy guidelines *[127]* and, if followed, will promote evidence-based prescribing of opioids for chronic non-cancer pain.

Methodology

In developing this guideline, we followed standards for trustworthy guidelines. *[127]* Moreover, we included innovative approaches for key standards such as patient involvement, panel composition and conflicts of interest management. We performed systematic reviews and applied the GRADE system to meet standards within evidence assessment and recommendation development. *[84] [90]*

Panel composition and conflict of interest management

The guideline development process included the following groups:

1. A four-member Steering Committee responsible for planning, oversight and policy decisions.
2. A 15-member Guideline Panel composed of 13 clinicians, most of whom had extensive methodological training, one of whom was a medical regulator, and two patient representatives. The panel had extensive input into the development and presentation of the recommendations, voted on all recommendations, and is ultimately responsible for the recommendations and their presentation.
3. A 13-member multi-disciplinary Clinical Expert Committee with expertise in the management of chronic pain and the prescribing of opioids had an advisory role to the panel.
4. A 16-member Patient Advisory Committee had an advisory role to the panel.

Conflict of Interest Management

Our guideline team placed emphasis on the management of both intellectual and financial conflicts of interest in the development of our clinical practice recommendations. Our aim was to ensure that the guideline recommendations were subject to minimal influence from financial or intellectual interests. For this reason, we elected to comprise the voting panel of individuals without overt financial or intellectual conflicts of interest.

To ensure that the necessary expertise in management of chronic pain and use of opioids was present in the development of our guidelines, we enlisted 13 clinicians to serve on a Clinical Expert Committee. These individuals were not voting panel members and were not present when the recommendations were developed. This committee was composed of experts with a range of views on the role of opioids in the management of chronic pain, including several who viewed opioids as having an important role and several who viewed the practice with extreme skepticism. This commitee informed the selection of guideline recommendation topics, provided clinical practice guidance in areas where evidence was absent or limited, and reviewed the final guideline.

All members of both the Guideline Panel and Clinical Expert Committee completed declaration of interest forms at the beginning of the guideline process. The steering committee reviewed these forms. Voting panel members were requested to complete the form a second time in January 2017, immediately before drafting the final recommendations (these forms are available at the National Pain Centre website: http://nationalpaincentre.mcmaster.ca/).

Patient Involvement

To maximize patient involvement in our guideline, in addition to the two patient representatives on our Guideline Panel, we created a Patient Advisory Committee composed of 16 chronic pain patients.

We recruited patients identified by our clinical experts, and by reaching out to chronic pain organizations across Canada, advertising this advisory group to their members. We selected patients from regions across Canada, as well as seeking a variety of opinions regarding the use of opioids in the management of chronic pain. Because some elements of the guideline would address the decision to initiate or not initiate opioid therapy, previous or current use of opioids for the treatment of chronic pain was not a requirement for inclusion on the Patient Advisory Committee, although 15 of 16 members had used or were using opioids. We also included a member who had experience with opioid addiction, and another whose family member had suffered a fatal overdose with prescription opioids to ensure these viewpoints were represented.

The Patient Advisory Committee provided feedback on our research questions and outcome measures, and informed the development of our values and preferences statement via email and telephone discussions.

Selection and prioritization of questions and outcomes

Research questions

We reviewed the 2010 Canadian Guideline for Safe & Effective use of Opioids for Chronic Non-Cancer Pain as well as other published guidelines addressing the use of opioids for chronic non-cancer pain, *[150] [97] [141] [219] [151] [180] [208]* and summarized all prior guideline recommendations. We held a national stakeholder meeting in July 2015 to discuss prior recommendations, and other topics where clinicians would find recommendations helpful in the 2017 Canadian Opioid Guideline. In December 2015, we held a second meeting attended by our Clinical Expert Committee, Guideline Panel and research team to finalize questions and discuss methodological challenges associated with the research questions.

Each recommendation topic endorsed by the group was then used to generate a research question to be informed by a systematic review of the published evidence. Question format used the PICO (population, intervention, comparator, and outcome) structure.*[230]*

Outcomes

We asked our stakeholders to provide lists of outcomes of interest for each research question. The steering committee selected a maximum of seven outcomes per question, *[88]* representing both benefits and harms that might occur during opioid therapy. For research questions focusing on patient harms and benefits associated with opioid use, the selection of outcomes was guided by recommendations made by the

Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT). *[205] [206]* The Guideline Panel and Patient Advisory Committee reviewed and approved the following selected outcomes as the key outcomes from most of questions: pain, physical functioning, gastrointestinal adverse events, addiction to prescription opioids, diversion of prescription opioids, fatal opioid overdose, and non-fatal opioid overdose.

Systematic reviews

We conducted systematic reviews to inform our guideline recommendations. The Guideline Panel and the Evidence Synthesis Team interacted to ensure harmonisation of the scope, approach, and output of both processes. We created evidence summaries using the GRADE system as detailed below, to provide a clear description of benefits and harms and a rating of the certainty of the evidence on an outcome-by-outcome basis. We also reviewed the evidence surrounding cost-effectiveness of opioids compared to other treatments for chronic pain, as well as the economic impact of opioid-related adverse events.

Identifying the evidence

Each PICO question was informed by one or more systematic reviews of the published literature. Led by an experienced research librarian, we developed comprehensive search strategies in CINAHL, EMBASE, MEDLINE, AMED, PsychINFO, and the Cochrane Central Registry of Controlled Trials (search strategies are available at nationalpaincentre.mcmaster.ca/guidelines). We also scanned the bibliographies of all retrieved articles for additional relevant studies.

Using standardized forms, reviewers screened, independently and in duplicate, titles and abstracts of identified studies, and acquired the full text publication of all reports deemed potentially eligible. Teams of reviewers then independently applied eligibility criteria to the full text of potentially eligible reports. Disagreements were resolved by discussion or through involvement of an arbitrator.

Data abstraction

Teams of reviewers abstracted data, independently and in duplicate, from each eligible study, using standardized forms in an online data abstraction program (DistillerSR, Evidence Partners, Ottawa, Canada; http://systematic-review.ca/) and a detailed instruction manual. Data abstracted included demographic information, methodology, intervention details, and outcome data. When a trial used more than one instrument to measure the same outcome category (e.g. pain), we chose only one assessment based on the following prioritization, in descending order of importance: (1) most commonly used instrument across trials, (2) validated instrument, and (3) instrument with the most precise estimation of effect.

Evaluating risk of bias in individual studies

Reviewers assessed the risk of bias from eligible randomized trials using a modified Cochrane risk of bias instrument that include response options of "definitely or probably yes" (assigned a low risk of bias) or "definitely or probably no" (assigned a high risk of bias), an approach we have previously shown to be valid. *[5]* We assessed the risk of bias in observational studies using criteria from the *Users' Guides to the Medical Literature, [169]* including representativeness of the study population, validity of exposure and outcome assessment, loss to follow-up, and whether predictive models were optimally adjusted.

Statistical analyses

We performed all meta-analyses using random effects models. For dichotomous outcomes, e.g. gastrointestinal adverse events, we calculated the relative risk (RR) and the associated 95% confidence interval (CI). We also reported absolute risk reduction estimates derived from estimates of baseline risk acquired from observational studies or, if not available, from the median of the control groups from eligible randomized controlled trials (RCTs). For continuous outcomes, e.g. pain or physical functioning, we pooled effect estimates across trials and calculated the weighted mean difference (WMD) by converting different instruments to the most common scale, i.e. 10cm pain visual analogue scale (VAS) and SF-36 physical component summary (PCS) score. *[201]* We used change scores for pooling of effect estimates to account for within-person variability, rather than end-of-study scores. If change scores were not reported, we calculated them using the baseline and end-of-study score and a correlation coefficient.

To optimize interpretation of the WMD, we calculated the proportion of patients in the intervention and control groups that achieved improvements in pain reduction or physical functioning greater than the anchor-based minimally important difference (MID) by assuming normal distributions of pain or physical functioning score in both groups. We then calculated the relative risk and absolute risk reduction of achieving the MID. *[28]*

For observational studies, we pooled adjusted odds ratios using random effects models. For one-arm observational studies, we pooled incidence or prevalence estimates for benefits or harms using random effects models.

Assessment of heterogeneity and subgroup analyses

For pooled effect estimates from RCTs, we examined heterogeneity using both a χ^2 test and the I^2 statistic. For pooled measures of

association from observational studies, we evaluated heterogeneity through visual inspection of forest plots, because statistical tests of heterogeneity can be misleading when sample sizes are large and CIs are therefore narrow. *[182]*

We tested the following a priori subgroup hypotheses to explain variability among studies: 1) clinical condition category; 2) receipt of disability benefits or involved in litigation versus those that are not; 3) cross-over trials vs parallel trials; 4) enriched enrolment trials vs not; and 5) risk of bias (on a component-by-component basis). Enriched enrolment trials attempt to identify a study population in which the effect of an intervention can be most readily demonstrated prior to randomization, by providing the intervention and/or control and identifying and excluding patients that report large placebo responses, intolerable adverse events, or poor response to opioids. We did not conduct subgroup analyses if there was only one study in a given subgroup. We conducted tests of interaction to establish if subgroups differed significantly from one another, and assessed the credibility of significant subgroup effects ($p<0.05$) using the criteria suggested by Sun and colleagues. *[199]* In addition, we performed meta-regressions to detect if length of follow-up and the proportion of loss to follow-up were associated with treatment effects.

Quality of evidence
We used the GRADE approach (https://cebgrade.mcmaster.ca/aboutgrade.html) to determine the quality of evidence on an outcome-by-outcome basis, based on study design (randomized trials or observational studies) and using the following domains: risk of bias, inconsistency, indirectness, imprecision, and the risk of publication bias. *[83] [84] [85] [86] [90] [87] [89]* We restricted our assessment of publication bias to outcomes with 10 or more studies. The quality of evidence was categorized into one of four levels: high, moderate, low, or very low. *[13]*

Patient values and preferences
To complement the research findings and to guide our Panel in making recommendations, we developed a values and preferences statement (nationalpaincentre/mcmaster.ca/guidelines). This statement was informed by a systematic review of the literature on patient values and preferences for opioid therapy, and through discussions with our Patient Advisory Committee.

Systematic review
We searched the literature for studies examining patient preferences for alternative approaches to managing chronic non-cancer pain, and studies that assessed how opioid-using chronic non-cancer pain patients value alternative health states and their experiences with treatment. This review found that patients placed a high value on pain relief, but also placed high value on avoiding adverse effects such as nausea, vomiting, constipation, and personality changes. We identified no any studies assessing values and preferences with respect to rare but serious harms such as addiction, overdose, or diversion. *[80]*

Patient Advisory Committee
To acquire first-hand perspectives on patient values and preferences, we engaged our Patient Advisory Committee in a series of discussions regarding opioid use and trade-offs between pain relief and adverse events, including rare but serious ones.

We used information from these two sources to create our values and preferences statement, which informs the Panel's recommendations.

Development of recommendations

We applied the GRADE system to move from evidence to recommendations. *[7] [8] [10] [11]*
We conducted a two-day, in-person meeting in January 2017. Our Guideline Panel and clinical experts attended the first day, as did representatives from Health Canada. The primary purpose was to discuss issues for which there was no, or very limited, research evidence in order to develop clinical expert guidance.

Voting members of the Guideline Panel, as well as two Health Canada representatives, who were present as observers with permission to provide input, attended the second day. Panellists reviewed relevant evidence for each recommendation. After each evidence review, all panel members used anonymous, online voting software (ietd.epistemonikos.org) to select their recommendation according to the GRADE approach: strong in favour, weak in favour, weak against, or strong against.

For each recommendation, the Panel considered the certainty in the evidence and the balance of benefits and harms, in the context of our values and preferences statement. Endorsement by 80% of panel members was required for acceptance of a recommendation. If we did not achieve 80% agreement, further discussion and another vote followed. In all cases we were able to achieve consensus for the final recommendation. The panel and expert committee provided feedback following the meeting, which in one case involved additional analyses. Changes in recommendations after the panel meeting were largely cosmetic (i.e. wording changes to the recommendations or associated remarks; the most substantive change was merging two recommendations together). All changes after the meeting required consensus of panel members.

Any panel member who disagreed with a recommendation was permitted to register a dissenting statement at the face-to-face meeting; however, this did not occur. New formal dissent could only be registered after the face-to-face meeting with the Panel in which recommendations were finalized if new important evidence became available. In one instance the panel provided formal feedback regarding the importance of additional post-meeting analyses (see following).

Our systematic reviews either identified sufficient evidence to justify making a formal clinical practice recommendation or identified a lack of sufficient evidence, in which case we did not make a formal recommendation but instead convened a clinical expert subcommittee to offer expert impressions and guidance. For systematic reviews that identified evidence, we created an evidence profile to summarize the results.

The Panel also endorsed three good practice statements, actionable guidance regarding interventions with compelling indirect evidence of large net benefits. *[82]* Input from medical regulators guided our selection of good practice statements.

Using the GRADE approach, recommendations are labeled as either "strong" or "weak"; "recommend" is used for strong recommendations and "suggest" for weak recommendations. Table 1 provides the suggested interpretation of strong and weak recommendations by patients, clinicians and health care policy makers.

Table 1: The GRADE approach's interpretation of strong and weak guideline recommendations

Implications for:	Strong recommendation	Weak recommendation
Patients	All or almost all informed individuals would choose the recommended course of action, and only a very small proportion would not.	The majority of informed individuals would choose the suggested course of action, but an appreciable minority would not.
Clinicians	All or almost all individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policy makers	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

Development of final recommendations

After the meeting, the recommendations were shared with the Clinical Expert Committee for review and feedback, with the understanding that no changes to either the direction (for or against) or strength (weak or strong) would be made unless new and compelling evidence or rationale was provided to the Panel.

To solicit feedback from patients, clinicians, and other stakeholders, we posted the draft recommendations for the guideline on the National Pain Centre website for one month. We encouraged participation by inviting 429 stakeholders by email and announced the opportunity for review through a national press release and on social media. All individuals who submitted comments first had to declare any relevant financial conflicts of interest, because organizations with funding from opioid manufacturers have shown greater opposition to guidelines that recommend reduced prescribing of opioids. *[135]* The comment period closed on February 28, 2017. The steering committee reviewed and summarized more than 500 comments for the Guideline Panel. Comments were carefully considered when drafting the final guideline.

Based on expert panel comments, feedback from the website posting, and their own reflections following the meeting, the panel made numerous cosmetic changes to the wording and presentation of the guidelines. In no case was the direction or strength of any recommendation changed because of feedback. An important substantive issue was raised regarding whether there are chronic pain conditions for which opioids should not be prescribed. To explore this issue, we considered whether there were clinical conditions that might modify opioid effects (i.e. subgroup hypotheses), and conducted corresponding additional analyses. These analyses failed to suggest any effect modification across clinical condition (i.e. similar effects on pain and function across clinical conditions).

External Review

We sent the guideline to an external Evaluation Committee to determine adherence to the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines (http://www.nationalacademies.org/hmd/Reports/2011/Clinical-Practice-Guidelines-We-Can-Trust.aspx). Any deficits identified were addressed before finalization of the guideline.

Guideline Format

In 2015/2016 we interviewed 12 pain physicians in Ontario, Canada, some of whom reported they did not use the 2010 Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain in practice. Reasons included suboptimal format and excessive length. *[37]* To reduce the burden on readers, the current guideline has prioritized succinct and clear statements. Further, we have partnered with the Making GRADE the Irresistible Choice (MAGIC) non-profit initiative to optimize dissemination of the guidelines to health care professionals and their patients. Beyond making the guideline recommendations available on the National Pain Centre website and in scientific journal publications we have provided the guideline recommendations, with extensive underlying content, in digitally structured and multilayered formats available on all devices (www.magicapp.org). *[124] [212]* Clinicians will find recommendations first and can select tabs to access supporting information. Of particular relevance to prescribers and their patients are the sections with succinct text on rationale, practical information and tables with evidence summaries. The evidence summaries provide information about benefits and harms of treatment alternatives, in absolute numbers and with certainty in the evidence reported for all patient-important outcomes. Shared decision-making can be facilitated by consultation decision-aids. *[4]*

Update of the guideline

The National Pain Centre aims to provide an ongoing review of new evidence with dynamic updating of recommendations as needed, what can be labelled a "living guideline". *[4]* Having all the content digitally structured and published in MAGICapp facilitates dynamic updating from a technical perspective; however, updating of guidelines requires resources for which the National Pain Centre is seeking funds. If no funds are secured for a dynamic updating process, we plan - at a minimum - to update this guideline within 5 years of publication (estimated 2022).

3 - Initiation and Dosing of Opioids in Patients with Chronic Noncancer Pain

This section provides guidance on whether or not to initiate opioid therapy, in what circumstances, and in which patient populations. Practical guidance is offered regarding optimal dosing when beginning patients on a trial of opioid therapy.

Recommendation 1: When considering therapy for patients with chronic non-cancer pain

Strong Recommendation

We recommend optimization of non-opioid pharmacotherapy and non-pharmacological therapy, rather than a trial of opioids

Practical Info

Table 2 lists some of the specific treatments available for management of chronic non-cancer pain and the evidence for each of the treatments.

Table 2: Non-opioid therapies for chronic non-cancer pain

Chronic non-cancer pain condition(s)	Quality of Evidence	Therapies with some evidence of effectiveness
Chronic low back pain	Moderate to high	NSAIDS, duloxetine, and benzodiazepines are more effective than placebo, sham, no treatment, usual care, or wait list*[41]*
Rheumatoid arthritis, osteoarthritis, fibromyalgia, low back pain, intermittent claudication, dysmenorrhoea, mechanical neck disorder, spinal cord injury, post-polio syndrome, and patellofemoral pain	Low	Physical activity reduced the severity of pain and improved physical function. Harms included muscle soreness.*[71]*
Fibromyalgia	Moderate	Regular physical exercise probably reduces pain in patients with fibromyalgia.*[168]*
Chronic low back pain	Low to moderate	Evidence of small to moderate short-term benefits for Tai chi, mindfulness based-stress reduction, exercise, multidisciplinary rehabilitation, spinal manipulation, massage therapy, and acupuncture. Effects on function were generally smaller than effects on pain.*[41] [40]*
Back pain, knee osteoarthritis, neck pain, fibromyalgia, severe headaches or migraines	Low or very low	Acupuncture, yoga, massage therapy, spinal manipulation, osteopathic manipulation, Tai Chi, and relaxation approaches may help some patients manage pain.*[149]*

CADTH has compiled the best available evidence to inform decisions on non-opioid therapies for chronic non-cancer pain. Find the evidence at www.cadth.ca/opioids and www.cadth.ca/pain.

Key Info

Benefits and harms

Substantial net benefits of the recommended alternative

Opioids may have similar effects on pain relief when compared to NSAIDs, tricyclic antidepressants, or nabilone (a synthetic

cannabinoid) (low quality evidence). Use of opioids for chronic non-cancer pain may result in similar improvements in physical function when compared to NSAIDs, anticonvulsants, tricyclic antidepressants, or nabilone. Opioids increase the rate of gastrointestinal adverse events compared to NSAIDs (high quality evidence), and may increase the rate of gastrointestinal adverse events compared to anticonvulsants and tricyclic antidepressants (low quality evidence). *[30]* Opioids are associated with a 5.5% risk of addiction and, at very low doses (<20 MED/day), a 0.2% risk of non-fatal overdose*[54]* and a 0.1% risk of fatal overdose*[113]*; risk of overdose increases at higher doses of opioids. In 2013, 4.9% of Americans admitted to nonmedical use of prescription opioids. Data from population surveys suggest similar rates among Canadian adults. *[60]*

Three studies have reported larger associations between opioid dose and the risk of non-fatal *[225] [54]*and fatal *[23]* overdose; however, none were eligible for our review. Our eligibility criteria required that all patients be prescribed opioids at baseline, and that ≥85% of patients were treated for chronic non-cancer pain. The analysis for risk based on opioid dose reported by Dunn et al. (2010) included >50% of patients that were not using any opioids. The cohorts studied by Bohnert et al. (2011) and Zedler et al. (2014) both included less than 85% of patients with chronic non-cancer pain.

Quality of evidence Low

The quality evidence for pain, physical function, and gastrointestinal side effects for opioids versus NSAIDS, opioids versus anticonvulsants, and opioids versus antidepressants, ranged from low to moderate. Confidence intervals were wide, including important benefit and no clinically meaningful effect. Risk of bias was high in studies of opioids versus antidepressants (>25% loss to follow up) and opioids versus anticonvulsants (lack of allocation concealment and blinding).

We assumed death from opioids, non-fatal overdose from opioids, addiction to prescription opioids, and diversion of opioids occur only in those prescribed opioids for CNCP and not those with CNCP not prescribed opioids. Thus we have high confidence that the event rate from these outcomes in those not prescribed opioids is zero. Therefore, from single arm studies of patients with opioids, we can be confident that the rate of the events represents the difference in rate of events in those prescribed opioids versus those not prescribed opioids.

Preference and values Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
Patients with chronic non-cancer pain may place little importance on avoiding rare but serious side effects such as addiction, overdose, or death, and are often willing to trade the risk of these effects for small but important pain relief. However, if patients actually experience a rare but serious adverse event, their values tend to align more closely with societal values.

Resources and other considerations Important issues, or potential issues not investigated

Cost-effectiveness of opioids versus non-opioid alternatives
NSAID-based treatment may have lower mean costs and higher effectiveness relative to opioids. A cost-effectiveness acceptability curve suggested that the probability of NSAIDs being cost effective was higher than the probability of opioids being cost effective across all levels of a willingness-to-pay threshold. *[114] [193]* Naproxen-based regimens in particular may be more cost effective compared to opioids and other NSAIDs, such as ibuprofen and celecoxib. *[114]* Carbamazepine may have a higher effectiveness relative to opioids (tramadol) as has another anticonvulsant (gabapentin), and the antidepressant amitriptyline may have lower mean costs and higher effectiveness than tramadol. *[36]*

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse. *[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary. *[194] [222]*Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioid *[59]* and drug-related criminal behaviour. *[177]* Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity. *[177]*

Rationale

Opioids, when added to non-opioids, may achieve on average modest improvements in pain and function relative to other pain treatments

at the cost of rare non-fatal and fatal unintentional overdose, very frequent physical dependence, and frequent addiction. As first-line treatment for patients with chronic non-cancer pain, several non-opioid therapies may achieve a similar magnitude of improvement in pain and function (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs], graduated exercise, cognitive behavioral therapy) but without the harms of dependence, addiction, and non-fatal overdose.

In general, GRADE discourages strong recommendations when the quality of evidence for critical outcomes is low or very low. There are, however, five paradigmatic situations in which strong recommendations may be warranted despite low or very low quality of evidence. One of these is when low quality evidence suggests equivalence of two alternatives, but high quality evidence suggests greater harm of one. For our first recommendation, low quality evidence (much of it indirect) suggests equivalence of opioid therapy with a number of other drug and non-drug interventions, while high quality evidence demonstrates greater harm with opioids.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain considering first line therapy for pain
Intervention: Trial of opioids.
Comparator: Optimization of therapy with NSAIDs.

Summary

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with NSAIDs.	Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects up to 6 months	Relative risk 2.52 (CI 95% 1.54 - 4.13) Based on data from 3,675 patients in 7 studies. (Randomized controlled) Follow up 6-26 weeks	**37** per 1000	**93** per 1000 Difference: **56 more** per 1000 (CI 95% 20 more - 116 more)	**High**	Opioid therapy results in a small increase in gastrointestinal side effects.
Pain 1-6 months	Measured by: 10-cm VAS Scale: 0-10 Lower better Based on data from: 2,250 patients in 13 studies. (Randomized controlled) Follow up 1-6 months	Difference: **MD 0.49 fewer** (CI 95% 1.24 fewer - 0.26 more)		**Low** Due to serious inconsistency, Due to serious imprecision	Opioid therapy may result in little or no difference in pain compared to NSAIDS.
Physical Function 1-4 months	Measured by: SF-36 Scale: 0-100 High better Based on data from: 1,972 patients in 8 studies. (Randomized controlled) Follow up 4-16 weeks	Difference: **MD 1.5 fewer** (CI 95% 3.08 fewer - 0.08 more)		**Moderate** Due to serious imprecision	Opioid therapy likely results in little or no difference in physical function compared to NSAIDS.

Addiction FU not reported	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency.	Opioid therapy likely results in an important risk of addiction.
Fatal Overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy results in a rare but important risk of fatal overdose.
Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy likely results in a small but important increase in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1 studies	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.	**Moderate** Due to serious risk of bias.	Opioid therapy likely results in an important increase in the risk of diversion.

Details about studies used and certainty down- and upgrading

Gastrointestinal side effects	**Intervention:** Systematic review with included studies: [186], [161], [154], [50], [19], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Pain	**Intervention:** Systematic review with included studies: [156], [136], [160], [158], [50], [19], [121], [111], [186], [165], [214], [200], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: Serious** The magnitude of statistical heterogeneity was high, with I^2: 94.5 % ; **Indirectness: No serious** **Imprecision: Serious** Wide confidence intervals which include benefit and harm ; **Publication bias: No serious**
Physical Function	**Intervention:** Systematic review with included studies: [161], [160], [200], [19], [111], [50], [158], [156], **Baseline/comparator:** Control arm of reference	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Wide confidence intervals include both benefit and harm ; **Publication bias: No serious**

	used for intervention	
Addiction	**Intervention:** Systematic review **Other** [55] [14] [142] [187] [1] [64] [47] [159] [100]	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates varied substantially, from 0.7% to 15.7% ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal Overdose	**Intervention:** Primary study **Other** [113]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Primary study **Other** [54]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** The study setting was Group Health Cooperative (GHC), which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State ; **Imprecision: Serious** Small number of events ; **Publication bias: No serious**
Diversion	**Intervention:** Systematic review **Other** [94]	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

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Clinical Question/ PICO

Population: Patients with chronic non-cancer pain considering first line therapy for pain

Intervention: Trial of opioids.

Comparator: Optimization of therapy with anticonvulsants.

Summary

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with anticonvulsants.	**Absolute effect estimates** Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**

Pain (difference in patients who achieve the MID or greater) 4-6 weeks	Relative risk 1.26 (CI 95% 1.05 - 1.42) Based on data from 303 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	**618** per 1000 **779** per 1000 Difference: **161 more** per 1000 (CI 95% 31 more - 260 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioid therapy may result in a large increase in the proportion of patients who achieve a 1 cm reduction on a 10-cm VAS compared to anticonvulsants.
Gastrointestinal side effects 4-6 weeks	Relative risk 10.64 (CI 95% 2.01 - 56.24) Based on data from 342 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	**6** per 1000 **64** per 1000 Difference: **58 more** per 1000 (CI 95% 6 more - 331 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioid therapy may result in an increase in gastrointestinal side effects compared to anticonvulsants.
Pain 4-6 weeks	Measured by: 10-cm VAS Scale: 0-10 Lower better Based on data from: 303 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	Difference: **MD 0.9 fewer** (CI 95% 1.65 fewer - 0.14 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioid therapy may result in a small but important improvement in pain compared to anticonvulsants.
Physical Function 4-6 weeks	Measured by: SF-36 Scale: 0-100 High better Based on data from: 303 patients in 3 studies. (Randomized controlled) Follow up 4-6 weeks	Difference: **MD 0.45 more** (CI 95% 5.77 fewer - 6.66 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioids may result in little to no difference in physical function compared to anticonvulsants.
Addiction FU not reported	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency	Opioid therapy likely results in an important risk of addiction.
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy results in a rare but important risk of fatal overdose.
Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy likely results in a small but important increase in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1	Among US adults, the prevalence of nonmedical use of prescription opioids was	**Moderate** Due to serious risk	Opioid therapy likely results in an increase in

	studies	4.9% (95% CI, 4.58%-5.22%) in 2013.	of bias	the risk of diversion.

Details about studies used and certainty down- and upgrading

Pain (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [185], [122], [73], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (Sakai et al 2015, Ko et al 2010) had no allocation concealment and no blinding ; **Inconsistency: No serious** The magnitude of statistical heterogeneity was high, with I^2=71 % ; **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes both important benefit and no clinically meaningful effect ; **Publication bias: No serious**
Gastrointestinal side effects	**Intervention:** Systematic review with included studies: [185], [122], [73], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (Sakai et al 2015, Ko et al 2010) had no allocation concealment and no blinding ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Wide confidence intervals ; **Publication bias: No serious**
Pain	**Intervention:** Systematic review **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (Sakai et al 2015, Ko et al 2010) had no allocation concealment and no blinding ; **Inconsistency: No serious** The magnitude of statistical heterogeneity was high, with I^2=71 %. ; **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes both important benefit and no clinically meaningful effect ; **Publication bias: No serious**
Physical Function	**Intervention:** Systematic review with included studies: [122], [73], [185], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Two out of three studies (Sakai et al 2015, Ko et al 2010) had no allocation concealment and no blinding ; **Inconsistency: No serious** The magnitude of statistical heterogeneity was high, with I^2:67 % ; **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes both benefit and harm ; **Publication bias: No serious**
Addiction	**Intervention:** Systematic review **Other** [100] [55] [14] [142] [187] [1] [64] [47] [159]	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates varied substantially, from 0.7% to 15.7% ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention:** Systematic review **Other** [113]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain. ; **Imprecision: No serious** **Publication bias: No serious**

Non-fatal overdose	**Intervention:** Systematic review **Other** [54]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was Group Health Cooperative (GHC), which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State ; **Imprecision: Serious** Small number of events and no confidence interval provided ; **Publication bias: No serious**
Diversion	**Intervention:** Systematic review **Other** [94]	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

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Clinical Question/ PICO

Population: Patients with chronic non-cancer pain considering first line therapy for pain
Intervention: Trial of opioids.
Comparator: Optimization of therapy with tricyclic antidepressants.

Summary

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with tricyclic antidepressants.	Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain	Measured by: 10-cm VAS			**Low**	Opioids may result in

5-8 weeks	Scale: 0-10 Lower better Based on data from: 183 patients in 3 studies. (Randomized controlled) Follow up 5-8 weeks	Difference: **MD 0.15 fewer** (CI 95% 1.04 fewer - 0.74 more)	Due to serious risk of bias, Due to serious imprecision	little to no difference in pain compared to tricyclic antidepressants.
Physical Function 5-6 weeks	Measured by: SF-36 Scale: 0-100 High better Based on data from: 107 patients in 2 studies. (Randomized controlled) Follow up 5-6 weeks	Difference: **MD 5.29 fewer** (CI 95% 13.7 fewer - 3.12 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioids may result in little to no difference in physical function compared to tricyclic antidepressants.
Addiction	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency.	Opioid therapy likely results in an important risk of addiction.
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy results in a rare but important risk of fatal overdose.
Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Opioid therapy likely results in a small but important increase in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1 studies	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.	**Moderate** Due to serious risk of bias.	Opioid therapy likely results in an increase in the risk of diversion.

Details about studies used and certainty down- and upgrading

Pain	**Intervention:** Systematic review with included studies: [74], [227], [120], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** High loss to follow up in all studies (>25%) ; **Inconsistency: No serious** **Indirectness: No serious** Follow up time is short, max 6 weeks ; **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**
Physical Function	**Intervention:** Systematic review with included studies: [120], [74], **Baseline/comparator:**	**Risk of bias: Serious** High loss to follow up in all studies (>25%) ; **Inconsistency: No serious** **Indirectness: No serious** Follow up time is short, max 6 weeks ; **Imprecision: Serious** Confidence interval includes benefit and harm ;

	Control arm of reference used for intervention	**Publication bias: No serious**
Addiction	**Intervention:** Systematic review	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates varied substantially, from 0.7%-15.7% ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Systematic review	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was Group Health Cooperative, which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State ; **Imprecision: Serious** Small number of events and no confidence interval provided ; **Publication bias: No serious**
Diversion	**Intervention:** Systematic review	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

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Clinical Question/ PICO

Population: Patients with chronic non-cancer pain considering first line therapy for pain
Intervention: Trial of opioids.
Comparator: Optimization of therapy with nabilone.

Summary

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with nabilone. Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 6 weeks	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 73 patients in 1 studies. (Randomized controlled) Follow up 6 weeks	Difference: **MD 0.13 fewer** (CI 95% 1.04 fewer - 0.77 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioids may result in little to no difference in pain compared to nabilone.
Physical function 6 weeks	Measured by: SF-36 Scale: 0-100 High better Based on data from: 71 patients in 1 studies. (Randomized controlled) Follow up 6 weeks	Difference: **MD 1.2 fewer** (CI 95% 4.5 fewer - 2.1 more)	**Low** Due to serious risk of bias, Due to serious imprecision	Opioids may result in little to no difference in physical function compared to nabilone.

Details about studies used and certainty down- and upgrading

Pain	**Intervention:** Primary study [65], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Did not report randomization or allocation; LTFU 33% ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes benefit and harm ;
Physical function	**Intervention:** Primary study [65], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Did not report randomization or allocation; LTFU 33% ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes benefit and harm ;

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Clinical Question/ PICO

Population: Patients with chronic non-cancer pain considering first line therapy for pain
Intervention: Trial of opioids.
Comparator: Optimization of therapy with mexiletine.

Summary

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Optimization of therapy with mexiletine.	Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 2 months	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 60 patients in 1 studies. (Randomized controlled) Follow up 8 weeks	Difference: **MD 1.3 fewer** (CI 95% 2.15 fewer - 0.45 fewer)		**Moderate** Due to serious risk of bias	Opioid therapy likely results in a small but important improvement in pain compared to mexiletine.
Details about studies used and certainty down- and upgrading					
Pain	**Intervention:** Primary study [224], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Loss to follow-up 42% ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious**			

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Recommendation 2: For patients with chronic noncancer pain, without current or past substance use disorder and without other active psychiatric disorders, who have persistent problematic pain despite optimized nonopioid therapy

Weak Recommendation

We suggest adding a trial of opioids rather than continued therapy without opioids.

By a trial of opioids, we mean initiation, titration, and monitoring of response, with discontinuation of opioids if important improvement in pain or function is not achieved. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses. The mental illnesses identified in studies as risk factors for adverse outcomes were generally anxiety and depression, including ICD-9 definitions, as well as "psychiatric diagnosis", "mood disorder", and post-traumatic stress disorder.

Practical Info

Table 3 lists the possible options for initiating opioid therapy. Table 4 indicates opioids that should not be used for first prescription.

Table 3: Opioid options for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Morphine	Avoid in renal insufficiency
Oxycodone	~1.5x as potent as morphine. Available in a tamper-resistant formulation
Hydromorphone	~5x as powerful as morphine. Available in a tamper-resistant formulation
Oxycodone/Naloxone	Naloxone combination may minimize constipation and possibly act as an abuse deterrant
Buphrenorphine	Oral formulations preferred over transdermal for initial trial
Codeine	
Tapentadol	Available in a tamper-resistant formulation. Combined noradrenaline reuptake inhibitor and weak opioid
Tramadol	A prodrug (serotonin–norepinephrine reuptake inhibitor) that is converted to an opioid in a highly variable fashion.

Table 4: Opioids that are not recommended for initiating a trial of therapy for patients with chronic non-cancer pain

Opioid	Comments
Methadone	Requires a specific Health Canada exemption to provide
Fentanyl (transdermal)	Not in opioid-naïve patients
Meperidine	Limited effectiveness; toxic metabolite accumulates in high doses or in renal insufficiency
Pentazocine	Limited effectiveness. High incidence of dysphoria

Some Guiding Principles for Initiation of Opioids

- Despite the availability of various screening instruments, none have been shown to predict patients unsuitable for opioid therapy*[119]*
- Start at the lowest available dose of the opioid
- Prescriptions should be provided by the primary treating physician only, for no more than 28 days at a time. Intervals may be shorter when initiating therapy, in cases of suspected diversion or during dose escalation
- In patients with continuous pain including pain at rest, clinicians can prescribe controlled release opioids for both for comfort and simplicity of treatment during the day. Activity related pain might not require sustained release treatment and opioid therapy may be

initiated with immediate release alone (See Guidance Statement 2).
- During dosage titration, advise patients to avoid driving a motor vehicle until a stable dosage is established and it is certain the opioid does not cause sedation. This is especially true when taking opioids with alcohol, benzodiazepines (see Guidance Statement 3), or other sedating drugs

- A reasonable trial of therapy should be accomplished within 3-6 months; opioids provide less pain relief after 3-months and some patients may continue use to address inter-dose withdrawal symptoms
- Patients will develop tolerance and a withdrawal syndrome within as little as two to four weeks. This will significantly hamper any effort to taper opioids if the trial fails.
- Other potential adverse effects of opioids that warrant consideration include falls, fractures, sleep-disordered breathing (including sleep apnea, see Guidance Statement 4), depression and a worsening of pain itself (opioid-induced hyperalgesia)

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

Adding opioids to non-opioid therapy results in a reduction in pain (risk difference [RD] for achieving an important reduction in pain is 12.3%), and an increase in functional improvement (RD for achieving an important improvement in function is 10.0%), vs continuing established therapy without opioids. Opioids increase the risk of gastrointestinal adverse events vs non-opioid therapy alone (64 more events per 1000 patients treated).*[30]* Opioids are associated with a 5.5% risk of addiction and, at very low doses (<20 MED/day), a 0.2% risk of non-fatal overdose and a 0.1% risk of fatal overdose; risk of overdose increases at higher doses of opioids. In 2013, 4.9% of Americans admitted to nonmedical use of prescription opioids. Data from population surveys suggest similar rates among Canadian adults.*[60]*

Quality of evidence

Moderate

The evidence for pain, physical function, and gastrointestinal side effects was based on high-quality randomized trials enrolling 12,000-17,000 patients. Most of the studies were commercially funded by pharmaceutical companies.

We assumed death from opioids, non-fatal overdose from opioids, addiction to prescription opioids, and diversion of opioids occur only in those prescribed opioids for CNCP and not those with CNCP not prescribed opioids. Thus we have high confidence that the event rate from these outcomes in those not prescribed opioids is zero. Therefore, from single arm studies of patients with opioids, we can be confident that the rate of the events represents the difference in rate of events in those prescribed opioids versus those not prescribed opioids.

Preference and values

Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
Patients with chronic non-cancer pain may place little importance on avoiding rare but serious side effects such as addiction, overdose, or death, and are often willing to trade the risk of these effects for small but important pain relief. However, if patients actually experience a rare but serious adverse event, their values tend to align more closely with societal values.

Resources and other considerations

Important issues, or potential issues not investigated

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse.*[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary.*[194] [222]* Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioid*[59]* and drug-related criminal behaviour.*[177]* Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Rationale

Opioids, when added to non-opioids achieve, on average, modest improvements in pain and function. Adverse effects include relatively

frequent constipation, nausea and vomiting, sedation, addiction, and a small but important risk of unintentional overdose, which can be fatal. The risk of unintentional overdose increases progressively with the daily dose prescribed.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain, without current or past substance use disorder and without other current serious psychiatric disorders, whose therapy is optimized with non-opioids with persistent problematic pain

Intervention: Trial of opioids.

Comparator: Continue established therapy without opioids.

Summary

Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continue established therapy without opioids.	Trial of opioids.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain (difference in patients who achieve the MID or greater) 3-6 months	Relative risk 1.25 (CI 95% 1.21 - 1.29) Based on data from 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months	**448** per 1000	**560** per 1000 Difference: **112 more** per 1000 (CI 95% 94 more - 130 more)	**High**	Opioid therapy results in a small but important increase in the the proportion of patients who will achieve a 1 cm reduction of pain on a 10 cm VAS compared with placebo.
Physical function (difference in patients who achieve the MID or greater) 1-6 months	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000	**526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy results in a small but important increase in the the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale compared with placebo.
Gastrointestinal side effects 4-26 weeks	Relative risk 3.08 (CI 95% 2.53 - 3.75) Based on data from 14,449 patients in 36 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000	**86** per 1000 Difference: **58 more** per 1000 (CI 95% 43 more - 77 more)	**High**	Opioid therapy results in an increase in gastrointestinal side effects
Pain	Measured by: 10 cm VAS			**High**	Opioid therapy results in

3-6 months	Scale: 0-10 Lower better Based on data from: 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months	Difference: **MD 0.64 fewer** (CI 95% 0.76 fewer - 0.53 fewer)		a small but important improvement in pain
Physical function 1-6 months	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy results in a small but important improvement in physical function
Addiction FU not reported	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency	Opioid therapy likely results in an important risk of addiction.
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Opioid therapy results in a rare but important risk of fatal overdose.
Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Risk of non-fatal overdose is 0.2%.	**Moderate** Due to serious imprecision	Opioid therapy likely results in a small but important increase in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1 studies	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI, 4.58%-5.22%) in 2013.	**Moderate** Due to serious risk of bias	Opioid therapy likely results in an important increase in the risk of diversion.

Details about studies used and certainty down- and upgrading

Pain (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [27], [20], [33], [50], [115], [67], [172], [163], [190], [174], [215], [203], [220], [69], [3], [26], [92], [95], [56], [171], [116], [184], [173], [213], [197],	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Asymmetrical funnel plot ;

	[221], [217], **Baseline/comparator:** Control arm of reference used for intervention	
Physical function (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [44], [221], [215], [3], [50], [56], [35], [78], [69], [115], [91], [144], [131], [174], [171], [213], [197], [226], [217], [33], [20], [42], [26], [73], [66], [92], [79], [139], [116], [172], [163], [202], [184], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Gastrointestinal side effects	**Intervention:** Systematic review with included studies: [63], [27], [75], [67], [92], [79], [143], [115], [163], [147], [197], [184], [216], [203], [25], [221], [20], [33], [24], [69], [66], [91], [78], [129], [95], [152], [144], [190], [171], [44], [213], [202], [3], [226], [50], [217], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Pain	**Intervention:** Systematic review with included studies: [203], [215], [174], [190], [220], [33], [56], [3], [26], [116], [171], [69], [95], [197], [213], [173], [184], [217], [221], [50], [67], [20], [27], [163], [172], [92], [115], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Asymmetrical funnel plot, Mostly commercially funded studies ;
Physical function	**Intervention:** Systematic review with included studies: [172], [184], [139], [163], [221], [3], [202], [215], [44], [56], [26], [35], [91], [115], [69], [78], [171], [174], [131], [144], [217], [20], [226], [197], [213],	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;

	[50], [66], [33], [42], [92], [116], [73], [79], **Baseline/comparator:** Control arm of reference used for intervention	
Addiction	**Intervention:** Systematic review **Other** [14] [142] [187] [1] [64] [47] [159] [100] [55]	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates vary widely (0.7%-15.7%) ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention:** Primary study **Other** [113]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Primary study **Other** [54]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** The study setting was Group Health Cooperative (GHC), which provides comprehensive care on a prepaid basis to about 500 000 persons in Washington State ; **Imprecision: Serious** Small number of events and no confidence interval provided ; **Publication bias: No serious**
Diversion	**Intervention:** Primary study **Other** [94]	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

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Recommendation 3: For patients with chronic noncancer pain with an active substance use disorder

Strong Recommendation | AGAINST

We recommend against the use of opioids

Clinicians should facilitate treatment of the underlying substance use disorders, if not yet addressed. The studies that identified substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Practical Info

Patients with chronic pain and probable substance use should be screened with the CAGE substance abuse screening tool *[153]* or similar validated questionnaire for alcohol use, and validated substance abuse/misuse tools such as the Current Opioid Misuse Measure (COMM).*[31] [32]* Although not evidence-based,*[130]* urine drug testing and review of prescription drug monitoring data is suggested initially and periodically (See Guidance Statement 6).

Key Info

Benefits and harms

Substantial net benefits of the recommended alternative

Patients with active substance use disorder are not represented in trials exploring the effectiveness of opioids for chronic non-cancer pain; however, we have assumed that the small but important benefits on pain and physical function, and increased risks for gastrointestinal adverse events, apply to patients with active substance use disorder. In patients with active substance use disorder, the evidence suggests that opioids are associated with a 8.9% risk of addiction and, at very low doses (<20 MED/day), a 0.9% risk of non-fatal overdose and a 0.5% risk of fatal overdose; risk of overdose increases at higher doses of opioids.

Quality of evidence

Low

The quality of evidence for fatal and non-fatal overdose is low due to very serious indirectness. The estimates of effect are based on the risk of opioid abuse, which is a proxy outcome for the risk of fatal and non-fatal overdose.
The quality of evidence for pain and physical function is high, based on high-quality randomized trials.

Preference and values

Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
Patients with chronic non-cancer pain may place little importance on avoiding rare but serious side effects such as addiction, overdose, or death, and are often willing to trade the risk of these effects for small but important pain relief. However, if patients

actually experience a rare but serious adverse event, their values tend to align more closely with societal values.

Resources and other considerations

Important issues, or potential issues not investigated

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse.*[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary.*[194] [222]*Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioids*[59]* and drug-related criminal behaviour.*[177]* Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Rationale

Low quality evidence suggests a possible substantial increase in the very serious adverse outcomes of unintentional non-fatal overdose and death in patients with active substance abuse disorder using opioids. Compared to individuals without active substance use disorder, patients with chronic non-cancer pain and active substance use disorder are at higher risk for opioid addiction (risk increases from 5.5% to 8.9%), non-fatal overdose (risk increases from 0.2% to 0.9% at <20 MED/day, with increasing risk at higher doses) and fatal overdose (risk increases from 0.1% to 0.5% at <20 MED/day, with increasing risk at higher doses).*[29]* Moderate quality evidence does not support an association between smoking status and opioid misuse (adjusted OR 1.29, 95%CI 0.97 to 1.7).*[104][14][46][109]*

In general, GRADE discourages strong recommendations when the quality of evidence for critical outcomes is low or very low. One paradigmatic situation in which strong recommendations may be warranted despite low or very low quality of evidence is when high quality evidence suggests modest benefits and low or very low quality evidence suggests the possibility of catastrophic harm. For recommendation 3, high quality evidence suggests modest benefit and low quality evidence suggests an elevated risk of serious harm.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain with an active substance use disorder whose non-opioid therapy has been optimized

Intervention: Trial of opioids

Comparator: Continue established therapy without opioids

Summary

We did not find any evidence for difference in pain, physical function, or gastrointestinal side effects in patients with an active substance use disorder compared to patients without an active substance use disorder.
Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continue established therapy without opioids	**Absolute effect estimates** Trial of opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain (difference in patients who achieve the MID or greater) 3-6 months	Relative risk 1.25 (CI 95% 1.21 - 1.29) Based on data from 13,876 patients in 27 studies. (Randomized	**448** per 1000	**560** per 1000 Difference: **112 more** per 1000	**High**	Opioid therapy increases the proportion of patients who will achieve a 1 cm reduction of pain on a 10 cm VAS.

	controlled) Follow up 3-6 months	(CI 95% 94 more - 130 more)		
Physical function (difference in patients who achieve the MID or greater) 1-6 months	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000 **526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale.
Gastrointestinal side effects 1-6 months	Relative risk 3.08 (CI 95% 2.53 - 3.75) Based on data from 14,449 patients in 36 studies. (Randomized controlled) Follow up 4-26 weeks	**28** per 1000 **86** per 1000 Difference: **58 more** per 1000 (CI 95% 43 more - 77 more)	**High**	Opioid therapy results in an increase in gastrointestinal side effects in patients with active substance use disorder.
Pain 3-6 months	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months	Difference: **MD 0.64 fewer** (CI 95% 0.76 fewer - 0.53 fewer)	**High**	Opioid therapy results in a small but important improvement in pain in patients with an active substance use disorder.
Physical function 1-6 months	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy results in a small but important improvement in physical function physical function in patients with an active substance use disorder.
Addiction 1 year	Based on data from 171 patients in 1 studies	Risk of addiction in patients with active substance use disorder is 8.9% (95% CI 3.7%-20%).	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of addiction in patients with an active substance use disorder.
Fatal overdose 2-4 years	Based on data from 18,122 patients in 3 studies	Risk of fatal overdose in patients with active substance use disorder is 0.46% (95%CI 0.19%-1.1%).	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of fatal overdose in patients with active substance use disorder.

Non-fatal overdose 2-4 years	Based on data from 18,122 patients in 3 studies	Risk of non-fatal overdose in patients with active substance use disorder is 0.91% (95% CI 0.39%-2.1%).	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of non-fatal overdose in patients with an active substance use disorder.
Details about studies used and certainty down- and upgrading				
Pain (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [221], [217], [27], [20], [50], [26], [115], [92], [172], [163], [190], [174], [215], [203], [220], [67], [56], [33], [3], [95], [69], [171], [116], [184], [173], [213], [197], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Asymmetrical funnel plot, Mostly commercially funded studies ;		
Physical function (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [226], [217], [33], [20], [42], [26], [73], [66], [92], [79], [139], [116], [172], [163], [202], [184], [44], [221], [215], [3], [50], [56], [35], [78], [69], [115], [91], [144], [131], [174], [171], [213], [197], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;		
Gastrointestinal side effects	**Intervention:** Systematic review with included studies: [33], [216], [226], [26], [217], [20], [50], [24], [78], [69], [95], [91], [144], [129], [171], [152], [202], [190], [63], [27], [213], [3], [221], [66], [67], [44], [79], [75], [115], [92], [147], [143], [184], [163], [203], [197], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**		
Pain	**Intervention:** Systematic review **Baseline/comparator:** Control arm of reference	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious**		

	used for intervention	
Physical function	**Intervention:** Systematic review **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious**
Addiction	**Intervention:** Systematic review **Other** [16]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention:** Systematic review **Other** [104] [55] [12]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Systematic review **Other** [104] [55] [12]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**

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Recommendation 4: For patients with chronic noncancer pain with an active psychiatric disorder whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest stabilizing the the psychiatric disorder before a trial of opioids is considered

Practical Info

Psychiatric comorbidity and emotional distress are common among patients with chronic non-cancer pain.*[204][101]* Moreover, patients with psychiatric disorders report more severe pain. *[101][125]* Patients with chronic pain should be screened for anxiety, post-traumatic stress disorder and depression with appropriate tools such as the Generalized Anxiety Disorder 7-item (GAD7) scale for anxiety,*[183]* the 4-item Primary Care PTSD Screen (PC-PTSD), *[164]* and the Patient Health Questionnaire (PHQ-9) for depression.*[125]* Mood, thought, and personality disorders should be treated prior to addressing complaints of chronic non-cancer pain. Pain often is often resolved or reduced if these disorders are well managed. Emotional distress and emotionally traumatic experiences should also be addressed, often with similar impact on pain complaints.

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

Patients with mental illness are not represented in trials exploring the effectiveness of opioids for chronic non-cancer pain; however, we have assumed that the small but important effects on pain and physical function, and increased risks for gastrointestinal adverse events, apply to patients with mental illness. In patients with current serious mental illness, the evidence suggests that opioids are associated with a 8.0% risk of addiction and, at very low doses (<20 MED/day), a 0.3% risk of non-fatal overdose and a 0.15% risk of fatal overdose; risk of overdose increases at higher doses of opioids.

Quality of evidence

Low

The quality of evidence for fatal and non-fatal overdose is low due to very serious indirectness. The estimates of effect are based on the risk of opioid abuse, which is a proxy outcome for the risk of fatal and non-fatal overdose.
The quality of evidence for pain and physical function is high, based on high-quality randomized trials.

Preference and values

Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
Patients with chronic non-cancer pain may place little importance on avoiding rare but serious side effects such as addiction, overdose, or death, and are often willing to trade the risk of these effects for small but important pain relief. However, if patients actually experience a rare but serious adverse event, their values tend to align more closely with societal values.

Resources and other considerations

Important issues, or potential issues not investigated

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse.*[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2551 per patient per year in Europe to a mean annual excess cost of 15,183 USD per Medicaid beneficiary.*[194] [222]*Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioids*[59]* and drug-related criminal behaviour.*[177]*Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Rationale

Low quality evidence suggests a possible large increase in the very serious adverse outcomes of unintentional non-fatal overdose and

death in patients with serious psychiatric disorder using opioids. The mental illnesses identified in studies as risk factors for adverse outcomes were most typically anxiety and depression, including ICD-9 definitions, as well as "psychiatric diagnosis", "mood disorder" and post-traumatic stress disorder. Compared to individuals without mental illness, patients with chronic non-cancer pain and mental illness are at higher risk for opioid addiction (risk increases from 5.5% to 8.0%), non-fatal overdose (risk increases from 0.2% to 0.3% at <20 MED/day, with increasing risk at higher doses) and fatal overdose (risk increases from 0.1% to 0.15% at <20 MED/day, with increasing risk at higher doses). [168]

Clinical Question/ PICO

Population: Patients with chronic noncancer pain with an active psychiatric disorder whose non-opioid therapy has been optimized, and who still experience persistent problematic pain

Intervention: Trial of opioids

Comparator: Continue established therapy without opioids

Summary

We did not find any evidence for difference in pain, physical function, or gastrointestinal side effects in patients with a current serious psychiatric disorder compared to patients without a current serious psychiatric disorder.
Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continue established therapy without opioids	**Absolute effect estimates** Trial of opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain (difference in patients who achieve the MID or greater) 3-6 months	Relative risk 1.25 (CI 95% 1.21 - 1.29) Based on data from 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months	**448** per 1000	**560** per 1000 Difference: **112 more** per 1000 (CI 95% 94 more - 130 more)	**High**	Opioid therapy increases the proportion of patients who will achieve a 1 cm reduction of pain on a 10 cm VAS.
Physical function (difference in patients who achieve the MID or greater) 1-6 months	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000	**526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale.
Gastrointestinal side effects	Relative risk 3.08 (CI 95% 2.53 - 3.75)	**28**	**86**	**High**	Opioid therapy results in an increase in

1-6 months	Based on data from 14,449 patients in 36 studies. (Randomized controlled) Follow up 4-26 weeks	per 1000 per 1000 Difference: **58 more** per 1000 (CI 95% 43 more - 77 more)		gastrointestinal side effects in patients with active psychiatric disorders.
Pain 3-6 months	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months	Difference: **MD 0.64 fewer** (CI 95% 0.76 fewer - 0.53 fewer)	**High**	Opioid therapy results in a small but important improvement in pain in patients with active psychiatric disorders.
Physical function 1-6 months	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy results in a small but important improvement in physical function in patients with active psychiatric disorders.
Addiction 1-4 years	Based on data from 35,969 patients in 9 studies	The risk of addiction in patients with an active psychiatric disorder is 8.0% (95% CI 6.7%-9.5%)	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of addiction in patients with active psychiatric disorders.
Fatal overdose 1-4 years	Based on data from 35,969 patients in 9 studies	The risk of fatal overdose in patients with an active psychiatric disorder is 0.15% (95%CI 0.12%-0.18%)	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of fatal overdose in patients with active psychiatric disorders.
Non-fatal overdose 1-4 years	Based on data from 35,969 patients in 9 studies	The risk of non-fatal overdose in patients with an active psychiatric disorder is 0.3% (95%CI 0.25%-0.36%)	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of non-fatal overdose in patients with active psychiatric disorders.

Details about studies used and certainty down- and upgrading

Pain (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [220], [215], [95], [20], [26], [27], [92], [50], [171], [116], [184], [173], [213], [197], [221], [217], [56], [3], [67], [69], [33],	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Asymmetrical funnel plot ;

	[163], [115], [174], [172], [203], [190], **Baseline/comparator:** Control arm of reference used for intervention	
Physical function (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [217], [213], [20], [226], [26], [33], [66], [42], [79], [73], [116], [92], [163], [139], [184], [172], [215], [202], [50], [44], [221], [35], [3], [69], [56], [91], [78], [131], [115], [171], [144], [197], [174], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Gastrointestinal side effects	**Intervention:** Systematic review with included studies: [202], [190], [217], [44], [213], [3], [226], [50], [63], [27], [75], [67], [92], [79], [143], [115], [163], [147], [197], [184], [20], [216], [203], [24], [26], [221], [66], [33], [78], [69], [95], [91], [144], [129], [171], [152], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Pain	**Intervention:** Systematic review with included studies: [20], [27], [92], [115], [50], [67], [174], [190], [163], [172], [220], [203], [215], [26], [33], [3], [95], [116], [56], [69], [184], [197], [171], [173], [221], [213], [217], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Physical function	**Intervention:** Systematic review with included studies: [50], [66], [33], [42], [92], [116], [73], [79], [172], [184], [139], [163], [221], [3], [202], [215], [44], [56], [26], [35], [91], [115],	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

	[69], [78], [171], [174], [131], [144], [217], [20], [226], [197], [213], **Baseline/comparator:** Control arm of reference used for intervention	
Addiction	**Intervention:** Systematic review **Other** [104] [55] [109] [157] [12] [176] [191] [14] [46]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention:** Systematic review **Other** [176] [191] [14] [46] [109] [157] [104] [55] [12]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Systematic review **Other** [104] [191] [14] [46] [109] [157] [12] [176] [55]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**

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Recommendation 5: For patients with chronic noncancer pain with a history of substance use disorder, whose nonopioid therapy has been optimized, and who have persistent problematic pain

Weak Recommendation

We suggest continuing nonopioid therapy rather than a trial of opioids

The studies that identified a history of substance use disorder as a risk factor for adverse outcomes characterized the conditions as alcohol abuse and dependence, and narcotic abuse and dependence, and sometimes referred to ICD-9 diagnoses.

Practical Info

Patients with chronic pain and a history of substance use should be screened with the CAGE substance abuse screening tool*[153]* or similar validated questionnaire for alcohol use, and validated substance abuse/misuse tools such as the Current Opioid Misuse Measure (COMM). *[31][32]* Although not evidence-based,*[130]* urine drug testing and review of prescription drug monitoring data is suggested initially and periodically thereafter (see Guidance Statement 6).

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

Patients with prior substance use disorder are not represented in trials exploring the effectiveness of opioids for chronic non-cancer pain; however, we have assumed that the small but important effects on pain and physical function, and increased risks for gastrointestinal adverse events, apply to patients with prior substance use disorder. In patients with prior substance use disorder, the evidence suggests that opioids are associated with a 0.8% risk of non-fatal overdose and a 0.4% risk of fatal overdose at very low doses (<20 MED/day); risk of overdose increases at higher doses of opioids.

Quality of evidence

Low

The quality of evidence for fatal and non-fatal overdose is low due to very serious indirectness. The estimates of effect are based on the risk of opioid abuse, which is a proxy outcome for the risk of fatal and non-fatal overdose.
The quality of evidence for pain and physical function is high, based on high-quality randomized trials.

Preference and values

Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
Patients with chronic non-cancer pain may place little importance on avoiding rare but serious side effects such as addiction, overdose, or death, and are often willing to trade the risk of these effects for small but important pain relief. However, if patients actually experience a rare but serious adverse event, their values tend to align more closely with societal values.

Resources and other considerations

Important issues, or potential issues not investigated

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse.*[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary.*[194] [222]*Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioids*[59]* and drug-related criminal behaviour.*[177]*
Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Rationale

Low quality evidence suggests a possible appreciable increase in the very serious adverse outcomes of unintentional non-fatal overdose and death in patients with a history of substance use disorder using opioids. Compared to individuals without prior substance use disorder, patients with chronic non-cancer pain and prior substance use disorder are at higher risk for non-fatal overdose (risk increases from 0.2% to 0.8% at <20 MED/day, with increasing risk at higher doses) and fatal overdose (risk increases from 0.1% to 0.4% at <20 MED/day, with increasing risk at higher doses).168

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain with a history of substance use disorder, whose non-opioid therapy has been optimized, who still experience persistent problematic pain

Intervention: Trial of opioids

Comparator: Continuing established therapy without opioids

Summary

We did not find any evidence for difference in pain, physical function, or gastrointestinal side effects in patients with a history of substance use disorder compared to patients without a history of substance use disorder.
Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Continuing established therapy without opioids	Trial of opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain (difference in patients who achieve the MID or greater) 3-6 months	Relative risk 1.25 (CI 95% 1.21 - 1.29) Based on data from 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months	**448** per 1000	**560** per 1000 Difference: **112 more** per 1000 (CI 95% 94more - 130 more)	**High**	Opioid therapy increases the proportion of patients who will achieve a 1 cm reduction of pain on a 10 cm VAS.
Physical function (difference in patients who achieve the MID or greater) 1-6 months	Relative risk 1.24 (CI 95% 1.17 - 1.3) Based on data from 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	**424** per 1000	**526** per 1000 Difference: **102 more** per 1000 (CI 95% 72 more - 127 more)	**High**	Opioid therapy increases the proportion of patients who will achieve 5 point increase on the SF-36 physical component summary scale.
Gastrointestinal side effects 1-6 months	Relative risk 3.08 (CI 95% 2.53 - 3.75) Based on data from	**28** per 1000	**86** per 1000	**High**	Opioid therapy results in an increase in gastrointestinal side

	14,449 patients in 36 studies. (Randomized controlled) Follow up 4-26 weeks	Difference: **58 more** per 1000 (CI 95% 43 more - 77 more)		effects in patients with a history of substance use disorder.
Pain 3-6 months	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 13,876 patients in 27 studies. (Randomized controlled) Follow up 3-6 months	Difference: **MD 0.64 fewer** (CI 95% 0.76 fewer - 0.53 fewer)	**High**	Opioid therapy results in a small but important improvement in pain in patients with a history of substance use disorder.
Physical function 1-6 months	Measured by: SF-36 physical component summary scale Scale: 0-100 High better Based on data from: 12,058 patients in 33 studies. (Randomized controlled) Follow up 1-6 months	Difference: **MD 2.16 more** (CI 95% 1.56 more - 2.76 more)	**High**	Opioid therapy results in a small but important improvement in physical function in patients with a history of substance use disorder.
Fatal overdose 1-2 years	Based on data from 620 patients in 3 studies	Risk of fatal overdose in patients with a history of substance use disorder is 0.38% (95% CI 0.24%-0.62%)	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of fatal overdose in patients with a history of substance use disorder.
Non-fatal overdose 1-2 years	Based on data from 620 patients in 3 studies	Risk of fatal overdose in patients with a history of substance use disorder is 0.762% (95% CI 0.47%-1.23%)	**Low** Due to very serious indirectness	Opioid therapy may result in an increase in the risk of non-fatal overdose in patients with a history of substance use disorder.

Details about studies used and certainty down- and upgrading

Pain (difference in patients who achieve the MID or greater)	**Intervention:** Systematic review with included studies: [220], [215], [56], [3], [67], [69], [33], [116], [95], [173], [171], [197], [184], [217], [213], [221], [20], [26], [27], [92], [50], [163], [115], [174], [172], [203], [190], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Asymmetrical funnel plot ;
Physical function	**Intervention:** Systematic	**Risk of bias: No serious**

(difference in patients who achieve the MID or greater)	review with included studies: [217], [213], [50], [44], [226], [35], [3], [69], [56], [91], [78], [131], [115], [171], [144], [202], [184], [221], [215], [20], [174], [26], [33], [66], [42], [79], [73], [116], [92], [163], [139], [197], [172], **Baseline/comparator:** Control arm of reference used for intervention	**Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies, Removed studies with SE>3 (small study effect) ;
Gastrointestinal side effects	**Intervention:** Systematic review with included studies: [197], [184], [20], [216], [203], [24], [26], [221], [66], [33], [78], [69], [95], [91], [144], [129], [171], [152], [202], [190], [217], [44], [213], [3], [226], [50], [63], [27], [75], [67], [92], [79], [143], [115], [163], [147], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Pain	**Intervention:** Systematic review with included studies: [50], [67], [20], [27], [163], [172], [92], [115], [203], [215], [174], [190], [3], [220], [56], [69], [26], [33], [171], [173], [95], [116], [213], [217], [45], [184], [197], [221], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Physical function	**Intervention:** Systematic review with included studies: [73], [79], [50], [66], [139], [163], [92], [116], [202], [215], [172], [184], [26], [35], [221], [3], [69], [78], [44], [56], [131], [144], [91], [115], [197], [213], [171], [174], [33], [42], [217], [20], [226], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Fatal overdose	**Intervention:** Primary study **Other** [46] [109] [176]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Systematic review **Other** [46] [109] [176]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Very Serious** Differences between the outcomes of interest and those reported. Odds ratios are based on risk of opioid abuse ; **Imprecision: No serious** **Publication bias: No serious**

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Recommendations 6 and 7: For patients with chronic noncancer pain who are beginning long term opioid therapy

Strong Recommendation

Recommendation 6: We recommend restricting the prescribed dose to less 90mg morphine equivalents daily rather than no upper limit or a higher limit on dosing

Some patients may gain important benefit at a dose of more than 90mg morphine equivalents daily. Referral to a colleague for a second opinion regarding the possibility of increasing the dose to more than 90mg morphine equivalents daily may therefore be warranted in some individuals.

Key Info

Benefits and harms

Substantial net benefits of the recommended alternative

Meta-regression of within-trial comparisons of different doses of opioids found moderate-quality evidence against a dose-response effect for pain relief (p = 0.49) or functional recovery (p=0.22); *[69][217][50][171][228][229]* however, there is likely a dose-dependent increase in the risk of non-fatal opioid overdose: 0.2% for <20mg MED/day; 0.7% for 50-99mg MED/day; and 1.8% for ≥100mg MED/day. There is an increased risk of fatal opioid overdose with higher doses: 0.1% for <20mg MED/day; 0.14% for 20-49mg MED/day; 0.18% for 50-99mg MED/day; and 0.23% for ≥100mg MED/day.*[30]*

Quality of evidence

Moderate

The quality of evidence for pain, physical function, and fatal overdose is high. The evidence for non-fatal overdose is moderate, due to a small number of events.

Preference and values

Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
Patients with chronic non-cancer pain may place little importance on avoiding rare but serious side effects such as addiction, overdose, or death, and are often willing to trade the risk of these effects for small but important pain relief. However, if patients actually experience a rare but serious adverse event, their values tend to align more closely with societal values.

Resources and other considerations

Important issues, or potential issues not investigated

Our systematic review found evidence for an important increase in risk of fatal and non-fatal overdose at doses of opioid ≥100mg MED/day. Some Canadian provinces (e.g. Nova Scotia, British Columbia) have already adopted the CDC Guideline for Prescribing Opioids for Chronic Pain recommendation to avoid increasing dosage to ≥90mg MED/day or carefully justify a decision to titrate dosage to ≥90mg MED/day.*[53]* In order to ensure greater feasibility of adopting our recommendation, we reduced the recommended threshold for our strong recommendation from under 100mg MED/day to under 90mg MED/day.

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse.*[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary.*[194] [222]* Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioids*[59]* and drug-related criminal behaviour.*[177]* Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Rationale

Observational studies provide moderate quality evidence of a progressive increase in the likelihood of unintentional non-fatal overdose or death as the prescribed dose of opioids increases. These serious outcomes are very rare in those prescribed less than 50 morphine mg equivalents daily, but increase in those prescribed doses of 50 to 90, and though still rare, are further increased in those prescribed doses over 90 MED. This recommendation is not meant to guide use of opioids to treat opioid addiction or opioid use disorder.

Clinical Question/ PICO

Population:	Patients with chronic noncancer pain beginning opioid therapy
Intervention:	Limit opioid dose to a particular maximum dose
Comparator:	No maximum opioid dose

Summary

A clear dose-response relationship was demonstrated for the outcomes of fatal and non-fatal overdose.
A meta-regression was performed for pain, physical function, and gastrointestinal side effects that demonstrated no dose-response relationship with opioid dose and any of these three outcomes.
No evidence was found for a dose-response relationship between opioid dose and the outcomes of addiction and diversion. The studies that informed these two outcomes included patients on a variety of opioid doses. We therefore assume that the risks presented are applicable to all doses of opioids.
Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No maximum opioid dose	Limit opioid dose to a particular maximum dose	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 3 months	Based on data from 3,519 patients in 6 studies	Within-study comparisons found no evidence for a dose-response effect on pain (meta-regression p-value=0.49).		**High**	Limiting opioid dose to a particular maximum dose results in little or no difference in pain.
Physical function 3 months	Based on data from 3,172 patients in 4 studies	Within-study comparisons found no evidence for a dose-response effect on physical function (meta-regression p-value=0.22).		**High**	Limiting opioid dose to a particular maximum dose results in little or no difference in physical function.
Gastrointestinal side effects 3 months	Based on data from 3,519 patients in 6 studies	Within-study comparisons found no evidence for a dose-response effect on gastrointestinal side effects (meta-regression p-value=0.09).		**High**	Limiting opioid dose to a particular maximum dose results in little or no difference in gastrointestinal side effects.
Addiction	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)		**Moderate** Due to serious inconsistency	Limiting opioid dose to a particular maximum dose likely results in little or no difference on the risk of addiction.
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.		**High**	Limiting opioid dose to a particular maximum dose results in a reduction in the risk of fatal overdose.

Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Limiting opioid dose to a particular maximum dose likely results in a reduction in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1 studies	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58-5.22%) in 2013.	**Moderate** Due to serious risk of bias	Limiting opioid dose to a particular maximum dose likely results in little or no difference in the risk of diversion.

Details about studies used and certainty down- and upgrading

Pain	**Intervention:** Systematic review **Other** [50] [143] [69] [217] [171] [229]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Physical function	**Intervention:** Systematic review **Other** [171] [69] [50] [217]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Gastrointestinal side effects	**Intervention:** Systematic review **Other** [69] [171] [229] [217] [143] [50]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Addiction	**Intervention:** Primary study **Other** [187] [64] [47] [159] [14] [142] [100] [1] [55]	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates vary widely (0.7%-15.7%) ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention:** Primary study **Other** [113]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Primary study **Other** [54]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of events ;

		Publication bias: No serious
Diversion	**Intervention:** Primary study **Other** [94]	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Weak Recommendation

Recommendation 7: For patients with chronic noncancer pain who are beginning opioid therapy, we suggest restricting the prescribed dose to less than 50mg morphine equivalents daily.

The weak recommendation to restrict the prescribed dose to less than 50mg morphine equivalents daily acknowledges that there are likely to be some patients who would be ready to accept the increased risks associated with a dose higher than 50mg in order to potentially achieve improved pain control.

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

Meta-regression of within-trial comparisons of different doses of opioids found moderate-quality evidence against a dose-response effect for pain relief (p = 0.49) or functional recovery (p=0.22)*[69][217][50][171][228][229]* ; however, there is likely a dose-dependent increase in the risk of non-fatal opioid overdose: 0.2% for <20mg MED/day; 0.7% for 50-99mg MED/day; and 1.8% for ≥100mg MED/day. There is an increased risk of fatal opioid overdose with higher doses: 0.1% for <20mg MED/day; 0.14% for 20-49mg MED/day; 0.18% for 50-99mg MED/day; and 0.23% for ≥100mg MED/day.*[30]*

Quality of evidence

Moderate

The quality of evidence for pain, physical function, and fatal overdose is high. The evidence for non-fatal overdose is moderate, due to a small number of events.

Preference and values

Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
Patients with chronic non-cancer pain may place little importance on avoiding rare but serious side effects such as addiction, overdose, or death, and are often willing to trade the risk of these effects for small but important pain relief. However, if patients actually experience a rare but serious adverse event, their values tend to align more closely with societal values.

Resources and other considerations

Important issues, or potential issues not investigated

Our systematic review found evidence for an important increase in risk of fatal and non-fatal overdose at doses of opioid ≥100mg MED/day. Some Canadian provinces (e.g. Nova Scotia, British Columbia) have already adopted the CDC Guideline for Prescribing Opioids for Chronic Pain recommendation to avoid increasing dosage to ≥90mg MED/day or carefully justify a decision to titrate

dosage to ≥90mg MED/day.*[53]* In order to ensure greater feasibility of adopting our recommendation, we reduced the recommended threshold for our strong recommendation from under 100mg MED/day to under 90mg MED/day.

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse.*[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary.*[194][222]* Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioids*[59]* and drug-related criminal behaviour.*[177]* Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Rationale

Observational studies provide moderate quality evidence of a progressive increase in the likelihood of unintentional non-fatal overdose or death as the prescribed dose of opioids increases. These serious outcomes are very rare in those prescribed less than 50 morphine mg equivalents daily, but increase in those prescribed doses of 50 to 90, and though still rare, are further increased in those prescribed doses over 90 MED. This recommendation is not meant to guide use of opioids to treat opioid addiction or opioid use disorder.

Clinical Question/ PICO

Population: Patients with chronic noncancer pain beginning opioid therapy
Intervention: Limit opioid dose to a particular maximum dose
Comparator: No maximum opioid dose

Summary

A clear dose-response relationship was demonstrated for the outcomes of fatal and non-fatal overdose.
A meta-regression was performed for pain, physical function, and gastrointestinal side effects that demonstrated no dose-response relationship with opioid dose and any of these three outcomes.
No evidence was found for a dose-response relationship between opioid dose and the outcomes of addiction and diversion. The studies that informed these two outcomes included patients on a variety of opioid doses. We therefore assume that the risks presented are applicable to all doses of opioids.
Minimally important difference for pain on a 10-cm visual analogue scale (VAS) is a reduction of 1 cm.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No maximum opioid dose	Limit opioid dose to a particular maximum dose	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain 3 months	Based on data from 3,519 patients in 6 studies	Within-study comparisons found no evidence for a dose-response effect on pain (meta-regression p-value=0.49).		**High**	Limiting opioid dose to a particular maximum dose results in little or no difference in pain.
Physical function 3 months	Based on data from 3,172 patients in 4 studies	Within-study comparisons found no evidence for a dose-response effect on physical function (meta-regression p-value=0.22).		**High**	Limiting opioid dose to a particular maximum dose results in little or no difference in physical

				function.
Gastrointestinal side effects 3 months	Based on data from 3,519 patients in 6 studies	Within-study comparisons found no evidence for a dose-response effect on gastrointestinal side effects (meta-regression p-value=0.09).	**High**	Limiting opioid dose to a particular maximum dose results in little or no difference in gastrointestinal side effects.
Addiction	Based on data from 22,278 patients in 9 studies	Risk of opioid addiction is 5.5% (95% CI 3.91-7.03%)	**Moderate** Due to serious inconsistency	Limiting opioid dose to a particular maximum dose likely results in little or no difference on the risk of addiction.
Fatal overdose median 2.6 years	Based on data from 285,520 patients in 1 studies	Estimated annual fatal overdose rates were 0.10%, 0.14%, 0.18% , and 0.23% in patients receiving <20 mg morphine equivalent per day, 20-49 mg/day, 50-99 mg/day, and >100 mg per day respectively.	**High**	Limiting opioid dose to a particular maximum dose results in a reduction in the risk of fatal overdose.
Non-fatal overdose up to 10 years	Based on data from 9,940 patients in 1 studies	Estimated annual overdose rates were 0.2%, 0.7%, and 1.8% among patients receiving less than 20 mg/d, 50 to 99 mg/d, and more than 100 mg/d of opioids, respectively.	**Moderate** Due to serious imprecision	Limiting opioid dose to a particular maximum dose likely results in a reduction in the risk of non-fatal overdose.
Diversion 1 year	Based on data from 472,200 patients in 1 studies	Among US adults, the prevalence of nonmedical use of prescription opioids was 4.9% (95% CI 4.58-5.22%) in 2013.	**Moderate** Due to serious risk of bias	Limiting opioid dose to a particular maximum dose likely results in little or no difference in the risk of diversion.

Details about studies used and certainty down- and upgrading

Pain	**Intervention:** Systematic review **Other** [50] [143] [69] [217] [171] [229]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Physical function	**Intervention:** Systematic review **Other** [171] [69] [50] [217]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;

Gastrointestinal side effects	**Intervention:** Systematic review **Other** [69] [171] [229] [217] [143] [50]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious** Mostly commercially funded studies ;
Addiction	**Intervention:** Primary study **Other** [187] [64] [47] [159] [14] [142] [100] [1] [55]	**Risk of bias: No serious** **Inconsistency: Serious** Point estimates vary widely (0.7%-15.7%) ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Fatal overdose	**Intervention:** Primary study **Other** [113]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** Study setting was the Ontario Drug Benefit Database, including Ontarians eligible for drug coverage. This population may be systematically different than other populations with chronic non-cancer pain ; **Imprecision: No serious** **Publication bias: No serious**
Non-fatal overdose	**Intervention:** Primary study **Other** [54]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of events ; **Publication bias: No serious**
Diversion	**Intervention:** Primary study **Other** [94]	**Risk of bias: Serious** Response rate of 66%. Outcome was self-reported ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

4 - Rotation and Tapering of Opioids, for Patients with Chronic Noncancer Pain

This section provides guidance on the practices of opioid tapering and opioid rotation.

Recommendation 8: For patients with chronic noncancer pain who are currently using opioids, and have persistent problematic pain and/or problematic adverse effects

Weak Recommendation

We suggest rotation to other opioids rather than keeping the opioid the same

Rotation in such patients may be done in parallel with, and as a way of facilitating, dose reduction

Practical Info

Opioid rotation may be useful in some patients with uncontrolled pain, intolerable side effects and/or the need to switch to a new route of opioid administration (e.g. transdermal). One common scenario for opioid rotation is the switch from morphine to any other conventional opioid because active morphine metabolites can result in drowsiness and confusion – especially in the setting of renal failure. Recognizing that equianalgesic tables provide only a rough approximation of equivalent opioid potency, calculate the equianalgesic dose of the new opioid based on Table 5 and reduce the calculated dose by 25-50% to minimize the risk of inadvertent overdose. For patients in whom the rationale for opioid rotation is severe uncontrolled pain, administration of the equianalgesic dose without dose reduction may be reasonable. Rotation from conventional opioids to methadone is more complicated and is best carried out by experienced practitioners.*[58]*

Clinicians may consider the following guidance when opioid rotation is used as a strategy to reduce dose:

1. Decrease the total daily dose of the current oral opioid 10-30% while starting the new oral opioid at the lowest total daily dose for the formulation
2. Decrease the total daily dose of the current opioid 10-25% per week while titrating up the total daily dose of the new opioid weekly by 10-20% with a goal of switching over 3-4 weeks

Practitioners may wish to use the Switching Opioids Tool as a guide when rotating opioids: http://nationalpaincentre.mcmaster.ca/opioidmanager/documents/opioid_manager_switching_opioids.pdf

Table 5: Opioid conversion table

Opioids*	To convert to oral morphine equivalent, multiply by:	To convert from oral morphine, multiply by:	50 MED equivalent dose	90 MED equivalent dose
Oral preparations (mg/d)				
Codeine	0.15 (0.1-0.2)	6.67	334 mg/d	600 mg/d
Hydromorphone	5.0	0.2	10 mg/d	18 mg/d
Morphine	1.0	1	50mg/d	90mg/d
Oxycodone	1.5	0.667	33 mg/d	60 mg/d
Tapentadol	0.3-0.4	2.5-3.33	160	300
Tramadol	0.1 -0.2	6	300	540**

*Conversion ratios for opioids are subject to variations in kinetics governed by genetics and other drugs.
** The maximum recommended daily dose of tramadol is 300 mg - 400 mg depending on the formulation.

Key Info

Benefits and harms

Small net benefit, or little difference between alternatives

Opioid rotation may result in a large improvement in pain and physical function. Rotation probably has little or no effect on the outcomes of addiction or diversion. It is uncertain whether rotation affects the incidence of gastrointestinal side effects.

Quality of evidence

Low

Quality of evidence for pain and physical function was low, due to a lack of a comparison group, and two studies (Galvez et al., 2013 and Choquette et al., 2008) had high loss to follow up (25%). Quality of evidence for addiction, diversion, and success of opioid rotation was moderate.

Preference and values

Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief.

Resources and other considerations

Important issues, or potential issues not investigated

Economic impact of opioid misuse and abuse

The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse.*[72]* When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary.*[194] [222]*Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioids*[59]* and drug-related criminal behaviour.*[177]* Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain with persistent problematic pain and/or problematic side effects

Intervention: Rotation to other opioids

Comparator: No change in opioid therapy

Summary

Minimally important difference for pain on a 11 point Numeric Pain Rating Scale (NRS) is a reduction of 2 points.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No change in opioid therapy	 Rotation to other opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain up to 8 months	Based on data from 524 patients in 5 studies	Mean change score on 11 point numeric rating scale was -3.3 (95% CI -3.5 to -3.1)		**Low**	Rotation to other opioids may may result in a large reduction in pain.

Physical function 2-3 months	Based on data from 206 patients in 2 studies	Mean change score of SF-36 physical function subscale was 16.7 (95% CI 15.0-18.4)	**Low**	Rotation to other opioids may result in a large improvement in physical function.
Gastrointestinal side effects 2-3 months	Based on data from 610 patients in 6 studies	Risk of nausea was 21% (95% CI 9.0-33.1%) and risk of constipation was 17.6% (95%CI 12.6-22.5%).	**Very Low** Due to serious risk of bias	We are uncertain about the effect of rotation on gastrointestinal side effects.
Success of opioid rotation 2-34 months	Based on data from 349 patients in 4 studies	Across 4 studies, 253 out of 349 patients (72.5%) successfully rotated opioids.	**Moderate** Due to serious indirectness	Success of opioid rotation is likely high in this patient population.
Addiction 2-9 months	Based on data from 167 patients in 2 studies	Choquette et al (2008) reported no spontaneous reports of abuse or addiction. Quang-Cantagrel et al (2000) reported one case of addiction.	**Moderate** Due to serious indirectness	Rotation to other opioids likely results in little or no difference on risk of addiction.
Diversion 34 months	Based on data from 48 patients in 1 studies	Four patients (8.3%) failed treatment due to drug diversion.	**Moderate** Due to serious imprecision	Rotation to other opioids likely results in little or no difference on risk of diversion

Details about studies used and certainty down- and upgrading

Pain	**Intervention:** Systematic review **Other** [39] [140] [81] [70] [68]	**Risk of bias: No serious** Included studies lacked a comparison group. Galvez et al (2013) had 25% loss to follow up for efficacy outcomes, and Choquette et al (2008) had 24% loss to follow up for efficacy outcomes ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Physical function	**Intervention:** Systematic review **Other** [68] [39]	**Risk of bias: No serious** Included studies lacked a comparison group. Galvez et al (2013) had 25% loss to follow up for efficacy outcomes, and Choquette et al (2008) had 24% loss to follow up for efficacy outcomes ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

Gastrointestinal side effects	**Intervention:** Systematic review **Other** [192] [68] [39] [70] [166] [140]	**Risk of bias: Serious** Included studies lacked a comparison group ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Success of opioid rotation	**Intervention:** Systematic review **Other** [68] [179] [39] [140]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Success of rotation was not measured in the same way in each study: two studies (Malinoff et al and Rhodin et al) defined as “not discontinuing therapy” (ie, lack of efficacy or intolerable adverse events); Choquette et al and Galvez et al included patients enrolled in a trial, and counted success as “not discontinuing the trial” which included lack of efficacy and adverse events, but also “noncompliance” and “withdrawn consent” ; **Imprecision: No serious** **Publication bias: No serious**
Addiction	**Intervention:** Systematic review **Other** [39] [166]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Choquette et al (2008) relied on patients to "spontaneously" report addiction, and only followed patients for 2 months ; **Imprecision: No serious** **Publication bias: No serious**
Diversion	**Intervention:** Primary study **Other** [179]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Low number of patients ;

Recommendation 9: For patients with chronic noncancer pain who are currently using 90mg morphine equivalents of opioids per day or more

Weak Recommendation

We suggest tapering opioids to the lowest effective dose, potentially including discontinuation, rather than making no change in opioid therapy.

Some patients are likely to experience significant increase in pain or decrease in function that persists for more than one month after a small dose reduction; tapering may be paused and potentially abandoned in such patients.

Practical Info

There are a number of specific reasons to consider opioid tapering:

- Lack of improvement in pain and/or function
- Nonadherence to the treatment plan
- Signs of substance misuse
- Serious opioid-related adverse event
- Patient request

Otherwise, all patients on long-term opioids at all doses should be regularly evaluated and counselled about the benefits and harms of

ongoing therapy and the potential benefits of tapering.

Opioid benefits may attenuate with time (owing to tolerance and/or hyperalgesia) and for some patients may come to be defined, in whole or in part, by the relief of interdose withdrawal symptoms. The potential harms of opioids generally increase with dose, and some may not be attributed to the drugs (particularly depression, hormonal disturbance, sleep disturbance and opioid-induced hyperalgesia).

Patients on high doses (≥90mg MED/day) should be prioritized for gradual opioid tapering. The balance of benefits and harms often becomes unfavourable at doses above 90mg MED/day. For these patients the potential harms of therapy often outweigh the benefits the patient can achieve in terms of pain and function.

Patients should be actively engaged in a discussion about the merits of gradual dose reduction, including the potential for better pain control and quality of life. Prepare the patient for tapering by optimizing non-opioid strategies for pain management, setting realistic functional goals, optimizing psychosocial support, creating a schedule of dose reductions and follow-up visits and having a plan in place to manage withdrawal symptoms and emerging pain. Establishing a plan with patients takes the uncertainty out of the process and helps engage them in the process (see nationalpaincentre.mcmaster.ca/guidelines for a Patient Information Sheet for Tapering).

A gradual dose reduction of 5-10% of the morphine equivalent dose every 2-4 weeks with frequent follow up is a reasonable rate of opioid tapering. Switching the patient from immediate release to controlled release opioids on a fixed dosing schedule may assist some patients in adhering to the withdrawal plan. Patients and physicians may wish to consult a pharmacist to assist with scheduling dose reductions.

Alternative methods of tapering include:

- Reducing the dose rapidly over a few days/weeks or immediately: This method may result in severe withdrawal symptoms and is best carried out in a medically supervised withdrawal centre
- Tapering with methadone or buprenorphine-naloxone preparations: patients may be rotated to methadone or buprenorphine-naloxone and then gradually tapered. In Canada, all physicians prescribing methadone require a Federal exemption for pain or addiction. The requirement for supplementary training for the use of buprenorphine-naloxone varies from province to province. If unfamiliar, clinicians should consult with someone knowledgeable with buprenorphine-naloxone use.

In patients struggling with the tapering plan (distressing or intolerable pain/withdrawal symptoms/decreased function which persists longer than 4 weeks), pausing the taper and re-evaluating the patient's pain/clinical status/coping mechanisms and the approach to tapering can help formulate a go-forward plan. (See Recommendation #10)

In patients with the emergence of significant mental health symptoms and/or ambiguous drug-related behaviours, consultation with local experts is advised.

Patients should be encouraged to taper to the lowest opioid dose achievable without a loss of previously achieved function. Some patients may not eliminate use of opioids, but any reduction in dose may be beneficial.

Key Info

Benefits and harms — Small net benefit, or little difference between alternatives

Tapering may result in a large reduction in opioid dose, or cessation of opioids altogether. This may reduce the risk of opioid-related harms. It is uncertain whether tapering has an effect on pain.

Quality of evidence — Low

The quality of evidence for pain was very low, due to serious risk of bias (lack of a comparison group) and imprecision (small number of patients). The quality of evidence for success of tapering was low, due to imprecision (small number of patients) and indirectness (the two studies defined success of tapering in different ways. One study defined success as completely tapering opioids (Baron et al. 2006), and the other defined success as achieving a lower dose than baseline (Harden et al. 2015).

Preference and values — Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief. Patients

are also concerned about the negative effects of opioid withdrawal (such as severe suffering, increased pain, and functional limitation) that may result from efforts to wean or discontinue opioid use.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
In the case of patients tapering opioids, a high value is still placed on avoiding rare but serious side effects, but high value is also placed on avoiding severe suffering due to opioid withdrawal and on patient autonomy under these circumstances.

Resources and other considerations

Important issues, or potential issues not investigated

Economic impact of opioid misuse and abuse
The medical costs of opioid abuse are considerable, in part due to the comorbidities associated with opioid abuse*[72]* . When costs are subsidized by insurance schemes, this translates into an increased societal burden; estimates range from €900-2,551 per patient per year in Europe to a mean annual excess cost of $15,183 USD per Medicaid beneficiary*[194] [222]*. Moreover, risks are not limited to patients, as exemplified by the unintended exposure of children to prescription opioids*[59]* and drug-related criminal behaviour *[177]*. Indirect costs include the economic burden of untreated opioid dependence, crime, and loss of productivity.*[177]*

Rationale

Reduction in opioid dose may reduce adverse effects, including cognitive impairment and the likelihood of non-fatal or fatal unintentional overdose. If not done slowly, dose reduction may cause increased pain, decreased function, or highly aversive symptoms of opioid withdrawal.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain on opioids with persistent problematic pain
Intervention: Tapering of opioid
Comparator: Keeping the dose of opioid the same

Summary

Minimally important difference for pain on a 11 point Numeric Pain Rating Scale (NRS) is a reduction of 2 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Keeping the dose of opioid the same	**Absolute effect estimates** Tapering of opioid	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain up to 1 year	Based on data from 73 patients in 2 studies	Baron et al 2006 (n=23): Pain was reduced from mean (SD) of 8.00 (0.30) at baseline to 3.35 (0.33) at 6 months. Harden et al 2015 (n=50): 40% of patients reported less pain, 28% reported no change, and 33% reported more pain after tapering.		**Very Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain about the effect of tapering on pain.
Success of tapering	Based on data from 73 patients in 2 studies	Baron et al 2006 (n=23): 100% of patients successfully tapered opioids. Harden et al		**Low** Due to serious	Success of tapering may be high in this patient

up to 1 year		2015 (n=50): 47 out of 50 (94%) of patients successfully tapered opioids.	indirectness, Due to serious imprecision	population.

Details about studies used and certainty down- and upgrading

Pain	**Intervention:** Primary study **Other** [96] [15]	**Risk of bias: Serious** Two out of three studies (Baron et al 2006, Harden et al 2015) implemented tapering strategy without a comparison group ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients ;
Success of tapering	**Intervention:** Systematic review **Other** [15] [96]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** These two studies defined "success of tapering" differently. Baron et al 2006 enrolled patients into a voluntary inpatient "detoxification" program intended to taper off of prescription opioids if the patient or physician felt that the patient was not getting benefit from high doses of opioids. No patient was referred for diversion, overuse, abuse, or addiction to opioids. The goal of the program was to taper patients completely off opioids. Harden et al 2015 included patients drawn from a list of patients initiated on an opioid taper at a VA medical centre. A taper was considered successful if the patient's dose at 12 months was less than the baseline dose ; **Imprecision: Serious** Small number of patients ;

Recommendation 10: For patients with chronic noncancer pain who are using opioids and experiencing serious challenges in tapering

Strong Recommendation

We recommend a formal multidisciplinary program.

Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration that includes several health professionals whom physicians can access according to their availability (possibilities include, but are not limited to, a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist).

Practical Info

Serious challenges in tapering could include re-emergence of or new functional or psychological impairment, aberrant behaviors around opioid use, or behaviors indicative of an emerging or overt substance use disorder.

Key Info

Benefits and harms

Substantial net benefits of the recommended alternative

Multidisciplinary tapering programs are likely associated with successful cessation of opioids, but it is uncertain whether these programs have an effect on pain or physical function.

Quality of evidence Moderate

The quality of evidence for pain and physical function was very low, due to serious risk of bias and serious imprecision. The evidence for success of tapering was moderate, due to serious imprecision.

Preference and values Substantial variability is expected or uncertain

Patients place a high value on achieving pain relief, but also place a high value on avoiding the adverse events of severe nausea, vomiting, and constipation. Patients may place a higher value on avoiding these adverse events than on modest pain relief. Patients are also concerned about the negative effects of opioid withdrawal (such as severe suffering, increased pain, and functional limitation) that may result from efforts to wean or discontinue opioid use.
Society as a whole places high value on avoiding rare but serious side effects such as addiction, overdose, and death, reflected in decisions made regarding other drugs with severe rare side effects, and public and policy reactions to diversion, death, and addiction related to opioid use.
In the case of patients tapering opioids, a high value is still placed on avoiding rare but serious side effects, but high value is also placed on avoiding severe suffering due to opioid withdrawal and on patient autonomy under these circumstances.

Resources and other considerations Important issues, or potential issues not investigated

Multidisciplinary programs are very limited in their availability, the primary barrier being lack of funding from provincial Ministries of Health. Their effectiveness in complex pain is clear, but their cost-effectiveness is still controversial. They are generally confined to tertiary care academic centres where health professionals such as psychologists and physical therapists are part of the pain program. Other limitations to these programs include language, cultural and geographical barriers. For patients living a considerable distance from these centres, travelling for repeated visits may not be feasible. A further limitation is that this patient population must be motivated to pursue psychological and physical interventions – they must be active rather than passive participants in their care with realistic expectations of benefit.

Rationale

Studies provide moderate quality evidence that, in patients desiring a reduction or discontinuation of opioid therapy but experiencing serious challenges in tapering or discontinuing therapy, multi-disciplinary programs can substantially increase the likelihood of successful reduction or discontinuation.

Clinical Question/ PICO

Population: Patients who want to taper opioids who are above the threshold dose
Intervention: Multidisciplinary Program
Comparator: No Multidisciplinary Program

Summary

In the Krumova study, 24 out of 102 patients did not completely taper but reduced dose from a mean(SD) 366.5 (524) MED to 72.6 (53.2) MED. 6 patients returned to higher doses of opioids within 12-24 months.
In the Hooten study, 2 out of 101 patients did not completely taper. One patient reduced dose from 422 MED to 22 MED; the second patient reduced dose from 365 MED to 24 MED. Minimally important difference for pain on a 11 point Numeric Pain Rating Scale (NRS) is a reduction of 2 points. Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No Multidisciplinary Program	**Absolute effect estimates** Multidisciplinary Program	**Certainty in effect estimates** (Quality of evidence)	**Summary**

Pain 1-2 years	Based on data from 102 patients in 1 studies	Pain was reduced from 7.1 (1.8) at baseline to 5.9 (2.3) at follow up.	**Very Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain about the effect of multidisciplinary programs on pain.
Success of tapering up to 2 years	Based on data from 203 patients in 2 studies	Krumova et al 2013: 78 out of 102 (76.5%) successfully tapered odd opioids in a mean of 22 days. 31 reinitiated opioid treatment within 12-24 months. Hooten et al 2010: 99 out of 101 (98%) patients successfully tapered off opioids.	**Moderate** Due to serious imprecision	Multidisciplinary programs likely result in a large proportion of patients who successfully taper opioids.
Physical Function 1-2 years	Based on data from 102 patients in 1 studies	Physical function improved from 26.1 (7.7) at baseline to 27.8 (9.8) at follow up.	**Very Low** Due to serious risk of bias, Due to serious imprecision	We are uncertain about the effects of multidisciplinary programs on physical function.

Details about studies used and certainty down- and upgrading

Pain	**Intervention:** Primary study **Other** [126]	**Risk of bias: Serious** Studies lacked a comparison group ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients ;
Success of tapering	**Intervention:** Systematic review **Other** [126] [102]	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients ;
Physical Function	**Intervention:** Systematic review **Other** [126]	**Risk of bias: Serious** Studies lacked a comparison group ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Small number of patients ;

5 - Best Practice Statements

Informed consent

Practice Statement

Acquire informed consent prior to initiating opioid use for chronic non-cancer pain. A discussion about potential benefits, adverse effects, and complications will facilitate shared-care decision making regarding whether to proceed with opioid therapy.

Monitoring

Practice Statement

Clinicians should monitor their chronic non-cancer pain patients using opioid therapy for their response to treatment, and adjust treatment accordingly.

Contraindications

Practice Statement

Clinicians with chronic non-cancer pain patients prescribed opioids should address any potential contraindications and exchange relevant information with the patient's general practitioner (if they are not the general practitioner) and/or pharmacists.

6 - Expert Guidance

Guidance statement 1: Restriction in amounts of opioids prescribed

Dangers of overdose and diversion both mandate not prescribing large doses of opioids at one time. Regulators have approached this issue in different ways. The College of Physicians and Surgeons of Ontario advises they will consider investigation of physicians who prescribe 650 milligrams of morphine per day and the equivalent of 20,000 milligrams of morphine for a patient at one time (http://www.cpso.on.ca/Whatsnew/News-Releases/2016/Ensuring-Safe-Opioid-Prescribing). The College of Physicians and Surgeons of British Columbia have advised that prescribing opioid medications for more than two months at a single dispense is not medically appropriate (https://www.cpsbc.ca/for-physicians/college-connector/2014-V02-02/06). Neither approach, however, has been empirically shown to reduce risk of harms. Experts feel that it is reasonable to limit the amount of opioids prescribed at one time, but also recognize that such policies may inconvenience patients who are travelling for extended periods of time. Flexibility in such situations may be desirable.

Guidance statement 2: Immediate vs Controlled Release Opioids

In patients with continuous pain including pain at rest, clinicians can prescribe controlled release opioids both for comfort and simplicity of treatment. Activity related pain may not require sustained release treatment and opioid therapy may be initiated with immediate release alone.

The benefit and safety of controlled release or sustained release over immediate release preparations is not clearly established. Some patients, when switching from immediate release to comparable dose sustained release, require larger doses in order to acquire a similar analgesic effect. The release profile of all sustained or controlled release preparations is not the same and may vary for the same drug among patients. Individuals misusing opioids favour immediate release opioid preparations, regardless of the route of administration.*[43]*

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain prior to starting long-term opioid therapy
Intervention: Controlled release opioids
Comparator: Immediate release opioids

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Immediate release opioids	Controlled release opioids	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Gastrointestinal side effects 1 month	Relative risk 1.1 (CI 95% 0.75 - 1.62) Based on data from 874 patients in 5 studies.	**409** per 1000	**450** per 1000	**Very Low** Due to serious risk of bias, Due to serious	We are uncertain about the effect of CR versus IR opioids on gastrointestinal side

	(Randomized controlled) Follow up mean 1.38 months	Difference: **41 more** per 1000 (CI 95% 102 fewer - 254 more)	inconsistency, Due to serious imprecision	effects.
Pain 1 month	Measured by: 10 cm VAS Scale: 0-10 Lower better Based on data from: 874 patients in 5 studies. (Randomized controlled) Follow up mean 1.38 months	Difference: **MD 0.17 fewer** (CI 95% 0.59 fewer - 0.24 more)	**Moderate** Due to serious risk of bias	CR opioids likely result in little or no difference on pain compared to IR opioids.
Physical Function 1 month	Measured by: SF-36 physical component summary score Scale: 0-100 High better Based on data from: 296 patients in 2 studies. (Randomized controlled) Follow up mean 1.38 months	Difference: **MD 2.32 fewer** (CI 95% 6.4 fewer - 1.75 more)	**Low** Due to serious risk of bias, Due to serious inconsistency	CR opioids may result in little or no difference on physical function compared with IR opioids.

Details about studies used and certainty down- and upgrading

Gastrointestinal side effects	**Intervention:** Systematic review with included studies: [162], [110], [34], [18], [2], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Large portion of missing participant data (21%-57%) ; **Inconsistency: Serious** Point estimates vary widely ; **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes benefit and harm ;
Pain	**Intervention:** Systematic review with included studies: [162], [18], [2], [110], [34], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Large portion of missing participant data (21%-57%) ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**
Physical Function	**Intervention:** Systematic review with included studies: [110], [162], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Large portion of missing participant data (21%-57%) ; **Inconsistency: Serious** The magnitude of statistical heterogeneity was high, with I^2=61% ; **Indirectness: No serious** **Imprecision: No serious** **Publication bias: No serious**

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Guidance statement 3: Co-prescribing with opioids

Available studies yield conflicting results regarding the consequences of the concomitant use of opioids and sedatives such as benzodiazepines. Our systematic review identified 5 studies that explored the association of benzodiazepines with adverse events; 3 found a significant association with harms *[157] [134] [113]* and 2 did not.*[14] [77]* The pharmacology suggests that sedatives and opioids would enhance the depressant effect of the other, worsening the balance of harms vs. benefits and increasing the risk of cognitive effects, falls, motor vehicle accidents and drug-related death, though the supporting evidence is unavailable. The expert perspective is that opioids and benzodiazepines should very rarely be prescribed together.

Guidance statement 4: Sleep apnea

Patients with opioid-induced sleep apnea should be advised of the associated health risks, and particularly the risks of operating a motor vehicle. Clinicians may have a statutory duty to report to governmental licensing authorities.

There are three main treatment approaches available to clinicians managing patients with opioid-induced sleep disordered breathing:

Option 1: Reduce opioid dose without specific treatment for sleep apnea.

Since opiates themselves cause sedation and daytime sleepiness, and there are fewer sleep arousals in opioid-treated versus non opioid-treated sleep apnea patients, the value of specific sleep apnea treatment for daytime sleepiness is often in doubt. Decreasing the dose of opiates in patients with chronic non-cancer pain is a reasonable first-line therapy.*[210]* For opioid-induced central sleep apnea (CSA), reducing opioid dose may improve sleep apnea. The effects of opioid dose reduction on obstructive sleep apnea (OSA) are less certain. A repeat sleep study may be helpful to determine the impact of opioid dose reduction, particularly in patients with severe OSA/ CSA.

Option 2: Provide specific treatment for sleep apnea without reducing opioid dose.

If opioid dose reduction is not possible because of increase pain or decreased function, three main positive airway pressure (PAP) treatment options are available. Continuous positive airway pressure (CPAP) is generally effective for treatment of non-opioid-induced OSA, and is the treatment of choice for most patients with symptomatic OSA. The first line PAP therapy for either OSA or CSA should be CPAP. Should significant CSA persist (as determined by symptomatic response to CPAP as well as polysomnographic indices), alternatives include bilevel positive airway with a back-up rate and adaptive servo ventilation. Recognising that PAP therapies appear less well tolerated in this population than in the setting of non-opioid-induced sleep apnea, second-line treatments for OSA such as mandibular repositioning devices may be necessary in some patients.

Option 3: Reduce opioid dose and provide specific treatment for apnea.

In instances in which opioid dose reduction is possible but achieves only a partial amelioration of severe sleep apnea it may be necessary to add PAP therapy. If residual apnea is only mild-moderate in severity, either no specific therapy or more conservative approaches such as weight loss or a mandibular repositioning device may suffice.

Guidance statement 5: Hypogonadism

As there is a high prevalence of secondary hypogonadism in this patient population, clinicians treating men using chronic opioid therapy should consider an evaluation for hypogonadism.*[195][117] [93] [181]* Clinicians should advise patients who are diagnosed with opioid-induced hypogonadism regarding the potential short-term adverse effects, including reduced sexual function, amenorrhea, fatigue, mood changes and the long-term risk of osteoporosis. Patients should be offered opioid tapering as the initial strategy to correct hypogonadism. If opioid tapering is unsuccessful or declined, clinicians may offer testosterone supplementation therapy (TST).

Our systematic review identified very low quality evidence suggesting that testosterone supplementation may improve pain, sexual desire and depression in patients being treated for chronic noncancer pain. If patients and their clinicians decide to conduct a trial of TST, it should be administered and monitored in accordance with the current Canadian and US guidelines.*[146] [21]* All patients being considered for TST should be screened for contra-indications to therapy as outlined in the guidelines, undergo a discussion of the potential benefits and harms of therapy, and should be monitored in accordance with the recommendations made in the aforementioned guidelines. If there is no important response to therapy, TST should be discontinued.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain on long-term opioid therapy with clinical and biochemical evidence of hypogonadism.

Intervention: Hormone replacement therapy while maintaining current opioid dose.

Comparator: Taper opioids to treat hypogonadism.

Summary

Minimally important difference for pain on a 11 point Numeric Pain Rating Scale (NRS) is a reduction of 2 points.
Minimally important difference for physical function on a 100 point SF-36 physical component summary score is an increase of 5 points.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Taper opioids to treat hypogonadism.	Hormone replacement therapy while maintaining current opioid dose.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Pain reduction 3 months	Measured by: 11-point Numeric Rating Scale Scale: 0-11 Lower better Based on data from: 27 patients in 1 studies. (Observational (non-randomized)) Follow up 14 weeks	**2** points (Median)	**0** points (Median) Difference: **MD 2 fewer** (CI 95% 2.6 fewer - 1.4 fewer)	**Very Low** Due to serious indirectness, Due to serious imprecision	We are uncertain about the effect of testosterone replacement therapy on pain compared to tapering opioid therapy.
Sexual function 3 months	Measured by: International index of erectile function, erectile function subscale Scale: 0-30 High better Based on data from: 65 patients in 1 studies. (Randomized controlled) Follow up 14 weeks	Difference: **MD 0.36 more** (CI 95% 3.12 fewer - 3.84 more)		**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain about the effect of testosterone replacement therapy on sexual function compared to tapering opioid therapy.
Physical function 3 months	Measured by: Brief Pain Inventory pain interference subscale Scale: 0-70 Lower better Based on data from: 65 patients in 1 studies. (Randomized controlled) Follow up 14 weeks	**16.6** (Mean)	**18** (Mean) Difference: **MD 0.59 fewer** (CI 95% 1.54 fewer - 0.35 more)	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain about the effect of testosterone replacement therapy on physical function compared to tapering opioid therapy.
Depression 6-12 months	Based on data from 102 patients in 3 studies	Aloisi et al 2011 followed 9 patients for 12 months, reported no significant change in Center for Epidemiological Studies-Depression (CES-D) scores. Daniell et al 2006		**Very Low** Due to serious risk of bias, Due to serious	We are uncertain about the effect of testosterone replacement therapy on depression compared to tapering opioid therapy.

		followed 16 patients over 24 weeks, reported a change from "moderate" to "minimal" scores on the Beck Depression Inventory (BDI) from baseline to follow up (approximately 20 to 13, scale 0-63, higher worse). Blick et al 2012 followed 77 patients for 12 months (only 16 contributed data at follow-up), and reported lower scores on the Patient Health Questionnaire-9 (PHQ-9) at 12 months compared to baseline (approximately 11.25 to 5.5, scale 0-27, higher worse).	inconsistency, Due to serious indirectness

Details about studies used and certainty down- and upgrading

Pain reduction	**Intervention:** Primary study [167], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Comparison is testosterone replacement therapy versus placebo (Differences between the intervention/comparator of interest and those studied) ; **Imprecision: Serious** Only data from one study, Confidence interval includes benefit and harm ; **Publication bias: No serious**
Sexual function	**Intervention:** Primary study [17], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Selective outcome reporting ; **Inconsistency: No serious** **Indirectness: Serious** Differences between the intervention/comparator of interest and those studied ; **Imprecision: Serious** Only data from one study, Confidence interval includes benefit and harm ; **Publication bias: No serious**
Physical function	**Intervention:** Primary study [17], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: Serious** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Selective outcome reporting ; **Inconsistency: No serious** **Indirectness: Serious** Differences between the intervention/comparator of interest and those studied ; **Imprecision: Serious** Only data from one study; Confidence interval includes benefit and harm ; **Publication bias: No serious**
Depression	**Intervention:** Primary study **Other** [49] [6] [22]	**Risk of bias: Serious** One study (Blick et al., 2012) reported 79% loss to follow-up, one study (Daniell et al., 2006) recruited through radio adds and print media, which risks selection bias ; **Inconsistency: Serious** 1 study reported no effect, and 2 reported a significant improvement ; **Indirectness: Serious** Single armed studies looking only at testosterone replacement therapy. No comparison ; **Imprecision: No serious** **Publication bias: No serious**

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6.1 - Risk mitigation

Our systematic reviews found only low or very low quality evidence regarding strategies intended to reduce the adverse impact of opioid prescribing. In each case the evidence did not support the intervention, nor did it provide compelling evidence that the intervention was useless. This was the case for the use of urine drug screening (UDS), treatment agreements, naloxone co-prescription in the case of opioid use for chronic pain alone, rather than in the case of addiction, tamper-resistant formulations, patch exchange programs and choosing between immediate release (IR) vs. controlled release (CR) opioids.

Our Clinical Expert Committee felt, in general, that prescribers of opioids for chronic non-cancer pain may wish to consider implementation of risk mitigation strategies with the aim of reducing harm. However, there is also concern that prescribers adopting potentially ineffective risk mitigation strategies may become less vigilant about possible opioid-related harms, and more willing to prescribe opioids for chronic non-cancer pain.

Guidance statement 6: Urine drug screening

A baseline urine drug screen may be useful for patients currently receiving or being considered for a trial of opioids. Clinicians may repeat urine drug screening on an annual basis and more frequently if the patient is at elevated risk or in the presence of any aberrant drug-related behaviours. Approximately 30% of urine drug screening will demonstrate aberrant results, largely because of prescribed opioid non-detection and tetrahydrocannabinol.*[207]* However, formal study of urine drug screening for risk mitigation was limited to only one abstract report of a large retrospective cohort study that found no difference in rates of opioid overdose for those who did or did not receive baseline urine drug screening.

When ordering a urine drug screen, clinicians should ask patients about all medications/drugs recently taken, and be aware of local resources to assist them in assessing for potential false positive and false negative results. Different immunoassay testing kits have different response characteristics, and may require confirmation with other testing (gas chromatography/mass spectrometry for example). On site, point-of-care testing, though less accurate than delayed 'in lab' testing, may be preferable as one can discuss the results with the patient and make an immediate decision regarding the safety of opioid prescribing.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain prior to starting long term opioid therapy
Intervention: Urine drug screening for baseline substance use.
Comparator: No urine drug screening for baseline substance use.

Outcome Timeframe	Study results and measurements	Absolute effect estimates No urine drug screening for	 Urine drug screening for baseline	Certainty in effect estimates	Summary

			(Quality of evidence)	
Opioid overdose over 5 months	Hazard Ratio 1.36 (CI 95% 0.79 - 2.34) Based on data from 179,385 patients in 1 studies. (Observational (non-randomized)) Follow up median 159 days	**2** per 1000 **3** per 1000 Difference: **1 more** per 1000 (CI 95% 0 fewer - 3 more)	**Very Low** Due to serious imprecision	We are uncertain about the effect of urine drug screening on the risk of opioid overdose

Details about studies used and certainty down- and upgrading

Opioid overdose	**Intervention:** Primary study [130], **Baseline/comparator:** Primary study	**Risk of bias: No serious** Study is only available as a conference abstract ; **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**

References

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Guidance statement 7: Treatment agreements

The benefits of treatment agreements are limited by low-quality evidence with equivocal effects on opioid misuse. A written treatment agreement may, however, be useful in structuring a process of informed consent around opioid use, clarifying expectations for both patient and physician, and providing clarity regarding the nature of an opioid trial with endpoints, goals, and strategies in event of a failed trial.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain prior to starting long-term opioid therapy
Intervention: Formal structured treatment agreements.

Comparator: No formal structured treatment agreement.

Outcome Timeframe	Study results and measurements	Absolute effect estimates No formal structured treatment agreement.	 Formal structured treatment agreements.	Certainty in effect estimates (Quality of evidence)	Summary
Opioid misuse	Odds Ratio 1.28 (CI 95% 0.8 - 2.05) Based on data from 2,624 patients in 4 studies. (Observational (non-randomized)) Follow up not reported	**240** per 1000	**288** per 1000 Difference: **48 more** per 1000 (CI 95% 38 fewer - 153 more)	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	We are uncertain about the effect of treatment agreements on the risk of opioid misuse

Details about studies used and certainty down- and upgrading

Opioid misuse	**Intervention:** Systematic review with included studies: [118], [192], [128], [123], **Baseline/comparator:** Systematic review	**Risk of bias: Serious** Studies were unclear whether co-interventions were similar between groups; could not be confident that outcomes were not present at the start of the study ; **Inconsistency: No serious** **Indirectness: Serious** Two studies used exclusively Veteran's Affairs populations ; **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**

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Guidance statement 8: Tamper-resistant formulations

When available and affordable, tamper-resistant formulations may be used to reduce the risks of altering the intended delivery system (ie. from oral to nasal or intravenous injection). They do not reduce the most common mode of misuse (oral ingestion), but are less favoured by people who misuse opioids by any route*[43]*.

Not all payers reimburse for tamper-resistant formulations, and in some cases abuse of these formulations may lead to unique harms (e.g. particulate induced cardiac valve injury when injected). Tamper-resistant formulations are often more costly and the evidence of impact upon overall abuse of opioids, when some drugs are supplied in tamper-resistant formulations and others are not, is unclear.*[132]*

Guidance statement 9: Fentanyl patch exchange

When prescribing fentanyl or other drugs dispensed in a transdermal patch preparation, it may be advisable to ask patients to return used patches to the pharmacy when presenting for the next dispensing.

In Ontario this is required by law; it is a minimally disruptive strategy that can serve to reduce potential diversion by removing used patches from circulation, and also may lead to identification of medication misuse issues. The process of asking the patient to do this and explaining why draws patient attention to the risks of used patches when they might become available to others, for example young children. It can also trigger a discussion about medication safe storage in general.

Guidance statement 10: Naloxone

Clinicians may provide naloxone to patients receiving opioids for chronic pain who are identified as at risk due to high dose, medical history, or comorbidities. However, the available very low quality evidence does not provide support for the hypothesis that co-prescribing naloxone with opioids for patients with chronic noncancer pain reduces fatal overdose, all-cause mortality, or opioid-related hospitalization. Prescription of naloxone may be considered while rotating opioids, as patients may have difficulties understanding the concept of different potencies and take more than their prescribed dose.

There is evidence to support prescription of naloxone for patients who are addicted to opioids or recreational users, especially those using intravenous drugs, to be administered by family or friends in the case of overdose pending arrival of emergency services. Many patients at risk of opioid overdose are willing to be trained and use naloxone in the event of an emergency. Moreover, these programs are well received by staff, clients, and local agencies.*[133]*

It is possible that naloxone prescription will highlight the potential for serious adverse events such as overdose and death for patients and their families, leading to increased vigilance and critical consideration of the benefit of the treatment.

Clinical Question/ PICO

Population: Patients with chronic non-cancer pain prior to starting long-term opioid therapy.
Intervention: Provide take-home naloxone along with opioid prescription.
Comparator: Do not provide take-home naloxone along with opioid prescription.

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Do not provide take-home naloxone along with opioid prescription.	**Absolute effect estimates** Provide take-home naloxone along with opioid prescription.	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Fatal overdose up to 2 years	Relative risk 1.08 (CI 95% 0.18 - 6.4) Based on data from 1,985 patients in 1 studies. (Observational (non-randomized)) Follow up 1 month to 2 years	**2** per 1000	**2** per 1000 Difference: **0 fewer** per 1000 (CI 95% 2 fewer - 11 more)	**Very Low** Due to serious imprecision	We are uncertain about the effects of naloxone on risk of fatal overdose.
All-cause mortality up to 2 years	Relative risk 0.79 (CI 95% 0.61 - 1.02) Based on data from 1,985 patients in 1 studies. (Observational (non-randomized)) Follow up 1 month to 2 years	**2** per 1000	**2** per 1000 Difference: **0 fewer** per 1000 (CI 95% 1 fewer - 0 fewer)	**Very Low** Due to serious imprecision	We are uncertain about the effects of naloxone on all-cause mortality.
Hospitalization up to 2 years	Relative risk 1.44 (CI 95% 1.14 - 1.82) Based on data from 1,985 patients in 1 studies. (Observational (non-randomized)) Follow up 1 month to 2 years	**25** per 1000	**36** per 1000 Difference: **11 more** per 1000 (CI 95% 3 more - 21 more)	**Low** Due to serious imprecision	We are uncertain about the effects of naloxone on hospitalization.

Details about studies used and certainty down- and upgrading

Fatal overdose	**Intervention:** Systematic review with included studies: [45], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**
All-cause mortality	**Intervention:** Systematic review with included	**Risk of bias: No serious** Chances of being prescribed naloxone differed by clinic, resident vs attending, and age ;

	studies: [45], **Baseline/comparator:** Control arm of reference used for intervention	**Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**
Hospitalization	**Intervention:** Systematic review with included studies: [45], **Baseline/comparator:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Imprecision: Serious** Confidence interval includes benefit and harm ; **Publication bias: No serious**

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