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**SYDNEY**

# Evidence-Based Clinical Practice Guideline for Deprescribing Opioid Analgesics

**Technical Report**

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## Acronyms

<b>CBT</b>	Cognitive Behavioural Therapy
<b>CI</b>	Confidence Interval
<b>COI</b>	Conflict of Interest
<b>COPD</b>	Chronic Obstructive Pulmonary Disease
<b>ED</b>	Emergency Department
<b>EtD</b>	Evidence-to-decision
<b>GDG</b>	Guideline Development Group
<b>GRADE</b>	Grading of Recommendations Assessment, Development and Evaluation
<b>HR</b>	Hazard Ratio
<b>MBTs</b>	Mind-body therapies
<b>MID</b>	Minimally Important Difference
<b>NHMRC</b>	National Health and Medical Research Council
<b>NSAID</b>	Non-steroidal Anti-inflammatory Drug
<b>OMEDD</b>	Oral Morphine Equivalent Daily Dose
<b>OR</b>	Odds Ratio
<b>ODD</b>	Opioid Use Disorder
<b>PICO</b>	Population, Intervention, Comparison, Outcome
<b>PRISMA</b>	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
<b>QoL</b>	Quality of Life
<b>ROB</b>	Risk of Bias
<b>ROBIS</b>	Risk of Bias of Systematic Reviews
<b>RCT</b>	Randomised Controlled Trial
<b>RACGP</b>	The Royal Australian College of General Practitioners
<b>SCS</b>	Spinal Cord Stimulation
<b>SMD</b>	Standardised Mean Difference
<b>TGA</b>	Therapeutic Goods Administration
<b>UK</b>	United Kingdom
<b>USA</b>	United States of America
<b>WMD</b>	Weighted Mean Difference

## Introduction

Healthcare professionals across a range of disciplines acknowledge that opioid deprescribing is a complex and challenging practice, with continued prescribing the default behaviour.<sup>1</sup> Evidence-based opioid deprescribing guidelines have been identified as a valuable resource for healthcare professionals to support clinical decision-making and reduce suboptimal opioid use.<sup>1</sup> There are however currently no evidence-based guidelines internationally that specifically focus on the deprescribing of opioids. The Evidence-based Clinical Practice Guideline for Deprescribing Opioid Analgesics was developed to address the need for a systematic, evidence-based approach to opioid deprescribing in adults taking opioids for pain. It aims to assist healthcare professionals to identify individuals who are suitable to trial opioid deprescribing and provide advice on when and how to conduct deprescribing. The purpose of this technical report is to detail the steps undertaken to systematically review the evidence for each key clinical question in this guideline.

The evidence review was conducted primarily by the core guideline group with consultation from all members of the Guideline Development Group (GDG). Guideline development involved:

- i) Qualitative stakeholder perspective research with healthcare professionals and persons taking opioids.
- ii) Systematic evidence retrieval and synthesis using an overview of systematic reviews and the use of the GRADE process to assess the certainty of the evidence. Where no evidence was identified, existing relevant guidelines and primary studies were sought.
- iii) Utilisation of an evidence-to-decision framework to systematically consider the certainty of the evidence, the risks and benefits of deprescribing and opioid continuation, stakeholder values and preferences, acceptability, feasibility and resources requirements.
- iv) Formulation of evidence- or consensus-based recommendations by the members of the GDG.
- v) Release of the draft guideline for public consultation and subsequent revision.
- vi) Independent AGREE II review of the guideline.
- vii) Independent expert peer-review prior to the final submission to NHMRC.

## Scope

The Evidence-based Clinical Practice Guideline for Deprescribing Opioid Analgesics aims to provide recommendations on when, how and for whom opioid deprescribing should be considered. Local treatment guidelines should be used to determine if it is appropriate to start an opioid. This guideline does not provide comprehensive advice about pain management and healthcare professionals should refer to relevant clinical practice guidelines for further advice on this topic. Healthcare professional's judgement and the values, preferences and goals of the person taking opioids should be considered when enacting guideline recommendations.

### Target population

The target population of this guideline is adults (aged  $\geq 18$  years old) prescribed one or more opioids for any type of pain (e.g. acute, chronic, cancer-related, in end-of-life care). This includes single-ingredient and combination opioid preparations of any dose, formulation (immediate release, modified release, capsule, tablet, oral suspension, intravenous solution, patch, suppository) and route of administration (intravenous, oral, transdermal, rectal). Where applicable, indications (such as the type and duration of pain) are specified. Persons with opioid use disorders, prescribed opioids for opioid substitution therapy or people taking illicit opioids (e.g. heroin) are not the target population of this guideline, although there may be considerable overlap with persons taking opioids for pain. The target care setting is community primary care; however, recommendations may be relevant to other care settings (residential care, inpatient and outpatient).

### Target audience

The target audience for this guideline is healthcare professionals involved in the care of persons prescribed opioids in primary care. This is primarily General Practitioners (GPs). The guideline is to be used alongside healthcare professional judgement and person preferences and values. Additional audiences that may find this guideline useful include specialist physicians (e.g. general physicians, geriatricians, pain specialists, addiction specialists, rheumatologists), nurses (including nurse practitioners, registered nurses and enrolled nurses with endorsement) and pharmacists. The guideline may be applied in other care settings (e.g. acute care, across care transitions). The recommendations contained within this guideline may also be of use to policymakers when implementing policy or developing health service user resources.

### Key Clinical Questions

The following key clinical questions were addressed in this guideline:

- i) Does deprescribing of opioids result in benefits or harms compared to continuation?
- ii) What is the evidence on how to deprescribe opioids?
- iii) Which interventions are effective to facilitate opioid deprescribing?

The Population, Intervention, Comparison, Outcome (PICO) for each key clinical question is presented in [Box 1](#) and [Box 2](#). We intentionally kept the search strategy broad, placing no restrictions on the type of pain (acute, chronic non-cancer, cancer-survivor, end-of-life), characteristics of participants (co-morbidities, concomitant use of medicines) dose or duration of opioid use or intervention setting. Key clinical question 1 addressed outcomes of opioid deprescribing regardless of approach, whereas key clinical question 3 focussed on patient-focussed deprescribing interventions, which aim to reduce opioid use through modifying the person’s physical condition or behaviour, or providing them with an alternate treatment approach.

**Box 1. Key clinical question 1 and 2 PICO**

<b>Population</b>	People (aged ≥ 18 years old) who are currently prescribed an opioid (buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxycodone with naloxone, pethidine, tapentadol and tramadol) for pain relief / management.
<b>Intervention</b>	Opioid deprescribing (attempted discontinuation with or without dose reduction)
<b>Control</b>	Opioid continuation
<b>Outcome</b>	Reduction in opioid use in oral morphine milligram equivalent daily dose (OMEDD), Function, Pain, Quality of life, Adverse events

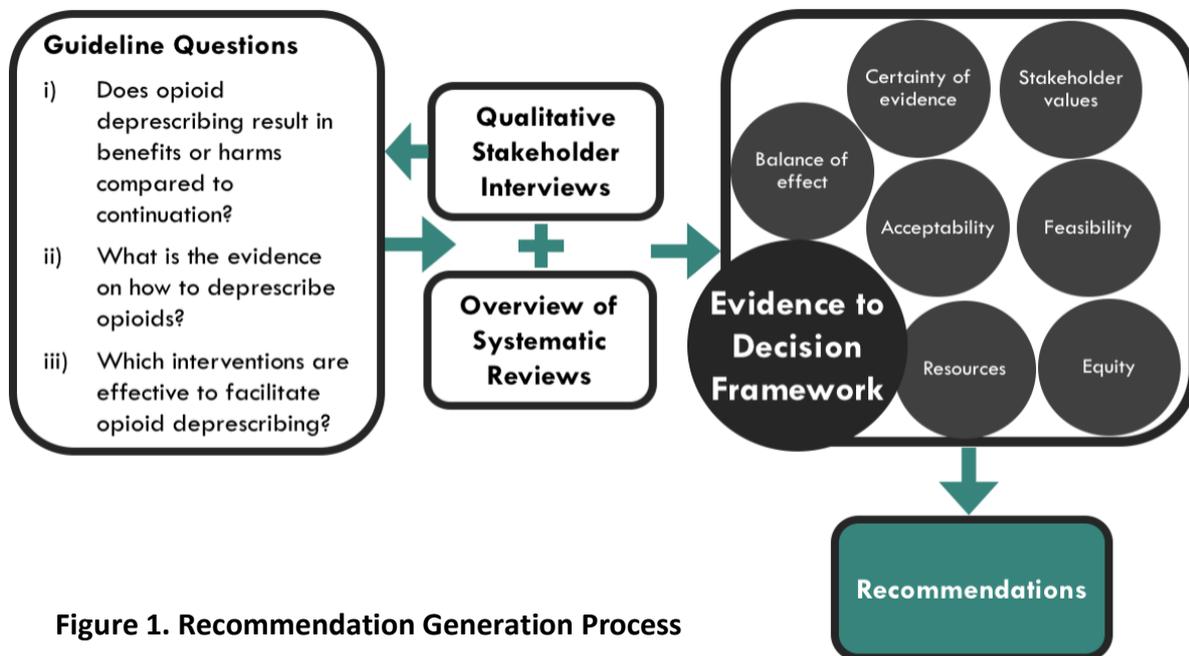
**Box 2. Key clinical question 3 PICO**

<b>Population</b>	People (aged ≥ 18 years old) who are currently prescribed an opioid (buprenorphine, codeine, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxycodone with naloxone, pethidine, tapentadol and tramadol) for pain relief / management.
<b>Intervention</b>	Any patient-focused intervention to facilitate opioid deprescribing (attempted discontinuation with or without dose reduction)
<b>Control</b>	Continuation of opioid or alternative intervention
<b>Outcome</b>	Reduction in opioid use in oral morphine milligram equivalent daily dose (OMEDD), Function, Pain, Quality of life, Adverse events

**Methods used to develop evidence-based recommendations**

Guideline development (summarised in [Figure 1](#)) involved i) qualitative stakeholder perspective research with healthcare professionals and persons taking opioids, ii) systematic evidence retrieval and synthesis, and the use of the GRADE process to assess the certainty of the evidence, iii) utilisation of an evidence-to-decision framework to systematically consider the certainty of the evidence, the risks and benefits of deprescribing and opioid continuation,

stakeholder values and preferences, acceptability, feasibility and resources requirements, and iv) development and refinement of recommendations.



**Figure 1. Recommendation Generation Process**

### Stakeholder Perspective Research

Two qualitative studies were conducted with i) healthcare professionals<sup>1</sup> and ii) persons taking opioids<sup>2</sup> to elucidate their beliefs and attitudes towards opioid deprescribing and identify perceived facilitators and barriers to achieving successful outcomes.

#### i) Healthcare professionals

A purposive sampling technique was used to recruit healthcare professionals with an interest and/or expertise in deprescribing. Two focus groups were used to identify areas of importance to healthcare professionals. Subsequent individual interviews were conducted with pain and addiction specialists, general practitioners, geriatricians, registered nurses and pharmacists who met the inclusion criteria of being a registered healthcare professional and having experience in the treatment of patients using opioid analgesics to enable in-depth exploration of themes. Data collection was undertaken by four pharmacy academics with experience in qualitative research. A semi-structured interview guide was developed from a review of the literature and discussion with experienced multidisciplinary healthcare professionals and academic co-investigators to ensure face and content validity. Open-ended questions focused on beliefs, attitudes and behaviours surrounding opioid deprescribing and the content and utility of prospective opioid deprescribing guidelines. All transcripts were audio-recorded, transcribed verbatim and de-identified to maintain participant confidentiality. A phenomenological approach was adopted for data analysis.<sup>3</sup> Multiple phases of inductive thematic analysis<sup>4</sup> were conducted, using NVivo V.12 software as the data management tool. Initial analysis involved a discussion among researchers of major themes, followed by independent open coding by AV Langford and CR Schneider. A coding index was

developed and applied to subsequent transcripts, regularly assessing coding consistency across transcripts. The coding index was refined throughout the analysis to ensure that the derived themes adequately represented the obtained data.

## **ii) Persons taking opioids**

A purposive sample of people taking one or more opioids for the management of pain was recruited. Participants with both acute and chronic pain conditions were sought. Study advertisements were distributed through PainAustralia, community pharmacies, and Facebook. An interview guide was developed from a review of the literature and discussion with experienced healthcare professionals and researchers. Interview questions related to the management of opioids, interactions with healthcare professionals and resources to support the development of opioid deprescribing guidelines. Interviews were conducted either face-to-face or over the telephone and were audio-recorded, transcribed verbatim, and de-identified. Initial data analysis was conducted in parallel with ongoing recruitment to allow for evaluation of sample size requirements in relation to thematic saturation. Inductive thematic analysis<sup>4</sup> preceded a deductive framework analysis.<sup>5</sup> Open coding was initially performed, whereby transcripts were coded descriptively using QSR International NVivo-12 software. AV Langford and CR Schneider developed the initial coding index by independently coding transcripts and comparing consistency in the themes observed. Coding categories were refined throughout the study with input from all members of the research team. Bandura's Social Cognitive Theory<sup>6</sup> was applied to the findings using a framework analysis approach.<sup>5</sup>

## **Overview of Systematic Reviews**

An overview approach was selected due to the large volume of existing primary and synthesised evidence in the field. The overview research protocol was registered in the Prospective Register of Systematic Reviews (PROSPERO protocol ID: CRD42020171781). Supplementary searches were conducted for some key clinical questions and are discussed in this document under the relevant key clinical question.

## **Search Strategy**

The search strategy was developed in collaboration with an experienced medical librarian. A combination of search terms relating to the three concepts of i) 'opioid', ii) 'pain' and iii) 'systematic review' were searched in August 2021. There was anticipated heterogeneity of deprescribing interventions and as such, a broad search strategy was implemented to ensure relevant reviews would not be omitted due to search term specifications. Five international electronic databases were searched; Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Excerpta Medical Database (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE) and PsycINFO. The search was limited to full publications, published in English from August 2011 to August 2021. The previous ten-year period was chosen to ensure recent and up to date evidence.

## Full search strategies executed in each database

### i) CINAHL

1. (MH "Analgesics, Opioid+") OR (MH "Narcotics+") OR (MH "Tramadol") OR (MH "Sufentanil") OR "opioid" OR (MH "Alphaprodine") OR (MH "Buprenorphine") OR (MH "Butorphanol") OR (MH "Dihydromorphinone") OR (MH "Codeine+") OR (MH "Methadone") OR (MH "Oxycodone") OR (MH "Pentazocine") OR (MH "Remifentanil")
2. (MH "Pain+") OR "pain" OR (MH "Nociceptive Pain+") OR (MH "Knee Pain+") OR (MH "Neck Pain") OR (MH "Chronic Pain") OR (MH "Abdominal Pain+") OR (MH "Arthralgia+") OR (MH "Back Pain+") OR (MH "Breakthrough Pain") OR (MH "Cancer Pain") OR (MH "Chest Pain+") OR (MH "Elbow Pain") OR (MH "Eye Pain") OR (MH "Facial Pain+") OR (MH "Groin Pain") OR (MH "Headache") OR (MH "Heel Pain") OR (MH "Muscle Pain") OR (MH "Neuralgia+") OR (MH "Pelvic Pain+") OR (MH "Pain, Procedural") OR (MH "Postoperative Pain") OR (MH "Referred Pain") OR (MH "Shoulder Pain") OR (MH "Treatment Related Pain") OR (MH "Pain Management") OR (MH "Visceral Pain") OR (MH "Low Back Pain")
3. (MH "Systematic Review") OR (MH "Cochrane Library") OR (MH "Meta Analysis") OR "systematic review or meta-analysis"
4. 1 AND 2 AND 3

### ii) COCHRANE

1. opioid\*.mp. [mp=title, abstract, full text, keywords, caption text]
2. opiate\*.mp. [mp=title, abstract, full text, keywords, caption text]
3. narcotic\*.mp. [mp=title, short title, abstract, full text, keywords, caption text]
4. morphine.mp. [mp=title, short title, abstract, full text, keywords, caption text]
5. oxycodone.mp. [mp=title, short title, abstract, full text, keywords, caption text]
6. fentanyl.mp. [mp=title, short title, abstract, full text, keywords, caption text]
7. tramadol.mp. [mp=title, short title, abstract, full text, keywords, caption text]
8. methadone.mp. [mp=title, short title, abstract, full text, keywords, caption text]
9. buprenorphine.mp. [mp=title, short title, abstract, full text, keywords, caption text]
10. codeine.mp. [mp=title, short title, abstract, full text, keywords, caption text]
11. hydromorphone.mp. [mp=title, short title, abstract, full text, keywords, caption text]
12. hydrocodone.mp. [mp=title, short title, abstract, full text, keywords, caption text]
13. tapentadol.mp. [mp=title, short title, abstract, full text, keywords, caption text]
14. tramadol.mp. [mp=title, short title, abstract, full text, keywords, caption text]
15. targin.mp. [mp=title, short title, abstract, full text, keywords, caption text]
16. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. pain.mp. [mp=title, short title, abstract, full text, keywords, caption text]
18. headache.mp. [mp=title, short title, abstract, full text, keywords, caption text]
19. migraine.mp. [mp=title, short title, abstract, full text, keywords, caption text]

20. neuralgia.mp. [mp=title, short title, abstract, full text, keywords, caption text]
21. neuropath\*.mp. [mp=title, short title, abstract, full text, keywords, caption text]
22. arthrit\*.mp. [mp=title, short title, abstract, full text, keywords, caption text]
23. osteoarthriti\*.mp.
24. chronic pain.mp. [mp=title, short title, abstract, full text, keywords, caption text]
25. acute pain.mp. [mp=title, short title, abstract, full text, keywords, caption text]
26. back pain.mp. [mp=title, short title, abstract, full text, keywords, caption text]
27. musculoskeletal pain.mp. [mp=title, short title, abstract, full text, keywords, caption text]
28. Nociceptive pain.mp. [mp=title, short title, abstract, full text, keywords, caption text]
29. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30. 16 and 29

iii) EMBASE

1. exp narcotic agent/ or exp narcotic analgesic agent/ or exp narcotic antagonist/
2. opiate/ or \*opiate agonist/
3. opioid\*.mp.
4. 1 or 2 or 3
5. exp pain/
6. exp injury/
7. exp neuralgia/ or exp neuropathy/
8. exp musculoskeletal pain/ or exp musculoskeletal disease/
9. exp arthritis/ or exp arthropathy/
10. osteoarthritis.mp. or osteoarthritis/
11. 5 or 6 or 7 or 8 or 9 or 10
12. systematic review\*.mp.
13. 4 and 11 and 12
14. remove duplicates from 13

iv) MEDLINE

1. exp Narcotics/
2. (narcotic\* or opioid\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Pain/
5. exp Headache Disorders/
6. exp joint diseases/
7. exp muscular diseases/ or exp peripheral nervous system diseases/
8. exp "Wounds and Injuries"/

9. 4 or 5 or 6 or 7 or 8
10. systematic review\*.mp.
11. "systematic review"/
12. 10 or 11
13. 3 and 9 and 12
14. limit 13 to (english language and yr="2011 -Current")

v) PsycINFO

1. exp opiates/
2. exp narcotic agonists/ or exp analgesic drugs
3. 1 or 2
4. exp pain/ or exp fibromyalgia/ or exp oxycodone/ or exp pain management/ or exp pain measurement/
5. exp injuries/
6. exp arthritis/ or exp joint disorders/
7. exp musculoskeletal disorders/
8. exp neuralgia/ or exp peripheral neuropathy/
9. 4 or 5 or 6 or 7 or 8
10. systematic review\*.mp.
11. 3 and 9 and 10

Note: No population groups were specified in the search strategy. Although special populations (including Aboriginal and Torres Strait Islander peoples) were not explicitly specified, our search was inclusive. Therefore, relevant literature pertaining to such groups would have been identified by our search and considered for review. A section in the main draft guideline document has been included which considers the care of Aboriginal and Torres Strait Islander people and other special populations in the context of opioid deprescribing.

### **Eligibility criteria**

Systematic reviews (with or without meta-analyses) were included if they examined one or more intervention(s) that aimed to deprescribe opioid analgesics in adult populations (aged  $\geq 18$  years) and reported on opioid use before and after the implementation of the intervention. In this overview, opioid deprescribing was considered as the reduction or cessation of established opioid therapies. Perioperative interventions which reduced post-operative opioid requirements were not considered deprescribing interventions, nor was opioid rotation (where participants were switched immediately to another opioid medication for the same condition with no washout period), unless the intention of rotation was dose reduction. We included reviews that examined patient-targeted interventions and excluded reviews of interventions which targeted clinicians (e.g. academic detailing), organisations (e.g. hospital policies) or health systems (e.g. legislation, guidelines) as patient-targeted interventions were most relevant for making recommendations in this guideline. There were

no restrictions on the type of pain, duration of opioid use or intervention setting. Participants utilising opioids solely for opioid maintenance therapy were not included. Systematic reviews containing randomised control trials and non-randomised studies were included. Animal studies, commentaries, guidelines, protocols, editorials, conference abstracts and narrative reviews were excluded.

#### **Primary Outcomes of interest**

- Reduction in opioid use
- The proportion of the sample for which opioid use declined
- Pain
- Physical function
- Quality of life
- Adverse events

#### **Literature screening and data extraction**

Titles and abstracts of the search results were collated in EndNote X8™ for screening. Results were screened by two independent reviewers in accordance with pre-specified inclusion and exclusion criteria at the title, abstract, and full-text level. Disagreements regarding eligibility for inclusion were resolved by consensus in group meetings with core guideline group members. If several reviews regarding an intervention had been published and there was duplication of primary studies, we selected the review that included the most recent and largest number of eligible studies. Key characteristics were extracted, including: first author, year of publication, number and design of included primary studies, review aim, population, intervention(s), setting, outcomes and conclusions regarding intervention effectiveness.

At meeting 2, the GDG recommended supplementing the evidence review for key clinical questions 1 and 2, with primary studies or existing high quality clinical practice guidelines, where the overview of systematic reviews provided inadequate information. For key clinical question 1, a targeted search for potentially relevant guidelines was performed in clinical practice guideline databases as well as Google. Similarly, a targeted search for potentially relevant primary studies was performed for key clinical question 2 in Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Excerpta Medical Database (EMBASE), Medical Literature Analysis and Retrieval System Online (MEDLINE) and PsycINFO. Details of the search strategy and the findings are described in a section under each relevant key clinical question.

#### **Data synthesis**

The included studies were highly variable in their design, type of interventions and outcomes, therefore precluding a pooled meta-analysis. We analysed data by outcome and stratified results by intervention and pain type and synthesised descriptively. Qualitative data were synthesised using meta-aggregation and descriptive narratives.

### Risk of bias assessment

The risk of bias of the primary body of evidence was assessed by systematic review authors. We did not re-assess the risk of bias for the primary body of evidence when conducting the overview.<sup>7</sup> The risk of bias assessment tool used by the systematic review authors and a summary of risk of bias assessment is presented in [Table 3](#). The risk of bias assessments of the primary body of evidence were used to inform the GRADE ratings. In addition, the methodological quality of each included systematic review was assessed using ROBIS.<sup>8</sup> The tool consists of four domains. Based on the judgement for each domain, overall ratings of confidence in the review were determined as either 'Low', 'High' or 'Unclear'. Two reviewers independently applied the instrument, and discrepancies were reconciled through oral discussion. Ratings for each category can be viewed in [Appendix 2](#).

### Certainty of evidence assessment

Evidence from appraisal of the literature for each key clinical question was summarised into evidence tables. The certainty of evidence for each primary outcome was assessed by applying Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology<sup>9 10</sup> in accordance with the GRADE Handbook.<sup>11</sup> Two authors assessed GRADE level of evidence, with discrepancies resolved through discussion. Evidence was initially graded based on study design and was downgraded for the following five reasons: limitations, inconsistencies, indirectness, inaccuracy, and publication bias. The GRADE approach resulted in the assessment of the certainty of the evidence to be high, moderate, low or very low. [Table 1](#) contains a summary of the GRADE certainty of evidence ratings.

**Table 1.** GRADE Certainty of Evidence Ratings<sup>11</sup>

GRADE Rating	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

The evidence and GRADE ratings for each outcome were presented to members of the GDG for consideration in the formulation of guideline recommendations for each key clinical question. The lowest rating of quality (across outcomes) was assigned to the recommendations which resulted from that set of evidence.

### **Evidence-to-decision**

The GRADE evidence-to-decision framework provided a systematic approach to consider the evidence (results of the overview of reviews), certainty of evidence (as determined by the GRADE approach), benefits and harms of opioid deprescribing, stakeholder preferences (informed by qualitative studies), acceptability, feasibility, equity and cost and resource implications.<sup>12</sup> [Appendix 3](#) contains the evidence-to-decision (EtD) frameworks for each key clinical question. A systematic evidence review of cost and resource implications was out of the scope of this guideline, however a brief discussion on resource and cost implications is provided in the main guideline document.

### **Development of recommendations**

Recommendations were drafted by the core GDG team, through reviewing the summary of the evidence, stakeholder perspective research and populated EtD framework. After drafting, the recommendations were refined through group discussion with all GDG members via teleconference, followed by discussion with individual group members and email until unanimous consensus was reached. The recommendations contained within this guideline may be classed as one of the following:

- i) Recommendation for
- ii) Recommendation against
- iii) Conditional Recommendation for
- iv) Conditional Recommendation against, OR
- v) Consensus Recommendation.

Further details of each recommendation type can be found in [Table 2](#). The terminology “we recommend” is used for recommendations, and “we suggest” is used for conditional and consensus-based recommendations.<sup>13</sup>

### **Development of evidence-based recommendations**

GDG members used GRADE to review the evidence base and assign a strength to each recommendation. The body of evidence for each question was assessed first by the project team and given a preliminary certainty of evidence (High, Moderate, Low or Very Low) rating following the GRADE criteria. The GDG reviewed the evidence and adjusted the rating. The GDG also confirmed the wording of each recommendation and assigned a strength to the recommendation. The strength assigned to each recommendation reflects the GDGs confidence in the evidence, as well as the desirable and undesirable consequences of implementing each recommendation, as determined by the EtD framework.

### **Development of consensus-based recommendations**

Where the evidence synthesis produced no direct evidence relating to the key clinical questions, the GDG devised a consensus-based recommendation based on their clinical, consumer, policy and content expertise. This was done in accordance with NHMRC guidance

which states that “recommendations formulated in the absence of quality evidence (where a systematic review of the evidence was conducted as part of the search strategy) are clearly labelled as such. The preferred term for this type of recommendation is a consensus-based recommendation.”

### Development of practice points

Where the GDG felt that additional advice on a topic outside the scope of the search strategy was warranted, practice points were devised. Practice points are additional considerations and practical information to support recommendations, based on expert opinion rather than being derived directly from a systematic review of evidence.

**Table 2. Classification of Recommendations**

<b>Recommendation for</b>
A ‘recommendation for’ is given when the guideline development group is confident that the desirable effects of an intervention outweigh its undesirable effects. This implies that most or all individuals will be best served by the recommended course of action.
<b>Recommendation against</b>
A ‘recommendation against’ is given when the guideline development group is confident that the undesirable effects of an intervention outweigh its desirable effects. This implies that most or all individuals will be best served by the recommended course of action.
<b>Conditional Recommendation for</b>
A ‘conditional recommendation for’ is given when the guideline development group considers that the intervention’s desirable effects probably outweigh the undesirable effects but appreciable uncertainty exists. A conditional recommendation implies that not all individuals will be best served by the recommended course of action. There is a need to consider the individual person’s circumstances, preferences and values more carefully than usual.
<b>Conditional Recommendation against</b>
A ‘conditional recommendation against’ is given when the guideline development group considers that the intervention’s undesirable effects outweigh the desirable effects but appreciable uncertainty exists. A conditional recommendation implies that not all individuals will be best served by the recommended course of action. There is a need to consider the individual person’s circumstances, preferences and values more carefully than usual.
<b>Consensus Recommendation</b>
A consensus recommendation can be given for or against an intervention. This type of recommendation is used when there is not enough evidence to give an evidence-based recommendation but the guideline development group still considers it important to give a recommendation. These recommendations are made based on expert opinion and were formulated by a consensus process.

## Results of Stakeholder Perspective Studies

### Perspectives of healthcare professionals<sup>1</sup>

Two main themes were identified from an inductive thematic analysis; i) *The 'too hard' basket*: challenges of deprescribing and ii) *'Even if I want to, I don't know how'*: development of opioid deprescribing guidelines. The first theme related to the range of reported challenges which influence health professionals' willingness and ability to deprescribe opioids. Subthemes explored medication, patient, prescriber and health system-related challenges. The second theme acknowledged that participants feel current practices surrounding opioid management are suboptimal and that opioid deprescribing guidelines are required to direct and support clinical practice. A summary of the main findings is presented in the full guideline document.

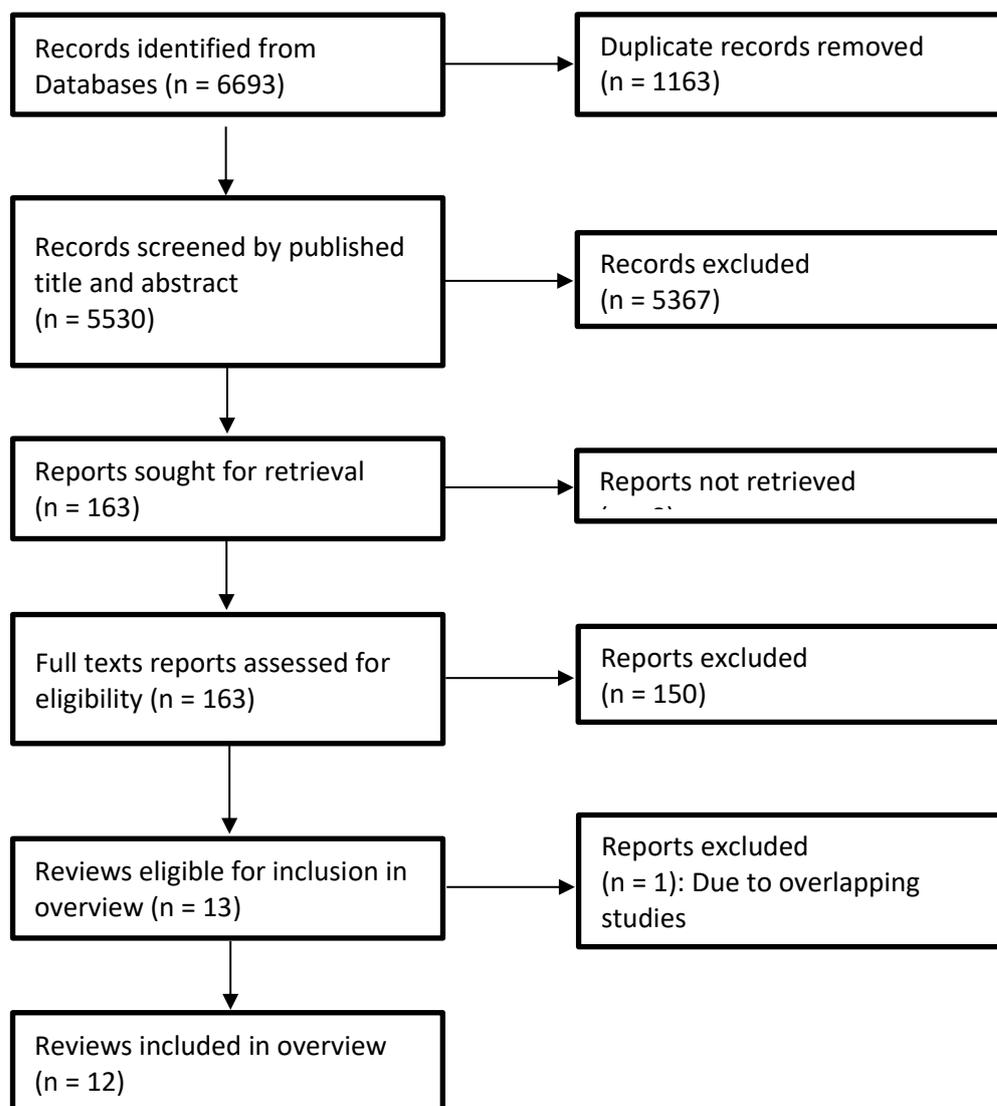
### Perspectives of persons taking opioids<sup>2</sup>

Twenty people using opioids were recruited and included in the analysis. Thematic framework analysis utilising Bandura's Social Cognitive Theory provided three overarching constructs; i) behavioural, i) cognitive and ii) environmental factors, governing health behaviors.<sup>5</sup> Inductively derived subthemes reflect specific barriers and enablers to opioid deprescribing as identified by participants. People taking opioids expressed a general desire to reduce or cease opioid therapies, however, they felt engaging and persevering with opioid deprescribing was difficult. Opioid deprescribing guidelines were viewed as an enabler to opioid deprescribing. A summary of the main findings is presented in the full guideline document.

## Results of Overview of Systematic Reviews

The search strategy identified 6693 articles for screening as shown in [Figure 2](#). Reviews ranged in publication date from 2012 to 2020 and contained between five and 67 individual studies. Five reviews<sup>14-18</sup> included exclusively RCTs and seven reviews included non-randomised controlled and observational studies. A range of pain types were examined including chronic non-cancer pain<sup>14 17 19-23</sup> and cancer-related pain.<sup>15 16 24</sup> Garland et al.<sup>18</sup> and Nielsen et al.<sup>18</sup> did not specify a singular pain type. Interventions were classified into categories based on the active intervention. Interventions were pharmacological (n=4)<sup>15 19 21 25</sup>, physical (n=3)<sup>16 19 21</sup> interventional (n=3),<sup>17 23 24</sup> psychological or behavioural (n=4)<sup>18 19 21</sup> or mixed (n=5)<sup>14 19-22</sup> in nature. Interventions were compared with either usual care, placebo, no treatment or alternative treatments (e.g. an alternative pharmacological or non-pharmacological intervention).

**Figure 2. PRISMA flow diagram of publication selection for inclusion in overview.**



## Summary of Findings

A 'Summary of Findings' for each key clinical question is presented in the main guideline document. A summary of the characteristics and findings of the reviews contained within the overview of systematic reviews is presented in [Table 3](#).

**Table 3: Summary of review characteristics and findings**

Type of evidence	Systematic Review	
Citation of review	Ferrer-Mileo L, et al. (2018) <sup>24</sup>	
Search last updated	2015	
Number of studies	22	
Objective	To summarize the current scientific evidence on the use of cryoablation to control cancer pain.	
Conclusion	Based on the limited evidence available to date, cryoablation is effective with few major side-effects in control of cancer pain.	
Review characteristics	What review authors looked for	What review authors found
Study Design	No restrictions	22 articles were included: 1 randomized clinical trial (RCT), 2 non-RCTs, 1 ambispective study, 9 retrospective studies, 2 non-specified cohort studies, 3 case series, and 4 case reports
Participants	Adults with cancer pain	Participants = 496 (1-69)  The median participant age was approximately 60 years (range 18 to 95) with females accounting for 50.4%.  Lung cancer was the most common primary tumour. 82.8% of the metastases were bone metastases, with or without soft tissue involvement
Intervention and comparison	Cryoablation vs no cryoablation	A: Cryoablation (+/- supplementary treatments) vs usual care  B: Cryoablation vs alternate intervention
Outcomes	Pain, quality of life, opioid deprescribing	Cryoablation decreased mean pain scores by 62.5% at 24 hours post-cryoablation, by 70% at 3 months, and by 80.9% at 6 months.  Cryoablation was associated with a 44.2% improvement in quality of life after 4 weeks and a 59.6% improvement at 8 weeks.  The need for opioids decreased by 75% at 24 hours and by 61.7% at 3 months
Countries	Not listed	
Setting	No restrictions	
Risk of Bias Assessment Tool	The Scottish Intercollegiate Guidelines Network (SIGN) system was used to evaluate the grade of evidence of each study reviewed.	
Risk of Bias assessment (as performed by review authors)	7 articles are classified as level 3 by SIGN guidelines, 9 articles as level 2-, 4 studies are 2+, 1 study is 2++, and 1 clinical trial is 1-. Some of the included studies were not specifically designed to assess the effect of cryoablation on pain control as a primary endpoint, with data relating to patient subgroups in some studies. Similarly, some studies published their results only as graphics or figures; in such	

	cases, reviewers had to estimate the data considering the risk for bias. The data collection techniques used in these studies were highly variable, thus making it difficult to compare the studies. Adjuvant treatments could have affected (positively or negatively) the real magnitude of the effects.	
Conflicts of interest of review authors	None declared	
Type of evidence	Systematic Review	
Citation of review	Fishbain DA, et al. (2019) <sup>20</sup>	
Search last updated	2017	
Number of studies	20	
Objective	To support or refute the hypothesis that opioid tapering in chronic pain patients improves pain or maintains the same pain level by taper completion but does not increase pain.	
Conclusion	<p>There is consistent evidence that opioid deprescribing in chronic pain patients reduces pain or maintains the same level of pain.</p> <p>65% of studies or 89% of participants were from multidisciplinary centres and received co-interventions. 25% of studies reported using adjuvants during tapering such as antidepressants or anticonvulsants.</p>	
Review characteristics	What review authors looked for	What review authors found
Study Design	Primary articles. Case reports were excluded.	20 (Non-RCTS: Pre-and post-cohort studies, group comparison)
Participants	<p>Chronic pain patients on opioids or with opioid addiction.</p> <p>Excluded those who underwent buprenorphine, ketamine, THC or intrathecal delivery system substitution without taper.</p>	<p>Participants = 2,109 (7-596)</p> <p>60% of studies involved more than one type of pain in the tapering group.</p>
Intervention and comparison	Opioid tapering vs Opioid continuation	<p><b>A:</b> Opioid tapering vs Opioid continuation</p> <p>The tapering procedure was described in 40% of studies. 45% of studies had participants tapered entirely from starting dose and 55% had reduced dose by the end of taper. The number of days of tapering ranged from 2-180 days and the average was 45 days.</p>
Outcomes	<p>Opioid reduction, pain</p> <p>Pain was measured in 50% of participants via the visual analogue scale, 20% via the numeric rating scale and 10% via the multidimensional pain inventory. The remaining 20% it was not stated how pain was measured.</p>	<p>80% of studies showed improved pain after tapering, 15% of studies showed pain was the same by taper completion.</p> <p>In 81.2% of studies, the reduction in pain was statistically significant. An additional 15% demonstrated that pain had improved but did not perform a statistical analysis. The 15% of studies which showed no change in pain represented 1.9% of chronic pain patients.</p> <p>One study reported that 97% of participants' pain dropped or was the same by the end of taper but was worse in 3%. The represents 0.09% of all patients across 20 studies.</p>
Countries	Not specified.	

Setting	<p><u>Inclusion criteria:</u> Multidisciplinary facility, pain facility, outpatient pain treatment clinical, medical hospital or clinic or addiction facility or clinic</p> <p><u>Demographics:</u> 10% Facility not stated, 5% medical,5% detoxification/addiction,5% psychiatry inpatient, 10% pain clinic, 65% multidisciplinary/ interdisciplinary/ functional restoration.</p>	
Risk of Bias Assessment Tool	Type of evidence and strength / consistency of the evidence determined in accordance with the Agency for Health Care Policy and Research for guideline development (AHCPR).	
Risk of Bias assessment (as performed by review authors)	The results of this review are based on type 3 and 4 studies. These studies represented lower levels of evidence and were not designed to test the hypothesis, with the evidence being marginal in quality with large amounts of missing data. There was a lack of controls for other treatments during opioid tapering (potential confounder). Retrospective studies are subject to more bias errors vs prospectively designed studies. There was great variability in the studies in whether the tapering procedure was described, the type of taper, the opioid range tapered from, the percentage of patients tapered entirely, the number of days tapering, etc. All of these factors could affect the success of the taper and potentially the pain levels perceived.	
Conflicts of interest of review authors	Neither of the authors had any direct or indirect funding support for this study.	
Type of evidence	Systematic Review	
Citation of review	Frank et al. (2017) <sup>49</sup>	
Search last updated	19 April 2017	
Number of studies	67 (11 randomized trials and 56 observational studies)	
Objective	To synthesize studies of the effectiveness of strategies to reduce or discontinue long term opioid therapy and patient outcomes after dose reduction among adults prescribed opioids for chronic pain.	
Conclusion of the review	<p>Very low quality evidence suggests that several types of interventions may be effective to reduce or discontinue long term opioid therapy and that pain, function, and quality of life may improve with opioid dose reduction.</p> <p>The fair quality studies reported improvement in pain severity (8 of 8 studies), function (5 of 5 studies), and quality of life (3 of 3 studies) after opioid dose reduction. However, the overall quality of the evidence was very low for all 6 pre-specified patient outcomes.</p>	
Review characteristics	What review authors looked for	What review authors found
Study Design	Eligible study designs included randomized trials, cohort studies, case-control studies, and case series. Case reports and cross-sectional studies, as well as studies that did not describe the clinical intervention or report patient-level data were excluded.	11 randomized controlled trials, 8 controlled observational studies, and 48 uncontrolled observational studies.
Participants	Adults (aged ≥18 years) who were prescribed long term opioid therapy for chronic pain (defined as pain lasting >3 months)	12546 (5-1457)  Mean daily dose ranged from 29 to 556 mg OMMED.
Intervention and comparison	Opioid dose reduction interventions  Vs	<b>A:</b> Interdisciplinary pain programs vs standard care  <b>B:</b> Buprenorphine-assisted dose reduction vs standard care

	Standard care	<p><b>C:</b> Behavioural interventions vs standard care</p> <p><b>D:</b> Detoxification vs standard care</p> <p><b>E:</b> Ketamine-assisted dose reduction vs standard care</p> <p><b>F:</b> Acupuncture vs standard care</p> <p><b>G:</b> Other outpatient programs vs standard care</p> <p><b>H:</b> Other interventional programs vs standard care</p>
Outcomes	Reduction or discontinue long term opioid therapy, pain severity, pain-related function, quality of life, opioid withdrawal symptoms, substance use, or adverse events	<p>Study interventions had an objective of opioid discontinuation or dose reduction in 43 and 12 studies, respectively; 12 studies reported on this outcome in secondary or exploratory analyses.</p> <p><u>Interdisciplinary pain programs:</u> Thirty-one studies (11 fair-quality and 20 poor quality) presented data from 19 distinct interdisciplinary pain programs. Ten fair-quality studies described programs that mandated discontinuation as a condition of enrolment; in these programs, 87% of participants discontinued opioid use at program completion (range, 74% to 100%).</p> <p><u>Behavioural interventions:</u> Six studies with 238 total participants assessed the effectiveness of behavioural interventions.</p> <p>The first good-quality trial compared a 4-month interactive voice response intervention versus usual care among patients with chronic pain (n = 51); a goal of opioid dose reduction was optional. The intervention reduced the mean opioid dose significantly at 4-month (P = 0.04) and 8-month (P = 0.004) follow-up compared with usual care.</p> <p>The second good-quality trial compared an 8-week group intervention based on mindfulness meditation and cognitive behavioural therapy with usual care among patients receiving long term opioid therapy (n = 35); the intervention did not explicitly encourage dose reduction. The mean change in the daily opioid dose from baseline to 26 weeks was 10.1 mg MED in the intervention</p>

		<p>group compared with 0.2 mg MED in the control group (P = 0.8).</p> <p>The third good-quality trial compared a 22-week opioid taper support intervention (motivational interviewing and pain self-management education delivered by a physician assistant) with usual care (n = 35); opioid dose reduction was the primary outcome. The intervention reduced the mean opioid dose by 43% compared with 19% in the usual care group at 22 weeks (P = 0.07).</p> <p><u>Pain severity:</u> Eight fair-quality studies included 1 controlled and 6 uncontrolled observational studies of interdisciplinary pain programs and 1 uncontrolled observational study of acupuncture; all 8 studies reported improved pain after opioid dose reduction. The effect of dose reduction on pain-related function was assessed in 17 studies (5 fair-quality and 12 poor-quality). The 5 fair-quality studies were observational studies of interdisciplinary pain programs (1 controlled and 4 uncontrolled); all 5 studies reported improved function after opioid dose reduction.</p> <p><u>Quality of life:</u> The effect of dose reduction on quality of life was assessed in 12 studies. Three fair-quality studies were uncontrolled observational studies of interdisciplinary pain programs and all reported improved quality of life after opioid dose reduction.</p> <p><u>Adverse events:</u> Opioid withdrawal symptoms were examined in 18 studies (3 fair-quality and 15 poor-quality); the reported incidence during opioid dose reduction ranged widely. Four poor-quality studies examined new-onset substance use. Eleven poor quality studies assessed adverse events; 5 assessed mortality outcomes, and 1 reported a single opioid related overdose death.</p>
Countries	United States, United Kingdom, Israel, Sweden, Germany, Canada, France, Norway, Australia.	
Setting	No restrictions of setting. Interventions occurred in outpatient settings, inpatient settings, or both in 42, 15, and 10 studies, respectively; 5 studies were conducted in primary care settings.	
Risk of Bias assessment tool	Two reviewers independently assessed study quality (risk of bias in individual studies) using criteria developed by the U.S. Preventive Services Task Force (USPSTF), which facilitate rating of study quality as good, fair, or poor.	

	The overall quality of the evidence was assessed using GRADE.	
Risk of Bias assessment (as performed by review authors)	Study quality was good for 3 studies, fair for 13 studies, and poor for 51 studies. The GRADE quality of evidence to address the effectiveness of strategies to reduce or discontinue long term opioid therapy was very low. For each of the 6 pre-specified patient outcomes, the GRADE quality of evidence was very low.	
Conflicts of interest of review authors	Primary Funding Source: Veterans Health Administration. The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript. Authors have disclosed no conflicts of interest.	
Type of evidence	Systematic Review	
Citation of review	Garland EL, et al. (2020) <sup>18</sup>	
Search last updated	March 2018	
Number of studies	60 (RCTs). 29 studies were included in the pain meta-analysis and 8 studies in the opioid dose meta-analysis.	
Objective	To evaluate the association of mind-body therapies with pain and opioid dose reduction in a diverse adult population with clinical pain.	
Conclusion	<p>Mind-body therapies (meditation, hypnosis, relaxation, guided imagery, therapeutic suggestion, cognitive behavioural therapy) were associated with improved pain and reduced opioid dose. (Cohen d = -0.26; 95% CI, -0.44 to 0.08). Meditation, CBT and hypnosis studies found improved opioid related outcomes, fewer studies of suggestion, guided imagery and relaxation reported such improvements. Small overall reductions in opioid dose were described.</p> <p>Most studies of meditation, hypnosis, and CBT reported significant therapeutic associations with opioid-related outcomes, including opioid dosing, craving, and opioid misuse, whereas comparatively fewer studies of suggestion, imagery, and relaxation reported significant associations with opioid related outcomes.</p>	
Review characteristics	What review authors looked for	What review authors found
Study Design	Randomized clinical trials and systematic reviews	Randomized clinical trials
Participants	<p>Adults (aged ≥18 years) prescribed opioids for chronic, acute, procedural, or cancer pain.</p> <p>Studies that did not include pain-related outcomes were excluded (e.g., studies of individuals with OUD who did not report pain).</p>	<p>The 60 studies focused on various clinical pain targets: procedural pain (n = 39), burn pain (n = 7), cancer pain (n = 5), chronic pain (n = 8), or heterogeneous acute pain conditions (n = 1).</p> <p>Studies tested meditation (n = 5), hypnosis (n = 25), relaxation (n = 14), guided imagery (n = 7), therapeutic suggestion (n = 6), and CBT (n = 7) interventions.</p> <p>Studies used a range of control conditions, including another MBT (n = 4), psychotherapy comparators (n = 11), attention control (n = 10), information control (n = 7), music controls (n = 6), waiting list control.</p>
Intervention and comparison	Psychologically oriented mind body therapies: Meditation, hypnosis, relaxation, guided imagery, therapeutic suggestion and cognitive behavioural therapy (CBT)	<p><b>A:</b> Mind-body therapy vs usual care</p> <p><b>B:</b> Mind-body therapy vs active control</p>

	Vs Active or placebo controls	
Outcomes	<p><u>Primary:</u> Pain intensity</p> <p><u>Secondary:</u> Opioid dose, opioid misuse, opioid craving, disability, or function</p>	<p>Overall, MBTs were associated with pain reduction (Cohen d = -0.51; 95%CI, -0.76 to -0.26) and reduced opioid dose (Cohen d = -0.26; 95%CI, -0.44 to -0.08).</p> <p>Moderate to large effect size improvements in pain outcomes were found for meditation (Cohen d = -0.70), hypnosis (Cohen d = -0.54), suggestion (Cohen d = -0.68), and cognitive behavioural therapy (Cohen d = -0.43) but not for other MBTs.</p> <p>Although most meditation (n = 4 [80%]), cognitive-behavioural therapy (n = 4 [57%]), and hypnosis (n = 12 [63%]) studies found improved opioid-related outcomes, fewer studies of suggestion, guided imagery, and relaxation reported such improvements.</p> <p><u>Pain-Related Outcome:</u> MBTs had a significant, moderate association with reduced pain (Cohen d = -0.51; 95%CI, -0.76 to -0.27; P &lt; .001). Computation of the Q (<math>\chi^2 = 287.21</math>, P &lt; .001) and I2 (90.53%) statistics showed some heterogeneity of effect sizes. These data were derived from 29 studies (n = 2916), with 1679 patients receiving an MBT.</p> <p><u>Opioid-Related Outcomes:</u> Overall, MBTs had a significant, small association with opioid use (Cohen d = -0.26; 95% CI, -0.44 to -0.08; P = .01) Computation of the Q (<math>\chi^2 = 6.70</math>, P = .82) and I2 (0.0%) statistics showed homogeneity of effect sizes. These data were derived from 8 distinct studies (n = 435), with 250 patients receiving an MBT.</p> <p><u>Mindfulness or Meditation Studies:</u> All 5 mindfulness or meditation studies (100%) reported significant improvements in pain severity, pain unpleasantness, interference, thermal pain sensitivity, and/or cessation of postsurgical pain. Meta-analytic results indicated that meditation had a significant strong association with pain reduction (Cohen d = -0.70; 95% CI, -1.09 to -0.31; P &lt; .001) with homogeneity of effect sizes (Q [<math>\chi^2 = 4.59</math>, P = .10]; I2 = 56.20%).</p> <p>Four of the 5 studies (80%) reported significant improvements in opioid misuse,</p>

	<p>opioid craving, time to opioid cessation, and/or opioid use; 1 of these studies reported reduced opioid analgesic use, but the analgesic outcome was an imprecise categorical variable. One study failed to find effects on opioid dose, and 2 other studies were unable to consistently and reliably collect opioid dosing data.</p> <p><u>Hypnosis Studies:</u> Fifteen of the hypnosis studies (65%) reported statistically significant improvements in pain intensity, pain unpleasantness, and/or pain affect. Meta-analytic results indicated that hypnosis had a significant moderate association with pain reduction (Cohen <math>d = -0.54</math>; 95%CI, <math>-0.87</math> to <math>-0.20</math>; <math>P &lt; .001</math>) with some heterogeneity of effect sizes (<math>Q [\chi^2 = 38.16, P &lt; .001]</math>; <math>I^2 = 73.90\%</math>).</p>
Countries	Not specified.
Setting	No restrictions of setting. In person and/or recordings.
Risk of Bias assessment tool	Risk of bias was assessed using the Cochrane risk of bias tool.
Risk of Bias assessment (as performed by review authors)	<p>Most studies used active or placebo controls and had low risk of bias, increasing confidence that the reported benefits are not solely the result of nonspecific therapeutic factors. The strength of the evidence for the therapeutic effects of MBTs on pain and opioid dose reduction was moderate, although this evidence varied by specific MBT. A funnel plot and the Egger statistic (<math>z = -0.30, P = .76</math>) did not indicate publication bias.</p> <p>Quantitative conclusions about outcome modifiers couldn't be drawn, such as dose or delivery format, or about durability of treatment effects because of high levels of study heterogeneity.</p> <p>Outcomes ranged from immediate post-intervention acute pain outcomes to outcomes that lasted 3 months or longer. Approximately one-third of studies had small samples and therefore may have been underpowered. Although most studies had low risk of bias, a number of trials had biases, such as lack of blinding of participants, personnel, and/or outcomes assessors, and lack of intention-to-treat analysis. Some studies were missing clinical trial reporting information. Funnel plots and the Egger statistic indicated some publication bias for meditation and suggestion studies.</p>
Conflicts of interest of review authors	Dr Garland reported serving as the director of the Center on Mindfulness and Integrative Health Intervention Development, which provides Mindfulness-Oriented Recovery Enhancement (MORE), mindfulness-based therapy, and cognitive behavioural therapy in the context of research trials for no cost to research participants; receiving honoraria and payment for delivering seminars, lectures, and teaching engagements (related to training practitioners in MORE and mindfulness) sponsored by institutions of higher education, government agencies, academic teaching hospitals, and medical centres; and receiving royalties from the sale of books related to MORE during the conduct of the study. Dr Keefe reported a patent pending.
Type of evidence	Systematic Review
Citation of review	Hassan, (2019) <sup>21</sup>
Search last updated	February 15, 2018

Number of studies	23	
Objective	To explore the effectiveness of the Integrative medicine approach or any of the Complementary and alternative therapies to reduce or cease opioid use in chronic pain patients.	
Conclusion	87% of studies ((20/23) demonstrated that IM approaches were associated with a statistically significant reduction in opioid use in addition to improvements in pain severity and interference, overall function and quality of life. 12/20 (60%) reported these reductions were sustained after 6-12months. There is positive preliminary evidence that the integrative medicines approaches including complementary and alternative therapies can help in reducing opioid use.	
Review characteristics	What review authors looked for	What review authors found
Study Design	No restrictions on study design	8 RCTs, 7 retrospective studies, 4 prospective observational, 3 cross-sectional, and 1 quasi-experimental study
Participants	Adults (aged ≥18 years) with chronic pain  Have pain for >3–6 months including back pain, chronic headaches, temporomandibular disorder, fibromyalgia, myofascial pain, musculoskeletal pain, neuropathic pain, HIV neuropathy, rheumatoid arthritis, and osteoarthritis  On opioid medications.	6421 (36-2897)  Nineteen studies included patients with any type of CP condition including musculoskeletal pain, neuropathic pain, and headaches, two studies only focused on patients with fibromyalgia and two studies focused on patients with back pain. Twelve studies included only patients specifically prescribed opioid treatments whereas the rest of the studies (N=11) included patients prescribed any type of analgesics including opioid
Intervention and comparison	Any integrative medicine approach that included one or more complementary and alternative therapy at any dose, by any route, administered in combination with pharmacological treatment, for the relief of chronic pain was included.	<b>A:</b> Interdisciplinary pain rehabilitation programs <b>B:</b> CBT <b>C:</b> Cannabis <b>D:</b> Acupuncture <b>E:</b> Education <b>F:</b> Mindfulness oriented recovery enhancement <b>G:</b> Therapeutic interactive voice response after CBT <b>H:</b> Physical therapy
Outcomes	<u>Primary:</u> Reduction or cessation of prescription opioids.  <u>Secondary:</u> Pain intensity/severity, psychological and physical functioning, adverse effects.	Twenty (87%) of the selected studies demonstrated that IM approaches were associated with a statistically significant reduction in opioid use, in addition to improvements in pain severity and interference, overall function, and quality of life (60%) out of those 20 studies reported that these reductions were sustained after the six- to 12-month follow-up period. In contrast, three studies (13%) assessed the effect of cannabis, MORE, and CBT, showing no reduction in opioid use post intervention.  <u>Interdisciplinary or Multidisciplinary Intervention:</u> Six studies assessed the impact of interdisciplinary or multidisciplinary

		<p>treatment programs. They lasted for three weeks in five studies, and the participants were followed up post-intervention for around three to six months post-treatment. Multidisciplinary programs were associated with significant clinical improvements across all outcome measures including pain severity, depression, and anxiety at discharge, six months, and 12 months of follow-up.</p> <p>One study, however, found no reduction in opioid use, although participants reported significant reductions in pain intensity, improvement in psychological general well-being, and improvement in the quality of sleep after attending the program compared with their counterparts' reports.</p> <p><u>Cognitive-Behavioural Therapy:</u> All three studies reported significant improvements in pain, function, and psychological health. However, one study showed no statistically significant decrease in the use of opioid medications.</p> <p><u>Therapeutic Interactive Voice Response After CBT:</u> An RCT assessed whether a TIVR-based intervention could decrease pain and reduce medication use at follow-up. Results demonstrated that TIVR decreased pain and depression, improved function and coping, and reduced opioid analgesic use post-CBT at both four- and eight-month follow-up post-CBT. In contrast, the control group showed increases in opioid use.</p> <p><u>Mindfulness-Oriented Recovery Enhancement:</u> An RCT assessing the effectiveness of mindfulness oriented recovery enhancement (MORE) demonstrated that MORE participants reported significantly lower levels of pain severity, functional interference, and less desire for opioids post-treatment than the control group.</p> <p><u>Education and Opioid Tapering Support:</u> One nonrandomized prospective controlled study compared chronic pain patients receiving opioid medication attending group medical visits with a matched control group receiving treatment as usual. The group medical visits lasted for six months and provided education about CAM. Results showed that none of the patients who</p>
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		<p>attended group medical visits for more than six months reported an increase in their opioid use. A pilot RCT evaluated the effectiveness of a prescription opioid taper support intervention. The intervention groups achieved more than double the percent reduction in morphine equivalent dose (MED) compared with the usual care.</p> <p><u>Physical Therapy:</u> A retrospective study assessed the effect of physical therapy on pain scores and pain medication prescriptions and usage among CP patients living with HIV. Results showed an overall trend of decreased medication usage during and after the intervention period in all pain medication categories except opioids.</p> <p><u>Acupuncture:</u> Two studies assessed the impact of acupuncture on pain medication use. A retrospective chart review was conducted to assess the impact of at least four acupuncture treatments within one year on pain medication use, pain severity, function, and quality of life among military patients with combat-related pain. All pain medication use was reduced. Patients also reported significantly better pain relief, better ability to function, and improved quality of life after one year.</p> <p>Another study evaluated the effect of electroacupuncture (EA) on opioid medication usage, pain, and associated side effects compared with sham EA. Results demonstrated that both groups significantly reduced opioid medication use over six weeks of treatment.</p> <p><u>Cannabinoids:</u> Seven studies were found that assessed the effect of cannabis use on opioid use. Three studies were prospective observational studies using a self-report online survey. Two studies were cross-sectional that assessed cannabis as a substitute for opioid use through online surveys and two were retrospective studies that examined whether using medical cannabis was associated with decreased opioid use. In all studies, participants were more likely to report reduced daily opioid use vs the control group or ceased opioid use altogether compared with the control group. One study, however, found no relationship between 1) cannabis</p>
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		use and pain severity or pain interference and 2) cannabis use and reduced prescribed opioid use or increased rates of opioid discontinuation after four years of follow-up. On the contrary, participants who used cannabis had a greater pain severity score, greater pain interference score, lower pain self-efficacy scores, and greater generalized anxiety disorder severity scores.
Countries	Not specified.	
Setting	No restrictions on setting. Two studies were conducted in inpatient settings, whereas the rest were outpatient programs. The duration of the interventions ranged between three weeks and 21 months for outpatient programs and was approximately three weeks for inpatient programs.	
Risk of Bias assessment tool	The Mixed Methods Appraisal Tool (MMAT), version 2011 was used to appraise the selected studies.	
Risk of Bias assessment (as performed by review authors)	The overall methodological quality of the studies was low. Almost half of the studies (N=12, 52%) did not report on the actual opioid intake or consumption by calculating patients' daily dose and converting it to MED, the total duration of opioid use, or how long patients had chronic pain.	
Conflicts of interest of review authors	No conflicts of interest reported.	
<b>Type of evidence</b>	<b>Systematic Review</b>	
Citation of review	He Y, et al. (2019) <sup>16</sup>	
Search last updated	March 31,2019	
Number of studies	17 (RCTs), 14 of these studies were used in the meta-analysis.	
Objective	To evaluate the existing randomized clinical trials (RCTs) for evidence of the association of acupuncture and acupressure with reduction in cancer pain.	
Conclusion of the review	<p>This systematic review and meta-analysis found that acupuncture and/or acupressure was significantly associated with reduced cancer pain and decreased use of opioid analgesics.</p> <p>Evidence from RCTs indicated with a moderate level of certainty that real acupuncture was associated with reduced pain intensity as compared with sham acupuncture or wait-list controls. Moderate quality evidence also suggested that acupuncture and acupressure were associated with reduced analgesic use.</p> <p>In most of these studies, baseline analgesic use was not specified, and in 2 studies, participants did not use analgesic therapy at baseline.</p>	
Review characteristics	What review authors looked for	What review authors found
Study Design	Randomised control trials	Randomised control trials
Participants	Patients with pain directly accompanying the development of cancer and/or chronic pain associated with cancer treatments.	1111 (53-226), 920 in meta-analysis.  Thirteen studies (76%) focused on a specific kind of cancer pain (6 aromatase inhibitor–induced arthralgia, 2 lung cancer pain, 1 gastric cancer pain, 1 pancreatic cancer pain, 1 malignant neuropathic pain, 1 osseous metastatic pain, and 1persistent pain after a surgical procedure, and 4 (24%) studies investigated general cancer pain with a mix of cancer diagnoses.
Intervention and comparison	Acupuncture Acupressure  Vs	<b>A:</b> Acupuncture Acupressure vs Sham control

	Sham control, analgesic therapy, or usual care for managing cancer pain	<p><b>B:</b> Acupuncture Acupressure vs analgesic therapy</p> <p><b>C:</b> Acupuncture Acupressure vs usual care</p>
Outcomes	<p><u>Primary:</u> Pain intensity measured by the Brief Pain Inventory, Numerical Rating Scale, Visual Analog Scale, or Verbal Rating Scale.</p> <p><u>Secondary:</u> Reducing analgesic dose.</p>	<p>Seven sham-controlled RCTs (35%) were notable for their high quality, being judged to have a low risk of bias for all their domains, and showed that real (compared with sham) acupuncture was associated with reduced pain intensity (mean difference [MD], -1.38 points; 95% CI, -2.13 to -0.64 points; I<sup>2</sup> = 81%).</p> <p>A favourable association was also seen when acupuncture and acupressure were combined with analgesic therapy in 6 RCTs for reducing pain intensity (MD, -1.44 points; 95% CI, -1.98 to -0.89; I<sup>2</sup> = 92%) and in 2 RCTs for reducing opioid dose (MD, -30.00 mg morphine equivalent daily dose; 95% CI, -37.5 mg to -22.5 mg).</p> <p>For pain intensity, pooled results from 7 blinded studies showed the association between pain reduction and real acupuncture rather than between pain reduction and sham acupuncture with substantial heterogeneity (mean difference, -1.38 points; 95% CI, -2.13 to -0.64; I<sup>2</sup> = 81%). Data from the 6 open-label RCTs showed the reduction in pain intensity was associated with a combination of acupuncture and acupressure when compared with analgesic therapy with considerable heterogeneity (mean difference, -1.44 points; 95% CI, -1.98 to -0.89; I<sup>2</sup> = 92%).</p> <p>Significant reduction without heterogeneity was found in 3 studies that compared acupuncture with wait-list controls (mean difference, -1.63 points; 95% CI, -2.14 to -1.13).</p> <p>Two open label studies reported the maintenance dose of analgesics during the trial, and the pooled results showed a significant decrease in analgesic dose in the integrative medicine group (acupuncture plus analgesic therapy) compared with the control group that received analgesics alone (mean difference, -30.00 mg morphine equivalent daily dose; 95% CI, -37.5 mg to -22.5 mg), without heterogeneity. In the subgroup analyses for intervention type, the</p>

	<p>pooled result of sham-controlled RCTs favoured manual acupuncture (3 studies) with reduced heterogeneity (mean difference, -0.88 points; 95% CI, -1.75 to -0.01; I<sup>2</sup> = 59%) and auricular acupuncture (2 studies) with increased effect size (mean difference, -2.98 points; 95% CI, -5.37 to -0.59; I<sup>2</sup> = 84%). By pooling the 2 open-label studies on acupressure, the effect size increased with reduced heterogeneity (mean difference, -1.75 points; 95%CI, -2.07 to -1.43; I<sup>2</sup> = 64%).</p> <p><u>Adverse events:</u> The adverse events reported were minor, did not require medical evaluation or any specific intervention, and consisted predominantly of skin and subcutaneous tissue disorder or slight pain from the application of treatment to the skin.</p> <p>Six RCTs reported no adverse events during the study period. In all of the trials included, no dropouts were attributed to adverse effects associated with acupuncture treatment.</p>
Countries	Seven of the 17 studies were conducted in China, 6 in the United States, and 1 study each in Australia, Brazil, France, and Korea.
Setting	No restrictions on setting. Outpatient acupuncture / acupressure.
Risk of Bias assessment tool	Cochrane Risk of Bias Tool. The quality of evidence was evaluated with GRADE.
Risk of Bias assessment (as performed by review authors)	<p>Six sham-controlled studies (35%) were notable for their high quality, as each of the 6 domains in these studies was judged to have a low risk of bias. 7 open-label, 2-group RCTs (41%) without sham acupuncture were rated as having a high risk of bias for blinding of the participants and outcome assessors. For the 3-group studies that compared real acupuncture with sham acupuncture or wait-list controls, blinding was rated as having a low risk of bias for the former comparison and a high risk of bias for the latter. Two studies (12%) were unclear about random sequence generation, and 9 (53%) were unclear on allocation concealment. Fifteen studies (88%) were at low risk of attrition bias, and 10 (59%) were at low risk of selective outcome reporting.</p> <p>The GRADE level of evidence was assessed as 'moderate'.</p>
Conflicts of interest of review authors	Dr May reported receiving internal funding from RMIT University through the China-Australia International Research Centre for Chinese Medicine to work on the topic of cancer pain. Dr Mao reported receiving grants from the National Cancer Institute during the conduct of the study. Dr H. Zhang reported receiving grants from the Traditional Chinese Medicine Bureau of Guangdong Province during the conduct of the study, internal funding from the Guangdong Provincial Hospital of Chinese Medicine for Specific Research on TCM Science and Technology, and internal funding from the Guangdong Provincial Hospital of Chinese Medicine and RMIT University through the China-Australia International Research Centre for Chinese Medicine. No other disclosures were reported.
Type of evidence	Systematic Review
Citation of review	Mackey et al. (2020) <sup>22</sup>

Search last updated	May 2020	
Number of studies	44	
Objective	To determine patient outcomes following long term opioid therapy dose reduction.	
Conclusion	<p>Patients on long term opioid therapy who voluntarily participate in intensive pain management interventions that incorporate opioid tapering may experience improvements in pain severity and pain-related function, while those who taper opioids with less intensive co-interventions may have unchanged pain and function. Findings are inconclusive for outcomes including serious harms such as overdose and suicide, as these outcomes have not been sufficiently studied.</p> <p>Evidence regarding patient outcomes following tapers remains unclear for serious harms including substance use, opioid overdose, and suicide.</p>	
Review characteristics	What review authors looked for	What review authors found
Study Design	Any study design	5 RCTs, 6 controlled observational studies, 33 uncontrolled observational studies
Participants	<p>Adults (aged ≥18 years) using opioids for &gt;3 months with chronic pain.</p> <p>Veteran population prioritised in evidence synthesis.</p>	46622 (7-31142)
Intervention and comparison	Any dose reduction or discontinuation of opioids (excluding studies of chronic pain interventions not explicitly designed to lower opioid doses).	<p><b>A:</b> Deprescribing vs treatment as usual</p> <p><b>B:</b> Deprescribing vs active control</p>
Outcomes	Pain severity, pain related function, quality of life, opioid withdrawal symptoms, patient satisfaction, retention in care, healthcare utilization, substance use, opioid overdose, suicidal ideation and self-directed violence.	<p><u>Pain:</u> Consistent low quality evidence suggests that mean pain scores and functional measures improved or did not significantly change for most patients who reduced or discontinued opioids.</p> <p>Among studies reporting mean pain scores at baseline and endpoint, improvements were greatest (19-47%) in studies of patients on higher baseline MEDD (99-177 mg) and more modest (8-10%) among studies of patients with lower baseline MEDD (47-61 mg).</p> <p>The more intense the intervention, the better the outcomes.</p> <p>Another RCT of a moderate-intensity intervention relied on voluntary opioid tapering and had a high dropout rate, prompting the study authors to deem the intervention unsuccessful.</p> <p>The least intensive intervention was an observational study of 51 patients in a community pain clinic with high baseline MEDD (288 mg) who voluntarily participated in a slow individualized taper with the use of a self-help book and had mean improvements in pain</p>

		<p>scores of 10%. In another observational study of tapering, 50 VHA patients with high baseline MEDD (64% &gt; 200 mg) who tapered opioids with usual care had less pain (40%) or unchanged pain (28%) at 6–12 months.</p> <p><u>Pain-Related Function:</u>  The most improvement was observed in a group of 1457 patients (baseline MEDD 117 mg) who participated in an intensive outpatient multimodal pain management program at the Cleveland Clinic. In this study, the mean score on the pain disability index (PDI) decreased from 42.95 at baseline to 18.29 at discharge (–57.4%) and was 23.7 after 6–12 months of follow-up (–44.8%).</p> <p>In a VHA study of an intensive intervention in which 705 veterans (baseline MEDD 61 mg) voluntarily participated in a 3-week interdisciplinary pain program incorporating opioid cessation, scores on the VA Pain Outcomes Questionnaire-interference in Activities of Daily Living (POQ-ADL) decreased from 16 at baseline to 13 at 3-week discharge (–18.8%).</p> <p>The smallest (and statistically nonsignificant) change came following the least intense intervention, in which an individualized taper was accompanied by a self-help book.</p> <p><u>Overdose:</u>  A 2019 retrospective study of Medicaid claims data in Vermont found that among a cohort of 694 Medicaid recipients who had a high prevalence of substance use disorders (60%) on ≥ 120 mg MEDD, almost half (49%) of 494 patients who discontinued opioids between 2013 and 2017 subsequently had an ED visit or hospitalization due to opioid poisoning or substance use disorder. In this study, opioids were most often discontinued without a gradual taper (median length of time to discontinuation was 1 day) and &lt; 1% of patients were prescribed medication to treat substance use disorders.</p> <p>The only large study of opioid overdose is a retrospective study of overdose rates following different phases of an opioid risk reduction initiative among patients in Washington’s Group Health practice (intervention group) compared to patients in Group Health’s contracted community clinics (control group). The within-group analysis demonstrated a significant decrease in overdose rates (relative</p>
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		<p>annual change 0.83, 95% CI 0.70 to 0.99), but the between-groups analysis did not. Overall, the results of this study provide inconsistent support that reducing opioid doses leads to lower overdose rates.</p> <p>In a retrospective study of 572 patients in a primary care clinic on long term opioid therapy during 2010–2015, 17 (4.9%) patients who discontinued opioids died of an overdose and 4 (1.75%) patients who continued prescription opioids died of an overdose. Opioid discontinuation was associated with a hazard ratio for overdose death of 2.94 (1.01 to 8.61) after adjusting for age and race. In another retrospective study of 43 VHA patients who stopped opioids due to opioid agreement violations, no patients overdosed.</p> <p><u>Suicide:</u> A retrospective study had 509 VHA patients who underwent clinician-initiated tapers due mostly (75%) to aberrant behaviours. 47 (9.2%) patients had new onset suicidal ideation and 12 patients (2.4%) had suicidal self-directed violence in the year following opioid discontinuation. Baseline PTSD (OR = 2.56, 95% CI 1.23 to 5.32) and psychotic disorders (OR = 3.19, 95% CI 1.14 to 8.89) were associated with suicidal ideation and suicidal self-direction violence, while other co-morbidities including substance use disorder and baseline MEDD were not.</p> <p><u>Retention in Primary Care or Usual Source of Healthcare:</u> The association between opioid dose reduction or discontinuation and retention in healthcare is unclear. The best evidence is a retrospective study of 1,624 patients on long term in an academic healthcare system in the Bronx, NY, which found that 78 of 207 patients who tapered opioids (4.8% of the total sample) terminated their care in the year following the taper (defined as no outpatient encounters in the healthcare system). In this study, opioid taper was significantly associated with termination of care (AOR 4.3, 95% CI 2.2 to 8.5) compared to continuing opioids.</p>
Countries	Denmark, United States, Canada	
Setting	<p>No setting restrictions. Largely outpatient pain clinics / centres.</p> <p>Authors prioritised evidence synthesis of studies conducted in a VHA setting or other outpatient settings.</p>	
Risk of Bias Assessment Tool	<p>Cochrane Risk of Bias Tool. GRADE for certainty of evidence.</p>	

Risk of Bias assessment (As performed by the review authors)	<p>The body of evidence has several limitations including a high proportion of uncontrolled observational studies (which introduce the potential for unmeasured confounders), unclear fidelity to interventions, and inadequate reporting of missing data and handling of missing data. Despite these limitations, within our subset of studies, findings regarding pain and pain-related function were consistent.</p> <p>Grading of Recommendations Assessment, Development and Evaluation was used to rate the quality of the evidence. Low confidence in the findings for pain and pain related function. Very low confidence in findings for adverse events. Authors have low confidence in these findings (low quality per GRADE).</p>	
Conflicts of interest of review authors	The authors declare that they do not have a conflict of interest.	
Type of evidence	Systematic Review	
Citation of review	Mathieson S, et al. (2020) <sup>14</sup>	
Search last updated	13th January 2020	
Number of studies	22	
Objective	To evaluate the efficacy of interventions designed to deprescribe opioid analgesics for pain relief in patients with chronic non-cancer pain.	
Conclusion	<p>Patient-focused interventions did not reduce opioid dose in the intermediate term nor did they increase the number of participants who ceased their dose, or increase the risk of serious adverse events or adverse events. One clinician intervention of education plus decision tools versus decision tools alone reduced the number of opioid prescriptions in the long term [e.g. dose reduction protocol, mean difference (MD) –19.9 MME, 95% CI –107.5 to 67.7], nor did they increase the number of participants who ceased their dose, or increase the risk of serious adverse events or adverse events. One clinician intervention of education plus decision tools versus decision tools alone reduced the number of opioid prescriptions (risk difference (RD) –0.1, 95% CI –0.2 to –0.1), dose (MD–5.3 MME, 95% CI –6.2 to –4.5) and use (RD–0.1, 95% CI –0.1 to –0.0) in the long term.</p>	
Review characteristics	What review authors looked for	What review authors found
Study Design	Randomised Controlled Trials	Randomised Controlled Trials
Participants	<p>Adult (≥ 18 years) patients with chronic pain (i.e. three months' duration or longer)</p> <p>Excluded trials enrolling patients with cancer or illicit drug use.</p>	<p>Patient focussed: 835 (12-411)</p> <p>Clinician focussed: 291 (53-238)</p>
Intervention and comparison	<p>Intervention to reduce or cease the prescription or use of prescription (non-illicit) opioids</p> <p>Vs</p> <p>Usual care (i.e. no intervention, continuation of medicine) or active control.</p>	<p><b>A:</b> Patient-focussed interventions vs usual care or active control</p> <p><b>B:</b> Clinician-focussed interventions vs usual care or active control</p>
Outcomes	<p>Primary: Reduction of opioid dose (MME mg/day)</p> <p>Secondary: Analgesic prescriptions, the proportion of participants who ceased or reduced their opioid use, the number of serious adverse events and adverse events reported, and the mean change in</p>	<p>Patient-focused interventions did not reduce opioid dose in the intermediate term [e.g. dose reduction protocol, mean difference (MD) - 19.9 MME, 95% CI - 107.5 to 67.7], nor did they increase the number of participants who ceased their dose, or increase the risk of serious adverse events or adverse events. One clinician intervention of education plus decision tools versus decision</p>

	<p>pain intensity, disability and quality-of-life scores.</p>	<p>tools alone reduced the number of opioid prescriptions (risk difference (RD) - 0.1, 95% CI - 0.2 to - 0.1), dose (MD - 5.3 MME, 95% CI - 6.2 to - 4.5) and use (RD - 0.1, 95% CI - 0.1 to - 0.0) in the long term.</p> <p><u>Reduction of opioid dose (MME mg/day):</u>  In the patient-focused intervention studies, the mean baseline opioid dose was relatively high at 154.9 MME/day (n=8 studies of 340 people with chronic pain, mean range 66.2–275.5 MME/day). Considerable statistical (I<sup>2</sup>=92%) and clinical heterogeneity prevented pooling data. Only one of the four studies showed a significant difference in the daily dose between groups using a dose-tapering protocol [mean difference (MD)–27.9 ME/day, 95% CI –41.1 to –14.7]; however, this study had a number of dropouts.</p> <p>One clinician-focused study (n=985 participants with 53 physicians) did significantly reduce daily opioid dose compared to decision tools alone in the long-term follow-up [27] (MD – 5.3 MME/ day, 95% CI –6.2 to –4.5).</p> <p><u>Analgesic prescriptions:</u>  Clinical heterogeneity prevented pooling of two patient-focused intervention studies in the immediate term (n=47); however, one study showed a borderline significant effect of dose reduction protocol (risk difference–0.3, 95% CI –0.6 to –0.0; 77.8% reduction of prescriptions in the intervention group vs 47.1% in the control group). At long-term follow-up, one patient-focused intervention of a dose reduction protocol (n=406) and one clinician-focused study did have a significant risk difference favouring the deprescribing interventions (risk difference–0.1, 95% CI –0.1 to –0.0; 10% reduction of prescriptions in the intervention group vs 1.9% in the control group; and risk difference–0.1, 95% CI –0.2 to –0.0; 47.1% reduction of prescriptions in the intervention group vs 35.8% in the control group, respectively).</p> <p><u>Proportion of participants who ceased or reduced their opioid use:</u>  None of the four patient-focused deprescribing interventions significantly reduced the proportion of patients with chronic pain who ceased their opioid analgesic compared to controls. One</p>
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		<p>clinician-focused study nearly showed statistical significance in the long term (risk difference -0.1, 95% CI -0.1 to 0.0; 21.3% ceased in the intervention group vs 16.8% in the control group).</p> <p>There were no significant effects of deprescribing interventions in the short term (n=170) or in the intermediate term (n=47) except a moderately large risk difference of borderline statistical significance favouring one patient-focused intervention of a dose reduction protocol (risk difference -0.3, 95% CI -0.6 to 0.0; 72.2% reduced their opioid use in the intervention group vs 41.2% in the control group). One clinician-focused intervention did have a significant risk difference favouring the intervention in reducing a patient's daily use in the long term (risk difference -0.1, 95% CI -0.1 to -0.0). Reduction was defined as 10% reduction in opioid dose within 30 days.</p> <p><u>Adverse events:</u>  Serious adverse events were reported in four studies of patient-focused interventions. Serious adverse events were infrequent (in the short term, one event in 93 participants in the intervention group, and zero events in 77 participants in the control group. In the intermediate term, one event in 18 participants in the intervention group, and zero events in 17 participants in the control group). There was no risk difference between groups for serious adverse events. Serious adverse events were chest pain and dyspnoea and an allergic reaction.</p> <p>Adverse events were reported in three studies of patient-focused interventions. There was no risk difference between groups for the number of participants reporting adverse events in the short term (risk difference 0.1, 95% CI -0.1 to 0.3) or in the intermediate term (risk difference 0.0, 95% CI -0.1 to 0.1) [24, 25]. Of the ten patient-focused interventions, there were 11 participants who withdrew due to adverse events (of which nine withdrawals were due to worsening symptoms/lack of efficacy). Five studies had no adverse event withdrawals, while two studies did not provide sufficient detail to determine if the reasons for study withdrawal were related to adverse events.</p>
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		<p><u>Pain intensity, disability and quality-of-life scores:</u>  Considerable statistical heterogeneity prevented pooling in the short and intermediate term (I<sup>2</sup>=100%, I<sup>2</sup>=95%, respectively). Overall, two studies reported greater reduction in pain in the intervention group compared to controls. Disability outcomes were reported in six studies of patient-focused interventions. Statistical heterogeneity prevented pooling in the short and intermediate term (I<sup>2</sup> = 99%, I<sup>2</sup>=57%, respectively). Overall, two studies demonstrated a greater reduction in disability compared to controls. Quality-of-life outcomes were reported in three studies of patient-focused interventions. Overall, one study had a small effect on quality-of-life mental and physical composite scores.</p>
Countries	United States of America, Australia, Denmark	
Setting	No restrictions of setting.	
Risk of Bias assessment tool	Cochrane Risk of Bias Tool. GRADE for certainty of evidence rating.	
Risk of Bias assessment (as performed by review authors)	No trials were low risk of bias using the Cochrane risk of bias tool. Heterogeneity prevented the assessment of the overall quality of evidence using a Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.	
Conflicts of interest of review authors	SM, GF, MH, JJ report no conflicts of interest. CM is funded by an NHMRC Senior Research Fellowship. He is chief investigator or co-investigator on multiple previous and current research grants from government agencies and charities in Australia and internationally. He has received travel expenses for speaking at conferences from the professional organisations hosting the conferences. He is an investigator on the SHaPED trial which received heat wraps at no cost from Flexeze. AM has received untied research funding from GlaxoSmithKline to the Sydney Pharmacy School for a postgraduate student scholarship under his supervision. MU is chief investigator or co-investigator on multiple previous and current research grants from the UK National Institute for Health Research, Arthritis Research UK and is a co-investigator on grants funded by the Australian NHMRC; he is an NIHR Senior Investigator. MU has received travel expenses for speaking at conferences from the professional organisations hosting the conferences. MU is a director and shareholder of Clinvivo Ltd that provides electronic data collection for health services research and is part of an academic partnership with Serco Ltd related to return to work initiatives. MU is a co-investigator on two NIHR funded studies receiving support in kind from Stryker Ltd. MU has accepted honoraria for teaching/lecturing from CARTA; was an editor of the NIHR journal series, and a member of the NIHR Journal Editors Group, for which he received a fee; and a co-investigator on an NIHR funded trial of opioid withdrawal ISRCTN49470934.	
Type of evidence	Systematic Review	
Citation of review	Nabal M, et al. (2011) <sup>15</sup>	
Search last updated	2010	
Number of studies	12	
Objective	To perform a systematic literature review of the evidence of the efficacy and toxicity of NSAIDs or paracetamol added to WHO Step III opioid treatment for cancer pain.	
Conclusion	The evidence from the available clinical trials is of limited amount and quality, but it weakly supports the proposal that the addition of an NSAIDs to WHO Step III	

	opioids can improve analgesia or reduce opioid dose requirement. There is insufficient evidence to support the use of paracetamol in combination with Step III opioids. Data on the toxicity of NSAIDs in this indication are insufficient owing to the small number of patients and the short duration of treatment reported in the studies.	
Review characteristics	What review authors looked for	What review authors found
Study Design	RCTs	RCTs
Participants	Persons with cancer pain	Participants = 196 – NSAIDs group Participants = 200 – Paracetamol group Demographics not described. Seven studies compared NSAIDs/opioid combinations with opioid alone <sup>8</sup> and five investigated paracetamol/opioid combinations.
Intervention and comparison	Step III opioid	A: Opioid + NSAID B: Opioid + Paracetamol
Outcomes (For each intervention / comparison pair)	Pain relief Side effects Opioid consumption	Three of the seven eligible studies showed an improvement in analgesia after the addition of one NSAIDs to Step III opioids, and two studies showed a decrease in the opioid dose needed to obtain the same level of analgesia.  Only one of five studies demonstrated a marginal analgesic advantage of combining paracetamol with morphine or hydromorphone
Countries	Not reported	
Setting	No restrictions identified. Not reported.	
Risk of Bias assessment tool	Cochrane Handbook for Systematic Reviews of Interventions	
Risk of Bias assessment (as performed by review authors)	Most studies were carried out on a small number of patients (Tables 2 and 3), and sample size calculations were not reported by several. Some studies had large losses to follow- up (>20%), and they often did not perform intention-to-treat analyses. Most studies had short follow-up (1–5days), and only two studies had longer observation periods (from 21 to 42 days). In four of them, there was evidence of sponsorship by industries.	
Conflicts of interest of review authors	None declared.	
<b>Type of evidence</b>	<b>Systematic Review</b>	
Citation of review	Nielsen S, et al. (2017) <sup>25</sup> - Only results of clinical studies included	
Search last updated	29 October 2015	
Number of studies	9	
Objective	To determine the opioid-sparing potential of cannabinoids.	
Conclusion of the review	One of the nine clinical studies (case series, n = 3) provided very-low-quality evidence of an opioid sparing effect. Prospective high-quality-controlled clinical trials are required to determine the opioid-sparing effect of cannabinoids.	
Review characteristics	What review authors looked for	What review authors found
Study Design	Human or animal studies.	5 Randomised control trials, 1 case series, 4 laboratory studies

Participants	Humans or animals.	750 (3-360)  Heterogeneous clinical populations included in the review: mixed pain conditions, chronic pain, cancer related pain, as well as healthy volunteers who were opioid / cannabinoid naive.
Intervention and comparison	Concurrently administered opioids and cannabinoids  vs  Opioid treatment alone or placebo.	<b>A:</b> Concurrently administered opioids and cannabinoids vs Opioid treatment alone.  <b>B:</b> Concurrently administered opioids and cannabinoids vs placebo.  One study had no placebo or control condition for comparison
Outcomes	Primary outcome: Evidence of the opioid sparing effect of cannabinoids.  Secondary outcomes: Analgesia, sleep, quality of life.	Three studies examined pain responses in participants concurrently being administered opioids and cannabinoids.  One study recruited people with mixed chronic non-cancer pain (n =24) who were prescribed opioids. A significant reduction in pain ratings was observed following co-administration of cannabinoids—39.6 (95% CI 35.8, 43.3) at baseline vs 29.1 (95% CI 25.4, 32.8) following co-administration.  In two studies, healthy volunteers (n =12 and 13, respectively) participated in crossover studies, with single doses of placebo, morphine alone, dronabinol alone, and dronabinol and morphine combined administered over four sessions and did not identify a synergistic effect on experimental pain in healthy controls.  One case series examining the effects of cannabinoid administration in patients with chronic non-cancer pain, three patients with mixed pain conditions reported reductions in opioid requirements after initiation of smoked cannabis plant material.  One small, nonrandomized study of patients with advanced cancer pain found that 5 out of 12 patients achieved pain control after receiving a cannabis infusion, compared with 2 out of 14 achieving pain control in the control group—a non-statistically different effect.  Two randomized controlled trials examined delta-9-THC: Cannabidiol (THC: CBD) combination oral sprays compared to a

	<p>placebo in patients with cancer pain who were taking opioids and found improved analgesia compared to the placebo. Johnson et al (2010) found no effect of THC: CBD on breakthrough opioid dose requirements. Portenoy et al (2012) conducted a dose ranging study, using fixed dose ranges of the THC: CBD combination. In this study, a significant analgesic effect was only found in the lowest dose group, with poorer tolerability observed for higher doses.</p> <p>Two controlled studies examined the effects of dronabinol: one in patients with mixed chronic pain and one in patients with prostate cancer. Narang et al (2008) found significantly reduced pain intensity with the opioid–cannabinoid combination compared to opioid alone. Additional improvements in sleep, energy, and social functioning were reported in a week open-label phase of the same study.</p> <p>Side effects such as nausea, drowsiness and dizziness were more frequent with higher doses of cannabinoids.</p>
Countries	Not specified.
Setting	No restrictions on setting. Setting of interventions not described in review.
Risk of Bias assessment tool	Not reported. GRADE ratings reported with risk of bias assessment criteria noted.
Risk of Bias assessment (as performed by review authors)	GRADE criteria used to score quality of clinical studies. 1 study was rated as very-low quality, 3 provided low-quality evidence, 2 were rated as moderate and 3 RCTs were deemed to be high quality. Important limitations identified in these clinical studies included a lack of placebo control, difficulties extrapolating from experimental to clinical pain, use of single doses, use of small sample sizes, and the mixed quality of the study design in general.
Conflicts of interest of review authors	SN is supported by a NHMRC Research Fellowship (#1013803). The National Drug and Alcohol Research Centre at the University of New South Wales is supported by funding from the Australian Government under the Substance Misuse Prevention and Service Improvements Grant Fund. The contents of the published material are solely the responsibility of the authors and do not reflect the funding bodies. MAW has received a grant to his institution from CanniMed. BLF has received speaker fees or consulting fees from Allergan, Mettrum, CCIC, Mylan Pharmaceutical, Pfizer, Ethypharm, Richter Pharmaceuticals, and Lundbeck. He also received salary/grant support from Pfizer and Bioprojet, and in kind support from GW Pharma, Mylan Pharmaceuticals, and Brainsway. SN and NL have been investigators on untied educational grants from Reckitt-Benckiser. SN and MF have been investigators on an untied education grant from Indivior. KEK has previously received a speaker’s honorarium from Pfizer and Mundipharma, in addition to fees from an advisory board and an educational grant from Seqirus. As Director of NDARC, MF notes that the National Drug and Alcohol Research Centre has received untied educational grants from Mundipharma and Indivior. MF took part in a single research advisory board with Indivior in 2014.
Type of evidence	Systematic Review
Citation of review	Pollard EM, et al. (2019) <sup>17</sup>
Search last updated	December 31, 2017

Number of studies	5	
Objective	To synthesize the evidence regarding the effect of spinal cord stimulation (SCS) on opioid and pain medication reduction in patients with intractable spine or limb pain.	
Conclusion of the review	Statistically significant decreases in opioid and pain medication use followed SCS. However, available data were limited, and the clinical significance of these findings will require further study. Ultimately, the inconsistency and heterogeneity with which pain medication changes were reported make difficult to draw conclusions.	
Review characteristics	What review authors looked for	What review authors found
Study Design	Randomised controlled trials	Randomised controlled trials
Participants	Patients with chronic and intractable back and/or limb pain of greater than one-year duration.	489 (36-171)  Mean age years: 54.6 intervention, 55.2 control. Male gender: 38% intervention, 41.4% control.  The trial populations include patients with painful diabetic neuropathy, failed back surgery syndrome, chronic back or leg pain and painful peripheral vascular disease.
Intervention and comparison	Spinal cord stimulation (SCS)  Vs  Medical therapy  OR  Conventional SCS vs high frequency SCS	<b>A:</b> Conventional SCS vs medical therapy  <b>B:</b> Conventional SCS vs high frequency SCS
Outcomes	Pain medication reduction  Pain medication outcomes were of two types in all the manuscripts reviewed:  1) A binary outcome of achieving a reduction or elimination in opioids or  2) Reduction in pain medication as measured by the Medication Quantification Scale (MQS) or morphine equivalent dosing (OMMED).	The odds of reducing opioid consumption were significantly increased in the Spinal Cord Stimulation group compared to medical therapy (OR 8.60, CI (1.93-38.30)). Two of the trials reported the results as mean medication dose reduction as measured by the Medication Quantification Scale (MQS) in the SCS group vs medical therapy group. MQS score significantly decreased in the SCS group and not in the medical group (WMD – 1.97, 95% CI {–3.67, –0.27}).  One trial reported a number of patients in high-frequency SCS who were able to reduce opioids vs number of patients in conventional SCS group who were able to reduce opioids. Thirty-four percent of the patients in the high-frequency group and 26% of the patients in the conventional SCS group were able to reduce opioid consumption; however, there was not a significant difference between groups (OR 1.43, 95% CI (0.74, 2.78)). In the high-frequency SCS group, average OMMED

		<p>decreased by 24.8 mg vs average OMMED decrease of 7.3 mg in the conventional SCS group. Again, the difference between groups did not reach statistical significance (–17.50, CI {–66.27, 31.27}).</p> <p><u>Adverse events:</u> Adverse events reporting differed considerably among different trials. Most adverse events were hardware related such as implant site reactions. There was one report of subdural hematoma associated with patient death.</p>
Countries	Netherlands, Denmark, Belgium, Germany., Canada, United States of America, Australia and Israel.	
Setting	No setting restrictions. Single centre and multicentre studies were included.	
Risk of Bias assessment tool	Cochrane Risk of Bias Tool	
Risk of Bias assessment (as performed by review authors)	Overall, the risk of bias across all the trials for the outcome of opioid reduction was moderate.	
Conflicts of interest of review authors	Tim J Lamer M.D. was involved in research funded by Boston Scientific and Medtronic. All funds were paid to his institution.	
<b>Type of evidence</b>	<b>Systematic Review</b>	
Citation of review	Ratnayake, et al. (2020) <sup>23</sup>	
Search last updated	2019	
Number of studies	7	
Objective	To summarize the effectiveness and complications of Spinal Cord Stimulation in the management of pain associated with chronic pancreatitis.	
Conclusion	Spinal Cord Stimulation has a potentially efficacious role in reducing pain and opioid use in patients with chronic pancreatitis.	
Review characteristics	What review authors looked for	What review authors found
Study Design	No restrictions	1 observational cohort study, 2 case series, and 4 case reports
Participants	Patients who underwent spinal cord stimulation for chronic visceral pain associated with chronic pancreatitis.	<p>31 (1-20)</p> <p>The estimated median age of the study group was 44 years (range 21-87 years) in primarily non-alcoholic chronic pancreatitis (74%, 23/31).</p> <p>The estimated median pain duration was seven years (range 2-18 years).</p>
Intervention and comparison	<p>Spinal cord stimulation</p> <p>Vs</p> <p>Absence of intervention, usual care or no comparator.</p> <p>All patients were trialled with percutaneously inserted leads for temporary stimulation for a period that ranged from 4 to 14 days.</p>	<p><b>A:</b> Spinal cord stimulation vs usual care</p> <p><b>B:</b> Spinal cord stimulation vs no comparator</p>

<p>Outcomes (For each intervention / comparison pair)</p>	<p><u>Primary:</u> Reduction in visual analogue scale (VAS) pain scores and morphine equivalent opioid usage.</p> <p><u>Secondary:</u> Trial period completion rate, follow-up time, and complications.</p>	<p>All patients reported an improvement in pain. The estimated median reduction of visual analogue pain scores was 61% (range 50%-100%) from a median of 8 cm (range 3-10) to a median of 3.3 cm (range 0-5).</p> <p>The morphine equivalent opioid usage showed an estimated median reduction of 69% (range 25%-100%) from a median of 154 mg (range 60-680) to a median of 53 mg (range 0-510 mg) post-SCS at the end of follow-up (less than one to greater than two years).</p> <p>Two studies reported complications with the SCS electrodes within the follow-up period. Lead infection at the site of the lead in two (6%) patients and lead migration in two (6%) patients were the only reported complications.</p> <p>Functional capacity was reported in two studies. One reported an improvement in the pain disability index from a score of 62 to 15 and the other reporting an improvement in the Korean brief pain inventory from 45 to 42.</p>
<p>Countries</p>	<p>Articles were published from the USA (N = 4), Korea (N = 1), New Zealand (N = 1), and United Kingdom (N = 1).</p>	
<p>Setting</p>	<p>No setting restrictions.</p>	
<p>Risk of Bias assessment tool</p>	<p>Risk of bias for all case reports and case series was assessed with Murad et al. (17), a non-randomized study risk of bias assessment tool comprised eight binary questions across four domains providing a total calculated score of eight.</p> <p>The risk of bias for the single observational cohort study was assessed with the aid of the methodological index for nonrandomized studies (MINORS) criteria</p>	
<p>Risk of Bias assessment (as performed by review authors)</p>	<p>Case reports: The median score was 4.5 out of 8 (range: 3-5). Significant deficiencies were observed pertaining to an appropriate length of follow-up (N = 5) and excluding alternative causes for observations (N = 5).</p> <p>Cohort study: The total score was 8 out of 16 where major deficiencies were observed in the prospective collection of data, loss to follow-up, appropriate follow-up period, and study size calculation.</p>	
<p>Conflicts of interest of review authors</p>	<p>The authors reported no conflict of interest.</p>	

### **Risk of Bias**

Where the authors of a systematic review conducted a risk of bias assessment of primary studies, we reported the tool used and the findings of this risk of bias assessment in accordance with guidance from the Cochrane Handbook.<sup>7</sup> These assessments are summarised in Table 3. The majority of reviews used the Cochrane Risk of Bias Tool, however, other tools such as the methodological index for nonrandomized studies (MINORS) criteria and The Mixed Methods Appraisal Tool (MMAT) were employed. The risk of bias assessments of the primary body of evidence was used to inform the risk of bias rating in GRADE.

The risk of bias assessment (ROBIS) ratings for reviews included in the overview of reviews is provided in [Appendix 2](#). In domain 1, which assessed any concerns regarding specification of study eligibility criteria, 12 reviews achieved a low risk of bias rating overall. Domain 3 assessed concerns regarding methods used to collect data and appraise studies and 10 studies achieved a low risk of bias rating. With regard to domain 4, which assessed concerns regarding the synthesis and findings, 3 were assessed as high risk of bias and 10 scored low risk of bias. The final section provides a rating for the overall risk of bias of the review in which six reviews achieved a low risk of bias rating and seven were rated as being at high risk of bias.

### **Certainty of Evidence (GRADE)**

Evidence was initially graded based on study design and was downgraded (one or two levels) for the following five reasons: limitations, inconsistencies, indirectness, inaccuracy, and other (including publication bias). The GRADE Summary of Findings Tables ([Table 5](#), [Table 7](#) and [Table 8](#)) provide details on the study design, outcomes, level of evidence and overall GRADE ratings for each key clinical question.

We present a summary of the assessments of each of the GRADE criteria below and the data used to assess each GRADE domain. Downgrading reasons are also included as footnotes for each GRADE table in accordance with the guidance of Santesso et al.<sup>26</sup>

### **Risk of Bias**

The risk of bias of the subset of studies contributing to the outcome of interest were informed by the risk of bias assessments conducted by the authors of the included systematic reviews. Specific reasons for downgrading due to risk of bias concerns are included as footnotes in each GRADE table. Common reasons for concerns and downgrading included: lack of blinding in RCTs, incomplete accounting of patients and outcome events, selective outcome reporting (particularly in relation to adverse events) and the use of unvalidated outcome measures (e.g. patient-reported outcomes). The body of evidence had a high proportion of uncontrolled observational studies with unclear fidelity to interventions and limitations in reporting of outcomes, and short term follow-up. The nature of the study design and outcomes created significant potential for re-call bias and there was difficulty in adequately controlling for confounders.

### **Inconsistency**

The certainty of evidence was downgraded for inconsistency when the results varied across the body of primary evidence and the variation could not be explained by underlying study differences (populations, interventions or outcomes). Specific reasons for downgrading due to inconsistency are included as footnotes in each GRADE table. Downgrading was performed where inconsistency reduced the GDGs confidence in relation to a particular outcome and recommendation. Where a meta-analysis (or other synthesis) was performed, we presented relevant I2 values. Where inconsistency could be explained by subgroups, the GDG considered individual recommendations for different populations (e.g. cancer survivor vs non-cancer pain populations) and focussed on effect estimates from studies with a lower risk of bias.

### **Imprecision**

Imprecision was assessed based on effect estimates where available, considering the confidence interval of benefit and harmful outcomes. Due to the nature of the evidence obtained, imprecision was often assessed based on number of events, or number of participants reported. The GDG often downgraded evidence based on the number of patients included in a study or review for a particular outcome or where there was a wide confidence interval (CI) around the estimate of the effect. Specific reasons for downgrading due to imprecision are included as footnotes in each GRADE table.

### **Indirectness**

Indirectness was assessed by considering the characteristics of primary studies and how these related to the guideline questions. Specific reasons for downgrading due to indirectness are included as footnotes in each GRADE table. There were significant concerns about the nature of the populations and interventions examined and their applicability to the guideline target population. This was particularly relevant for key clinical question 3, where the primary evidence focussed on pain-related outcomes rather than opioid deprescribing related outcomes.

### **Publication (reporting) bias**

Funnel plots contained in the included systematic reviews informed the GDGs assessment of publication bias. The GDG did not downgrade the evidence down for any outcome due to publication bias as we did not strongly suspect bias due to missing results. We do however note, that there was concern about the potential of selective reporting of outcomes due to the lack of reporting on adverse effects.

### **Strengths and Limitations**

We utilised a broad systematic search strategy and two independent authors conducted article screening and determined the overall quality of evidence according to the GRADE criteria. Potential limitations of this overview pertain to the inclusion of both randomised and observational studies, making it difficult to identify a cause-effect relationship between the

intervention and outcomes. Both date and language refinements were used and, as such, internationally relevant articles or articles published prior to the date range may have been missed. It is also possible that publication bias may have affected the results of this review as negative studies regarding the impact of interventions may not have been published. The overview methodology means that there may be primary studies on the effectiveness of interventions that have not been captured and additional supplementary searches were required for Key Clinical Question 2. Finally, due to the differences in outcome measure and study designs, we were not able to directly compare different interventions for opioid deprescribing in terms of overall effectiveness.

## Key Clinical Question 1: Does deprescribing of opioids result in benefits or harms compared to continuation?

The evidence informing Key Clinical Question 1 was derived from an overview of twelve systematic reviews (methods described previously). A supplemental search of existing guidelines was conducted to inform the benefits and harms of opioid deprescribing for individuals with opioid use disorders to inform Recommendation 6. This search was not systematically performed and involved reviewing the lists of guidelines from resources such as National Guideline Clearinghouse, NHMRC Clinical Guidelines Portal, NICE, SIGN, WHO and searching Pubmed and Google using terms relating to the concepts of ‘opioid’, ‘opioid use disorder’ ‘deprescribing’ and ‘guideline’. The search was conducted in August 2021. Nine guidelines were identified which contained recommendations relating to opioid deprescribing in adults with an opioid use disorder in the last ten years. Guidelines considered in the evidence review are presented in [Table 4](#). The GRADE Summary of Findings Table for Key Clinical Question 1 is presented in [Table 5](#).

**Table 4. Guidelines included in evidence review**

Guideline Authors	Guideline Title	Date (Year)
Adams E, et al. <sup>27</sup>	A Guideline for the Clinical Management of Opioid Use Disorder.	2017
Bruneau J, et al. <sup>28</sup>	Management of opioid use disorders: a national clinical practice guideline	2018
Gowing L, et al. <sup>29</sup>	National Guidelines for Medication-Assisted Treatment of Opioid Dependence.	2014
Handford C, et al. <sup>30</sup>	Buprenorphine/Naloxone for Opioid Dependence: Clinical Practice Guideline	2012
Kampan K and Jarvis M <sup>31</sup>	American Society of Addiction Medicine (ASAM) National Practice Guideline for the Use of Medications in the Treatment of Addiction Involving Opioid Use	2015
Korownyk C, et al. <sup>32</sup>	Managing opioid use disorder in primary care: PEER simplified guideline.	2019
Soyka M, et al. <sup>33</sup>	The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of substance use and related disorders. Part 2: Opioid dependence.	2011
Substance Abuse and Mental Health Services Administration. <sup>34</sup>	Medications for Opioid Use Disorder. Treatment Improvement Protocol (TIP) Series 63	2018
Waller RC. <sup>35</sup>	Medication Assisted Treatment Guidelines for Opioid Use Disorders	2014

## Evidence-Based Recommendations

### Conditional Recommendation For, Very Low Certainty Evidence

We suggest initiating deprescribing for persons taking opioids for chronic non-cancer pain, if (any of the following):

- a) there is a lack of overall and clinically meaningful improvement in function, quality of life or pain,
- b) there is a lack of progress towards meeting agreed therapeutic goals, OR
- c) the person is experiencing serious or intolerable opioid-related adverse effects in the physical, psychological or social domains.

### Summary of evidence from overview

Consistent low certainty evidence suggested that mean pain scores and functional measures improved, or did not significantly change, for most persons with chronic non-cancer pain who reduced or discontinued opioids. Reporting of quality of life measures were heterogeneous across reviews, however, very low certainty evidence suggests that quality of life may improve with opioid deprescribing. Opioid deprescribing may be associated with a reduction in opioid-related adverse effects. Serious harms of opioid deprescribing remain uncertain, including substance use, opioid overdose, and suicide.

### Conditional Recommendation Against, Moderate Certainty

We recommend avoiding opioid deprescribing for persons taking opioids with a severe opioid use disorder, and recommend providing evidence-based care such as transition to, or referral for, medication assisted treatment of opioid use disorder.

### Summary of evidence from overview

A retrospective study of Medicaid claims data found that among a cohort of 694 Medicaid recipients who had a high prevalence of substance use disorders (60%) on  $\geq 120$ mg OMEDD, almost half (49%) of participants who discontinued opioids subsequently had an ED visit or hospitalisation due to opioid poisoning or substance use disorder.<sup>22</sup> In this study, opioids were most often discontinued without a gradual taper (median length of time to discontinuation was 1 day) and  $< 1\%$  of participants were prescribed medication to treat substance use disorders.<sup>22</sup>

### Summary of evidence from supplementary guideline search

Supplementary searches provided moderate certainty evidence that opioid deprescribing, when performed without providing access to long-term opioid maintenance treatment and care, is associated with elevated risk of harm and death from drug overdose. Therefore, opioid deprescribing should not be initiated as a sole strategy for individuals with an opioid use disorder.<sup>27-35</sup> Evidence indicated that opioid agonist or partial agonist treatment with

methadone or buprenorphine maintenance therapy was more effective in preventing relapse than opioid withdrawal and cessation. Methadone and buprenorphine for opioid dependence have been found to increase retention in treatment and to decrease illicit opioid use among persons with an opioid use disorder, however, the evidence base primarily relates to the use of heroin rather than prescription opioids.

The GDG suggested that many individuals taking opioids for pain conditions may fulfil the criteria of a mild opioid use disorder in accordance with DSM-IV diagnostic criteria.<sup>36</sup> We therefore categorised this recommendation as ‘conditional’ as individuals with mild or moderate opioid use disorders may be suitable to trial opioid deprescribing if deemed suitable by the healthcare professional and person taking opioids. Further, the evidence informing this recommendation was largely in the context of individuals with severe opioid use disorders pertaining to illicit opioid use (heroin) rather than prescription opioids. Additionally, in terms of values and preferences, some persons taking opioids for pain may wish to attempt deprescribing or undertake withdrawal management without transition to opioid maintenance therapy. As such, there is a need to consider the individual person’s circumstances, preferences and values.

### **Consensus-Based Recommendations**

#### **Consensus Recommendation**

We suggest developing and implementing a deprescribing plan for persons being prescribed opioids at the point of opioid initiation.

#### **Summary of evidence from overview**

There was insufficient evidence to determine whether the development and implementation of a deprescribing plan at the point of opioid initiation reduces long-term opioid use or opioid-related harms, as no studies were identified on this topic. This recommendation is informed by evidence of persistent opioid use following initial opioid prescription.

#### **Consensus Recommendation**

We suggest initiating deprescribing for persons taking opioids for chronic cancer-survivor pain if, (any of the following):

- a) there is a lack of overall and clinically meaningful improvement from baseline in function, quality of life or pain,
- b) there is a lack of progress towards meeting agreed therapeutic goals, OR
- c) the person is experiencing serious or intolerable opioid-related adverse effects in the physical, psychological or social domains

### **Summary of evidence from overview**

There was insufficient evidence to inform an evidence-based recommendation for deprescribing opioids in persons with chronic cancer-survivor pain due to a lack of data on the benefits and harms of opioid deprescribing in this population.

#### **Consensus Recommendation**

We suggest considering deprescribing for persons taking opioids for chronic pain with one or more of the following clinical characteristics:

- a) Co-morbidities which may increase risk of opioid related harms e.g. sleep-disordered breathing or sleep apnoea, chronic obstructive pulmonary disease (COPD).
- b) Concomitant use of medicines or substances with sedating effects e.g. benzodiazepines, alcohol, gabapentinoids, antipsychotics and sedating antidepressants.
- c) High doses of prescribed opioids.

### **Summary of evidence from overview**

We did not find any studies within our overview of reviews which linked the identified demographics or clinical characteristics to the benefits and harms of opioid deprescribing.

#### **Consensus Recommendation**

We suggest avoiding deprescribing for persons taking opioids for pain or dyspnoea who are nearing the end-of-life.

### **Summary of evidence from overview**

There is insufficient evidence to inform the benefits and harms of opioid deprescribing for people with pain who are nearing the end-of-life. We did not find any studies that reported on opioid deprescribing in this population group.

**Table 5. GRADE Summary of Findings – Key Clinical Question 1**

No. of studies (Participants)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect	GRADE Certainty of Evidence Rating
<b>Opioid deprescribing compared to continuation (Chronic non-cancer pain)</b>							
<b>Pain</b>							
35 <sup>37-71</sup> (6305)	7 RCTs, 28 observational studies	Serious <sup>1,2</sup>	Not serious	Serious <sup>3,4</sup>	Not serious	Mean pain scores improved, or did not significantly change, for most persons with chronic non-cancer pain who reduced or discontinued opioids. 80% of studies showed improved pain after tapering, 15% of studies showed pain was the same by taper completion. Among studies reporting mean pain scores at baseline and endpoint, improvements were greatest (19-47%) in studies of patients on higher baseline OMEDD (99-177 mg) and more modest (8-10%) among studies of patients with lower baseline OMEDD (47-61 mg).	⊕⊕⊕⊕ LOW
<b>Function</b>							
11 <sup>38 57-61 63 65 66 72 73</sup> (4529)	1 RCT, 10 observational studies	Serious <sup>1,5</sup>	Not serious	Serious indirectness <sup>3</sup>	Not serious	Function may improve or remain unchanged following opioid deprescribing. Voluntary intensive pain management interventions may result in improvements in function. Those who deprescribe opioids with less intensive co-interventions may have unchanged function.	⊕⊕⊕⊕ LOW
<b>Quality of Life</b>							
16 <sup>41 45 47 49 65 69 70 72 74-81</sup> (3818)	3 RCT, 13 observational studies	Serious <sup>1,5</sup>	Not serious	Serious indirectness <sup>3</sup>	Serious <sup>6,8</sup>	Reporting of quality of life measures were heterogeneous across reviews, however, a majority of studies suggested that quality of life may improve with opioid deprescribing.	⊕⊕⊕⊕ VERY LOW
<b>Adverse events</b>							
7 <sup>73 82-87</sup> (32,834)	4 RCTs, 3 observational studies	Serious <sup>1,2</sup>	Serious <sup>7</sup>	Serious indirectness <sup>3</sup>	Serious <sup>6</sup>	There was no risk difference between groups (deprescribing intervention vs usual care) for the number of participants reporting adverse events in the short term (risk difference 0.1, 95% CI – 0.1 to 0.3) or in the intermediate term (risk difference 0.0, 95% CI – 0.1 to 0.1). Opioid deprescribing may be associated with a reduction in opioid-related adverse effects. Serious harms of opioid deprescribing remain uncertain, including substance use, opioid overdose, and suicide.	⊕⊕⊕⊕ VERY LOW
<b>Opioid deprescribing compared to continuation (Opioid use disorder)</b>							
<b>Adverse events</b>							

g <sup>27-35</sup> (unable to estimate)	Guidelines*	No serious risk of bias	No serious inconsistency	Serious indirectness <sup>8</sup>	No serious imprecision	Opioid deprescribing, when performed without providing access to long-term opioid maintenance treatment and care, is associated with elevated risk of harm and death from drug overdose.	⊕⊕⊕○ MODERATE
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Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations. OMEDD = Oral Morphine Equivalent Daily Dose, \*Note: GRADE assessment derived from assessments contained within included guidelines.

<sup>1</sup> High proportion of uncontrolled observational studies, significant potential for unmeasured confounders

<sup>2</sup> Inadequate reporting and handling of missing data

<sup>3</sup> Studies were not designed to answer the specific research question, variability in populations – sub-groups not adequately specified. Variable doses of opioids and deprescribing approaches.

<sup>4</sup> Tapering procedure was only described in 40% of studies, unclear fidelity to interventions

<sup>5</sup> Variable reporting of outcome measures and scales used to assess response, predominantly self-reported

<sup>6</sup> Many studies contain small sample sizes, small number of adverse effect events reported

<sup>7</sup> Inconsistency in primary studies for correlation between reducing opioid use and overdose rates

<sup>8</sup> Only applicable to severe opioid use disorder, may not reflect general population of persons taking opioids

## Key Clinical Question 2: What is the evidence on how to deprescribe opioids?

The evidence informing Key Clinical Question 2 was derived from an overview of twelve systematic reviews (methods described previously). The overview of systematic reviews found limited evidence to inform the best approach for opioid deprescribing. As such, a supplemental search of primary literature was conducted to inform the evidence on how best to deprescribe opioids. A search in EMBASE and MEDLINE was performed using terms relating to the concepts of 'opioid', 'pain' and 'deprescribing' in August 2021. No date restriction was used for this search. The search strategies are presented below.

### i) EMBASE

1. exp narcotic agent/ or exp narcotic analgesic agent/ or exp narcotic antagonist/
2. opiate/ or \*opiate agonist/
3. opioid\*.mp.
4. 1 or 2 or 3
5. exp pain/
6. exp injury/
7. exp neuralgia/ or exp neuropathy/
8. exp musculoskeletal pain/ or exp musculoskeletal disease/
9. exp arthritis/ or exp arthropathy/
10. osteoarthritis.mp. or osteoarthritis/
11. 5 or 6 or 7 or 8 or 9 or 10
12. deprescri\* or de-prescri\* or unprescri\* or cease\* or ceasing\* or cessation\* or withdraw\* or discontinu\* or stop\*.mp.
13. 4 and 11 and 12

### ii) MEDLINE

1. exp Narcotics/
2. (narcotic\* or opioid\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. 1 or 2
4. exp Pain/
5. exp Headache Disorders/
6. exp joint diseases/
7. exp muscular diseases/ or exp peripheral nervous system diseases/
8. exp "Wounds and Injuries"/
9. 4 or 5 or 6 or 7 or 8

10. deprescri\* or de-prescri\* or unprescri\* or cease\* or ceasing\* or cessation\* or withdraw\* or discontinu\* or stop\*.mp.
11. 3 and 9 and 10

Screening of primary study articles was performed by one author. Six primary studies were considered for inclusion. A summary of the included studies is presented in The GRADE Summary of Findings Table for Key Clinical Question 2 is presented in [Table 7](#).

**Table 6. Primary studies included in evidence review**

Authors	Study Title	Date (Year)
Hooten et al. <sup>88</sup>	Varenicline for opioid withdrawal in patients with chronic pain: a randomized, single-blinded, placebo controlled pilot trial.	2015
Tennant FS, et al. <sup>89</sup>	Treatment of Prescription Opioid Dependence: Comparison of Two Methods.	1982
Webster L, et al. <sup>86</sup>	Evaluation of the Tolerability of Switching Patients on Chronic Full $\mu$ -Opioid Agonist Therapy to Buccal Buprenorphine.	2016
Bienek N, et al. <sup>90</sup>	Intensity of Withdrawal Symptoms During Opioid Taper in Patients with Chronic Pain-Individualized or Fixed Starting Dosage?	2019
Ralphs JA, et al. <sup>91</sup>	Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods.	1994
Cowan DT, et al. <sup>81</sup>	A randomized, double-blind, placebo-controlled, cross-over pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine.	2005

### Evidence-Based Recommendations

Although the certainty of evidence for Recommendation 7 and 8 were rated as ‘Low’ and ‘Very Low’ respectively, a ‘Recommendation For’ has been presented. The GDG was confident that the desirable effects of the proposed interventions outweigh the undesirable effects and that most or all individuals will be best served by the recommended course of action.

#### **Recommendation For, Low Certainty of Evidence**

We recommend gradual tapering of opioids. Abrupt cessation of opioids without prior dose reduction may increase risks of harm.

### Summary of Evidence from overview

We were unable to evaluate which tapering characteristics were associated with the greatest benefits and harms, some information could be gleaned about the rate and nature of successful opioid deprescribing approaches. One cohort study contained within the overview of systematic reviews found that for people prescribed 120 mg OMEDD or more of long-term

opioid therapies, each additional week to discontinuation was associated with a 7% reduction in risk of an opioid-related emergency department visits or hospitalisation, supporting the benefit of gradual tapering.<sup>87</sup> Characteristics from studies included in the evidence synthesis which showed benefit included gradual reductions (over 22 weeks in 1 study).<sup>22</sup>

### **Summary of Evidence from primary studies**

There were very few relevant studies identified and evidence on the comparative effectiveness of opioid deprescribing approaches was largely limited to small, observational studies, or examined populations using opioid maintenance therapies.<sup>81 86 88-91</sup>

#### **Recommendation For, Very Low Certainty of Evidence**

We recommend tailoring the deprescribing plan based on the person's clinical characteristics, goals and preferences.

### **Summary of Evidence from overview**

Given the heterogeneity of studies examining opioid deprescribing and the limited reporting of deprescribing protocols and participant baseline characteristics, we were unable to assess the comparative effectiveness of different opioid tapering approaches on clinical outcomes such as pain and function. The evidence informing the benefits and harms of opioid deprescribing which demonstrated improvements in pain, function and quality of life were largely derived from studies involving voluntary opioid deprescribing.<sup>19 22</sup> Evidence of increased harms (suicide, overdose, illicit opioid use) in the context of involuntary opioid deprescribing informed the need for voluntary opioid deprescribing where possible.<sup>22 92</sup>

### **Summary of Evidence from primary studies**

There were very few relevant studies identified and evidence on the comparative effectiveness of opioid deprescribing approaches was largely limited to small, observational studies, or examined populations using opioid maintenance therapies.<sup>81 86 88-91</sup>

### **Consensus-Based Recommendations**

#### **Consensus Recommendation**

We suggest conducting regular monitoring and review of a person taking opioids throughout the opioid deprescribing process. Response against agreed therapeutic goals contained in a deprescribing plan should be regularly assessed.

### **Summary of Evidence from overview**

There was insufficient evidence to inform an evidence-based recommendation on monitoring associated with opioid deprescribing.

**Table 7. GRADE Summary of Findings – Key Clinical Question 2**

No. of studies (Participants)	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect	GRADE Certainty of Evidence Rating
<b>Comparative effectiveness of different deprescribing approaches</b>							
Pain, function and quality of life							
None	-	-	-	-	-	No direct evidence. Where tapering approach was documented, the majority of studies examined gradual or individualised tapers.	–
Adverse events							
1 <sup>87</sup> (494)	Uncontrolled Cohort study	Serious <sup>1</sup>	Not serious	Serious <sup>2</sup>	Not serious	For a cohort prescribed 120 mg OMEDD or more of long-term opioid therapies, each additional week to discontinuation was associated with a 7% reduction in risk of an opioid-related emergency department visits or hospitalization.	⊕⊕○○ LOW
<b>Comparative effectiveness of voluntary and involuntary deprescribing</b>							
Pain, function and quality of life							
None	-	-	-	-	-	No direct evidence. Where tapering approach was documented, the majority of studies examined voluntary, individualised tapers.	–
Adverse events							
1 <sup>82</sup> (509)	Retrospective case-control study	Serious <sup>1,3,4</sup>	Not serious	Serious <sup>5,6</sup>	Serious <sup>7</sup>	509 participants who underwent healthcare professional-initiated tapers, 47 (9.2%) participants had new-onset suicidal ideation and 12 participants (2.4%) had suicidal self-directed violence in the year following opioid discontinuation.	⊕○○○ VERY LOW

Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations. OMEDD = Oral Morphine Equivalent Daily Dose

<sup>1</sup> Failure to adequately control confounding, inadequately short follow-up

<sup>2</sup> Study population has limited generalisability (60% person with substance use disorder, mean OMEDD >=120mg)

<sup>3</sup> Use of unvalidated outcome measures (e.g. patient-reported outcomes), selection of exposed and unexposed in cohort studies from different populations

<sup>4</sup> Possible/unclear selective reporting of outcomes

<sup>5</sup> Study population has limited generalisability (94.3% male, chronic non-cancer pain, 75% of tapers due to aberrant behaviours)

<sup>6</sup> Patients with substance use disorders

<sup>7</sup> Relatively few patients and few events, wide confidence interval (CI) around the estimate of the effect

## Key Clinical Question 3: Which interventions are effective to facilitate opioid deprescribing?

The evidence informing Key Clinical Question 3 was derived from an overview of twelve systematic reviews (methods described previously). The GRADE Summary of Findings Table for Key Clinical Question 3 on the effectiveness of interventions to facilitate opioid deprescribing is presented in [Table 8](#).

### Evidence-Based Recommendations

#### Conditional Recommendation For, Low Certainty Evidence

When available, we suggest the use of interdisciplinary or multidisciplinary care which emphasises non-pharmacological and self-management strategies to deprescribe opioids.

#### Summary of Evidence from overview

Interdisciplinary, multidisciplinary and multimodal care which emphasised non-pharmacologic and self-management strategies showed the greatest evidence for effective opioid deprescribing.<sup>19 22</sup> Non-drug interventions in these programs included cognitive behavioural therapy, physiotherapy and occupational therapy. The direct evidence for the effect of interdisciplinary or multidisciplinary care on the outcome of opioid dose reduction is of low certainty. People on long-term opioid therapy who voluntarily participated in intensive multidisciplinary pain management interventions which incorporated opioid tapering experienced improvements in pain severity and function.<sup>17-22</sup> In contrast, those who tapered opioids with less intensive co-interventions were more likely to experience unchanged pain and function.<sup>19 22</sup>

#### Conditional Recommendation For, Very Low Certainty Evidence

We recommend the consideration of evidence-based co-interventions to support opioid deprescribing.

#### Summary of Evidence from overview

Evidence for the effectiveness of different co-interventions to achieve opioid reduction or cessation for the management of chronic pain was inconclusive and varied substantially across the interventions examined. Our overview identified reviews examining pharmacological, physical, interventional, psychological or behavioural, or mixed interventions. Opioid reduction varied widely across reviews and the interventions that were examined throughout the study periods. Consistent low certainty evidence suggests that regardless of intervention, mean pain scores and functional measures improved or did not significantly change for most persons who reduced or discontinued opioids.<sup>14 16-23 25</sup> Improvements in quality of life may accompany opioid dose reduction when using deprescribing co-interventions.<sup>14 19 22</sup>

**Table 8. GRADE Summary of Findings – Key Clinical Question 3**

Outcome: Opioid reduction / cessation								
Intervention	Number of Studies (participants)	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Effect	GRADE Rating
Cannabinoids	3 <sup>93-95</sup> (285)	2 controlled trials, 1 case series	Serious <sup>1</sup>	Serious <sup>2</sup>	Serious <sup>3</sup>	Serious <sup>4</sup>	Two controlled studies found no effect. One case series showed a reduction in opioid dose requirements with cannabinoid co-administration.	⊕○○○ VERY LOW
Buprenorphine	10 <sup>77 78 86 96-102</sup> (470)	3 RCTs, 7 observational	Serious <sup>5</sup>	Serious <sup>2</sup>	Serious <sup>3</sup>	Serious <sup>4</sup>	Mean opioid discontinuation rate, 91% (range, 33%–100%).	⊕○○○ VERY LOW
Ketamine	2 <sup>79 103</sup> (47)	controlled observational, 1 uncontrolled observational	Serious <sup>7</sup>	Not Serious	Not Serious	Serious <sup>4</sup>	Opioid discontinuation rates of 18% and 27%.	⊕⊕○○ LOW
Detoxification (Clonidine and benzodiazepines )	3 <sup>81 104 105</sup> (102)	1 RCT, 2 uncontrolled observational	Serious <sup>7</sup>	Not Serious	Not Serious	Serious <sup>4</sup>	Mean opioid discontinuation rate, 91% (range, 91%–100%).	⊕⊕○○ LOW
Nonsteroidal anti-inflammatory drugs (NSAIDs)	2 <sup>106 107</sup> (66)	2 RCTs	Serious <sup>6</sup>	Not Serious	Serious <sup>8</sup>	Not Serious	Two studies showed a reduction of opioid consumption – in one, morphine requirements were significantly reduced (95m to 83 mg). Second study reported reduction in morphine consumption with the addition of ketorolac without values provided.	⊕⊕○○ LOW
Acetaminophen (Paracetamol)	3 <sup>108-110</sup> (108)	3 RCTs	Serious <sup>6</sup>	Not Serious	Serious <sup>8</sup>	Not Serious	No evidence of effect.	⊕⊕○○ LOW
Acupuncture / acupressure	5 <sup>111 112 113-115</sup> (184)	3 RCTs, 3 uncontrolled observational	Serious <sup>9</sup>	Not Serious	Not Serious	Not Serious	Cancer Pain: MD, –30.00 mg morphine equivalent daily dose; 95% CI, –37.5 mg to –22.5 mg. Chronic non-cancer pain: Opioid discontinuation rates of 66% and 86%	⊕⊕⊕○ MODERATE
Physical therapy	1 <sup>116</sup> (46)	1 uncontrolled observational	Serious <sup>10</sup>	Not Serious	Not Serious	Serious <sup>4</sup>	Overall trend of decreased medication usage during and after the intervention in all pain medication categories except opioids. Opioid usage did not increase during the study period, rather remained the same.	⊕⊕○○ LOW
Cryoablation	22 <sup>117-138</sup> (496)	1 RCT, 21 observational	Serious <sup>11</sup>	Not Serious	Serious	Serious	Statistically significant reduction in postintervention opioid use (ranging from 60% after 24 hours to 77% at 3 months). 36% to 97%of patientsare able to stop taking opioids at some point during the follow-up (13,18,21)	⊕○○○ VERY LOW

Spinal cord stimulation (SCS)	5 <sup>139-143</sup> (489)	RCTs	Not Serious	Not Serious	Serious <sup>3</sup>	Not Serious	Median reduction of 69% (range 25%-100%) from a median of 154 mg (range 60-680) to a median of 53 mg (range 0-510 mg) post-SCS	⊕⊕⊕○ MODERATE
Therapeutic Interactive Voice Response (TIVR)	1 <sup>70</sup> (51)	RCT	Not serious	Not serious	Not serious	Serious <sup>4</sup>	Reduced the mean opioid dose significantly at 4-month (P = 0.04) and 8-month (P = 0.004) follow-up compared with usual care. At 8-month follow-up, 21% of intervention group had discontinued use of opioid analgesics.	⊕⊕⊕○ MODERATE
Mind-body therapies (MBTs)*	8 <sup>144-151</sup> (435)	3 RCTs, 2 controlled observational, 3 uncontrolled observational	Not serious	Serious <sup>2</sup>	Not serious	Not serious	Overall, MBTs had a significant, small association with opioid use (Cohen d = -0.26; 95% CI, -0.44 to -0.08; P = .01)	⊕⊕⊕○ MODERATE
Multidisciplinary pain programs	7 <sup>58 63-66 72 75</sup> (4274)	1 controlled observational, 6 uncontrolled observational	Serious <sup>1,9</sup>	Not Serious	Serious <sup>11</sup>	Serious <sup>4,12</sup>	Opioid discontinuation rate of 87% (range 29%-100%).	⊕⊕○○ LOW
Multi-component tapering support	2 <sup>73 74</sup> (70)	1 RCT, 1 uncontrolled observational study	Serious <sup>13</sup>	Not Serious	Not Serious	Serious <sup>14</sup>	One dose-reduction protocol reduced the daily opioid dose in the short term. Dose reduction protocol did not reduce opioid dose in the intermediate term [mean difference (MD) – 19.9 OMEDD, 95% CI – 107.5 to 67.7].	⊕⊕○○ LOW

Key to GRADE quality of evidence: ⊕⊕⊕⊕ = We are very confident in the reported associations; ⊕⊕⊕○ = We are moderately confident in the reported associations; ⊕⊕○○ = Our confidence in the reported associations is limited; ⊕○○○ = We are not confident about the reported associations. \*Includes Mindfulness / meditation, Therapeutic suggestion, Hypnosis, Guided imagery, Cognitive behavioural therapy (CBT)  
 OMEDD = Oral Morphine Equivalent Daily Dose, SCS = Spinal Cord Stimulation, MBTs = Mind-body therapies

<sup>1</sup>Nonrandomized design, lack of placebo control.

<sup>2</sup>Significant heterogeneity across studies

<sup>3</sup>Study population has limited generalisability (E.g. only a single dose was examined, cancer-pain and mixed conditions examined)

<sup>4</sup>Some studies present small sample size, small number of events reported

<sup>5</sup>Studies transitioned patients to buprenorphine with heterogeneity of induction protocol, dose, and duration of therapy

<sup>6</sup>Large loss to follow up in some studies (>20%), short follow up (1 to 14 days)

<sup>7</sup>Study quality rated as 'poor' by review authors

<sup>8</sup>Variability in drug and doses given, baseline characteristics not well defined

<sup>9</sup>High risk of performance and detection bias owing to nonblinding

<sup>10</sup>uncontrolled observational studies, significant potential for unmeasured confounders

<sup>11</sup>Intervention may have limited applicability due to access and means of participants

<sup>12</sup>Participant self-reported data without adequate blinding

<sup>13</sup>Suspected performance bias (blinding of participants and personnel)

<sup>14</sup>Considerable statistical (I<sup>2</sup> = 92%) and clinical heterogeneity

## Appendix 1 - Risk of bias of systematic reviews (ROBIS)

Appendix Table 1. Risk of Bias assessment (ROBIS)

Study	Domain 1	Domain 2	Domain 3	Domain 4	Overall
Ferrer-Mileo L, et al. (2018)	LOW	HIGH	LOW	HIGH	HIGH
Fishbain DA, et al. (2019)	LOW	UNCLEAR	LOW	HIGH	HIGH
Frank K, et al. (2017)	LOW	HIGH	LOW	LOW	HIGH
Garland EL, et al. (2020)	LOW	LOW	LOW	LOW	LOW
Hassan S, et al. (2019)	LOW	LOW	LOW	HIGH	HIGH
He Y, et al. (2019)	LOW	LOW	LOW	LOW	LOW
Mackey K, et al. (2020)	HIGH	HIGH	LOW	LOW	HIGH
Mathieson S, et al. (2020)	LOW	LOW	LOW	LOW	LOW
Nabal M, et al. (2011)	LOW	HIGH	UNCLEAR	LOW	HIGH
Nielsen S, et al. (2017)	LOW	LOW	LOW	LOW	LOW
Pollard EM, et al. (2019)	LOW	LOW	UNCLEAR	LOW	LOW
Ratnayake CB, et al. (2020)	LOW	HIGH	LOW	HIGH	HIGH

## Appendix 2 - Evidence-to-Decision Frameworks

Appendix Table 2. Evidence-to-decision Framework for Key Clinical Question 1

<b>Question</b>	Does deprescribing of opioids result in benefits or harms compared to continuation?		
<b>Population</b>	Adult (>18) taking opioids for any duration and for any pain condition		
<b>Intervention</b>	Opioid Deprescribing		
<b>Comparison</b>	Opioid Continuation		
<b>Main Outcomes</b>	Pain Physical Function Quality of life Adverse events		
<b>Settings</b>	No setting restrictions		
<b>Assessment</b>			
Criteria	Judgement	Summary of evidence	Additional considerations
Does the balance between desirable and undesirable effects favour the intervention (opioid deprescribing) or the comparison (opioid continuation)?	<input type="checkbox"/> Favour comparator <input type="checkbox"/> Probably favours comparator <input checked="" type="checkbox"/> Probably favours the intervention <input type="checkbox"/> Favour the intervention <input type="checkbox"/> Varies <input type="checkbox"/> Don't know	<p><b>Summary:</b> The evidence of benefits and harms of opioid deprescribing primarily relates to persons with chronic non-cancer pain. Important harms of opioid continuation were identified, including opioid-related adverse effects such as constipation and nausea. Serious and intolerable adverse effects such as opioid use disorders, respiratory depression and overdose were also of concern. There was a lack of evidence for the benefit of long term opioids in reducing pain and improving function for persons with chronic non-cancer pain.</p> <p><b>Benefits of opioid deprescribing vs continuation:</b> Consistent low quality evidence suggests that mean pain scores and functional measures improved or did not significantly change for most patients who reduced or discontinued opioids. Reporting of quality of life measures were heterogeneous across reviews, however, many studies reported improved quality of life after opioid dose</p>	<p>Is the baseline risk for benefit and harms of deprescribing similar across subgroups?</p> <p>Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p>There is a difference in baseline risk for benefit and harms of deprescribing for those with/without an opioid use disorder. There may also be differences based on clinical characteristics including the indication for opioid use, dose, co-morbidities and concomitant medication use.</p> <p>Should there be separate recommendations for subgroups?</p> <p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p>

reduction. Reduced opioid-related adverse effects such as nausea and constipation were associated with opioid deprescribing. The benefits of deprescribing on pain scores were greater for those on higher baseline opioid doses (measured in daily morphine milligram equivalents) compared to those with lower baseline doses.

**Harms of deprescribing vs continuation:** Across reviews, a small number of participants withdrew from the deprescribing cohorts due to worsening symptoms/lack of efficacy. Serious adverse events resulting from opioid deprescribing were infrequently reported but included suicidal self-directed violence and overdose. Evidence regarding the impact of deprescribing on serious harms including substance use, opioid overdose, and suicide was lacking.

Based on this evidence, the panel has identified specific conditions under which the risks associated with opioid continuation are believed to outweigh the benefits and therefore recommend deprescribing:

- a) there is a lack of overall improvement in function, quality of life and/or pain,
- b) there is a lack of progress toward meeting established therapeutic goals, OR
- c) the person is experiencing serious or intolerable opioid-related adverse effects in physical, psychological or social domains

**Subgroups:**

There was a relative lack of evidence pertaining to the benefits and harms of opioid deprescribing in persons with cancer-related or cancer-survivor pain. There was a small body of evidence which

Subgroups for consideration:

- End-of-life care pain
- Chronic cancer-survivor pain
- Individuals with opioid use disorders

Additionally, clinical characteristics may increase the risk of opioid-related harms. Baseline risk of adverse events with continued opioid use may be higher for persons with:

- a) Sleep disordered breathing or sleep apnoea
- b) Chronic Obstructive Pulmonary disease
- c) Concomitant use of medicines or substances with sedating effects. For example; benzodiazepines, alcohol, pregabalin.
- d) Polypharmacy or multiple medication use
- e) Prescribed higher doses of opioids

showed reduced pain and improved quality of life accompanying opioid deprescribing interventions for cancer patients. Due to the known harms of long-term opioid use, and increasing cancer survivorship, the panel expects to see similar benefit and harms in the population of cancer-survivors as those with chronic non-cancer pain.

We do not have evidence for benefits or harms of opioid deprescribing for persons with end-of-life care pain. The panel has placed an emphasis on symptom management for populations with limited life expectancy and therefore, recommended against opioid deprescribing in this population unless deemed appropriate by the treating clinician.

Persons with opioid use disorder were often excluded from the reviews which were examined in our overview of reviews. This population group is not routinely examined in the opioid deprescribing literature. We sought additional evidence to inform recommendations for this population. Moderate-quality evidence indicates that opioid deprescribing, when performed without providing access to long-term addiction treatment and care, is associated with elevated risk of harms and death from drug overdose. There was limited evidence pertaining to persons with mild-moderate opioid use disorders. As such, in the case of individuals with a suspected or diagnosed severe opioid use disorder, we recommend against using deprescribing as a sole strategy due to evidence of increased harms.

The certainty of evidence for the benefits of deprescribing is **very low to low**.

The certainty of evidence for the harms of deprescribing is **very low**.

What is the overall certainty of the evidence of effects?  
 Very low  
 Low  
 Moderate  
 High

**Key reasons for downgrading:** Study design, risk of bias, indirectness.

**Certainty of evidence for benefits:** Very low to low from overview of systematic reviews

<p>Given the benefits and harms, what choice do you expect patients to make?</p>	<input type="checkbox"/> Very high	<p>The certainty of evidence for harms of deprescribing in the population of persons with severe opioid use disorders is <b>moderate</b>.</p>	<p>containing both randomized controlled trials (RCTs) and non-randomised studies.</p>
	<p> <input type="checkbox"/> Favour comparator  <input checked="" type="checkbox"/> Probably favours comparator  <input type="checkbox"/> Probably favours the intervention  <input type="checkbox"/> Favour the intervention  <input checked="" type="checkbox"/> Varies  <input type="checkbox"/> Don't know         </p>	<p>Certainty of evidence was downgraded due to study design with systematic reviews including both RCTs and non-randomised studies. The panel had concerns about attrition bias in the intervention groups and the selective reporting of outcomes, particularly relating to adverse effects. Strict inclusion and exclusion criteria across studies limited generalisability. Populations examined in reviews and primary studies were relatively homogenous (predominantly middle aged, Caucasian women) with limited co-morbidities which may not be reflective of the general population using opioids. Outcomes were often measured in the short term and maintenance was not assessed.</p> <p>Both healthcare professionals and persons taking opioids expressed resistance to change. Opioid continuation, rather than deprescribing, was identified as the current default behaviour.</p> <p><b>Persons taking opioids:</b> Persons taking opioids expressed a general desire to reduce or cease opioid therapies, however they believed engaging and persevering with opioid deprescribing was difficult. Persons taking opioids placed a high value on achieving pain relief and maintaining quality of life, but also on avoiding the adverse events related to opioid use such as nausea, vomiting, fatigue, impaired cognition and constipation. Other adverse effects, including risk of addiction, were of lesser importance to the interviewed population. Persons taking opioids were also concerned about the negative effects of opioid deprescribing such as withdrawal effects, increased pain, and functional limitations.</p>	<p><b>Certainty of evidence for harms:</b> Very low from overview of systematic reviews containing both randomized controlled trials (RCTs) and non-randomised studies. Certainty of evidence of harms from additional systematic review sought which examines persons with opioid use disorders is moderate.</p> <p><b>Perspective taken:</b> Evidence suggests there are persons who wish to discontinue opioids to avoid side effects and the harms of long terms use. There are others who may be hesitant or may have failed or difficult deprescribing attempts due to increased pain and/or decreased function and quality of life after dose reduction or cessation.</p> <p><b>Source of values and preferences:</b> Two qualitative studies were conducted with key stakeholder groups (healthcare professionals and persons taking opioids) regarding opioid deprescribing and the development of opioid deprescribing guidelines.</p>

Significant emotional distress was caused by the perceived stigma associated with opioid use and persons taking opioids described judgement from family, friends, and healthcare professionals. Expressing a desire to initiate or continue opioids made some people feel type cast as “addicts” by healthcare professionals.

**Healthcare professionals:** Deprescribing of opioids was thought to be more challenging than continuation, requiring more time and effort. Opioids were considered more challenging to deprescribe than other medication classes due to medication related factors such as dependence and euphoria. Concerns about opioid continuation contributing to misuse, dependence, opioid-related overdoses and mortality were expressed by healthcare professionals. Conversely, there were concerns expressed about the potential harms of opioid deprescribing such as withdrawal symptoms and pain exacerbations. A lack of appropriate alternative analgesia available for pain management were viewed as a barrier to opioid deprescribing.

Healthcare professionals also expressed concerns about potential disruptions to patient-provider relationships if opioid deprescribing is not desired by the person taking opioids. This may be further exacerbated if there is difficult or failed deprescribing attempts.

It is likely that the deprescribing of opioids, if guided by an explicit and mutually agreed management plan, may be acceptable to both persons taking opioids and healthcare professionals.

**Persons taking opioids:** There may be acceptability concerns if opioid deprescribing is involuntary or occurs without the consent of the person taking opioids. In our qualitative study, persons taking opioids requested increased communication between

**Source of variability, if any:** There was substantial variability in values and preferences. Sources of variability may include pain category (e.g. acute pain, chronic pain), pain and function scores, duration of opioid use, opioid dose, education levels and health literacy.

**Method for determining values satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

Is the intervention acceptable to patients, their caregivers and healthcare providers?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

**Perspective taken:** Evidence suggests there are persons who wish to discontinue opioids to avoid side effects and the harms of long terms use. There are others who may be hesitant or may have failed or difficult deprescribing attempts due to increased pain and/or decreased function and quality of life after dose reduction or cessation. Several factors may influence the acceptability of

healthcare professionals and consumers about the deprescribing process, including potential benefits, expectations surrounding tapering, and assurance regarding continued support throughout deprescribing. Addressing these factors may increase the acceptability of opioid deprescribing.

The societal stigma toward opioid use disorders and opioid substitution therapy, coupled with the regulatory framework in Australia relating to the prescribing of opioid substitution therapy, may impact the acceptability of opioid deprescribing or alternative management options.

**Healthcare professionals:** Healthcare professionals may not find it acceptable to continue to prescribe opioids due to the nature of Australia's current regulatory framework. Opioid deprescribing may be more acceptable to healthcare professionals than ongoing opioid prescribing.

Planned opioid reduction at the point of prescribing was thought to create an expectation to deprescribe, minimising potential disruptions to therapeutic relationships during therapy withdrawal.

Opioid deprescribing may require close monitoring and engagement between the person taking opioids and the healthcare professional. As such, this may have implications for acceptability for primary healthcare professionals (general practitioners) due to increased workload in the form of additional time and effort spent engaging in opioid deprescribing.

opioid deprescribing for persons taking opioids and healthcare professionals.

**Source of acceptability:** Two qualitative studies were conducted with key stakeholder groups (healthcare professionals and persons taking opioids) regarding opioid deprescribing and the development of opioid deprescribing guidelines. Additional acceptability considerations have been proposed by guideline development group members.

**Source of variability, if any:** There is some variability between acceptability of opioid deprescribing between persons taking opioids and healthcare professionals.

**Method for determining acceptability satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

Is the intervention feasible for patients, their caregivers and healthcare providers?

No  
 Probably no  
 Probably yes  
 Yes  
 Varies  
 Don't know

How large are the resource requirements (costs)?

Large  
 Moderate  
 Neutral  
 Moderate savings  
 Large savings  
 Varies  
 Don't know

**Policymakers:** Given the potential net harms of opioids use at the population level, widespread use and continuation of opioids for chronic non-cancer pain may not be acceptable to policy-makers.

**Opioid deprescribing:** Opioid deprescribing may involve multidisciplinary and multimodal pain management strategies and services and therefore may be difficult to access or implement. This may particularly be the case in rural or remote areas, among socially-disadvantaged individuals, or in primary care settings where resources or access to multidisciplinary or specialist services are limited. In such cases the barriers to opioid deprescribing may make a recommendation difficult to implement without additional resources. Further detail relating to opioid deprescribing interventions can be found in evidence-to-decision (EtD) question 3.

**Opioid continuation:** Opioids are a widely-available and feasible treatment option. Direct costs of prescription opioid analgesics to individuals are generally relatively low, although prescribing rules in Australia require frequent visits to healthcare providers for ongoing prescriptions which may result in higher out-of-pocket costs.

The societal costs of chronic non-cancer pain are significant. Potential costs to society of widespread use of opioids for chronic non-cancer pain include direct and indirect costs relating to overdose, misuse, dependence and altered productivity. The societal costs of opioid misuse and abuse and are also considerable. Indirect costs include the economic burden of untreated opioid dependence, drug-related crime, illicit opioid use and loss of productivity.

**Is opioid deprescribing generally available?**

Yes  No

Yes, however co-interventions to support opioid deprescribing may be less readily available (See EtD Question 3 for further detail).

**Opportunity cost:** Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?

Yes  No

Economic and preventive benefits for harms at an individual and societal level.

**Is there lots of variability in resource requirements across settings?**

Yes  No

Deprescribing in isolation is a low resource intervention, feasible for primary and long term care. Additional monitoring required during deprescribing may increase resource requirements.

The addition of co-interventions to support deprescribing would increase the cost but may

What would be the impact on health equity?

- Large
- Moderate
- Negligible
- Varies
- Don't know

Socioeconomic factors are important determinants of chronic pain, opioid use and opioid-related adverse outcomes. Populations which are disproportionately impacted by opioid related harms may be expected to derive the greatest benefit from opioid deprescribing.

Populations which may require additional support or consideration when implementing opioid deprescribing and related co-interventions include: culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, Aged Care Facility residents, individuals with co-morbidities such as dementia, those in the justice system and those with a severe opioid use disorder.

provide benefits in terms of efficacy, and clinical outcomes. (See EtD Question 3 for further detail).

**Perspective taken:** Opioid deprescribing may have moderate impacts on health equity.

**Source of equity:**

Equity implications discussed amongst guideline development group.

**Source of variability, if any:** We anticipate substantial variability in equity implications across population groups.

**Method for determining equity satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

**Appendix Table 3. Evidence-to-decision Framework for Key Clinical Question 2**

<b>Question</b>	What is the evidence on how to deprescribe opioids?		
Population	Adult (>18) taking opioids for any duration and for any pain condition		
Intervention	Opioid Deprescribing		
Comparison	Opioid Continuation		
Main Outcomes	Pain Physical Function Quality of life Adverse events		
Settings	No setting restrictions		
<b>Assessment</b>			
<b>Criteria</b>	<b>Judgement</b>	<b>Summary of evidence</b>	<b>Additional considerations</b>
Does the balance between desirable and undesirable effects favour the intervention or the comparison?	<input type="checkbox"/> Favour comparator <input type="checkbox"/> Probably favours comparator <input checked="" type="checkbox"/> Probably favours the intervention <input type="checkbox"/> Favour the intervention <input type="checkbox"/> Varies <input type="checkbox"/> Don't know	<p><b>Rate of tapering:</b></p> <p>Abrupt opioid cessation can precipitate severe withdrawal effects. There is existing literature which demonstrates harms of abrupt opioid withdrawal such as serious withdrawal symptoms, uncontrolled pain, psychological distress and suicide.</p> <p>To our knowledge, there is no review or trial that directly compares rapid vs slower opioid deprescribing protocols in persons with chronic non-cancer pain. One primary study suggested that more gradual tapers reduced the risk of serious harms. In the cohort study of persons prescribed 120 mg OMEDD or more of long-term opioid therapy, each additional week to discontinuation associated with a 7% reduction in risk of an opioid-related emergency department visit or hospitalization.</p>	<p>Is the baseline risk for benefit of deprescribing similar across subgroups?</p> <p>Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p>There is no evidence to suggest different subgroups would benefit or harm from different mechanisms of opioid deprescribing at this time.</p> <p>Should there be separate recommendations for subgroups based on risk levels?</p> <p>Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p>Insufficient evidence to guide differences in recommendations for subgroups.</p>

In our overview of reviews, we were not able to evaluate which patient or tapering characteristics were associated with greater success of deprescribing or ascertain differences in clinical outcomes based on tapering schedule. This was largely due to the heterogeneity across patient baseline characteristics, interventions, and the lack of adequate reporting of tapering schedules used. When a tapering protocol was documented, it was often general and described gradual or individualised opioid reductions rather than specific schedules. Whether to taper the short-acting opioid first or the long-acting opioid first in sequence is not known nor has been compared.

Many of the tapering schedules were reported as being individualised to the specific participant and their needs. We acknowledge that individuals will have different starting doses and formulations of opioids. As such, the panel recommends individualised and person-centred opioid deprescribing. Individualisation of the rate and nature of deprescribing may require additional monitoring and input from healthcare professionals.

The evidence base for benefits and harms of opioid deprescribing derived from the overview of systematic reviews is largely from studies involving voluntary opioid deprescribing. We also note there is evidence relating to increased harms (suicide, overdose, illicit opioid use) in the context of involuntary opioid deprescribing.

What is the overall certainty of the evidence of effects?

- Very low
- Low
- Moderate
- High
- Very high

Given the benefits and harms, what choice do you expect patients to make?

- Favour comparator
- Probably favours comparator
- Probably favours the intervention
- Favour the intervention
- Varies
- Don't know

The certainty of evidence relating to the rate and nature of deprescribing is **very low**.

There are a lack of studies or reviews comparing opioid deprescribing schedules and their outcomes, as well as lack of evidence regarding the management of individuals who experience unsuccessful opioid deprescribing attempts or do not complete tapers. These populations are often excluded from analysis.

**Persons taking opioids:** Failed or difficult deprescribing attempts, either self-initiated or under the supervision of a healthcare professional, undermined beliefs in being able to discontinue opioids. Some participants spoke of severe withdrawal effects, pain exacerbations, or reduction in function when attempting deprescribing. Participants who experienced negative consequences of abrupt opioid withdrawal spoke of mistrust of healthcare professionals and expressed trepidation in reattempting deprescribing. Many participants had trialled other medications for pain without significant improvement in symptoms and opted to continue opioids. By contrast, previous successful dose reduction attempts positively influenced self-efficacy. Observed improvements in opioid-related side effects and decreased pill burdens encouraged continuation of deprescribing.

Persons taking opioids requested increased communication between healthcare professionals and themselves about the deprescribing process, including potential benefits, expectations surrounding tapering, and assurance regarding continued support throughout deprescribing. Opioid consumers advocated for

**Key reasons for downgrading:** Study design, risk of bias, indirectness, missing data.

**Certainty of evidence:** Very low from overview of systematic reviews containing both randomized controlled trials (RCTs) and non-randomised studies, as well as primary studies.

**Perspective taken:** Persons engaging in opioid deprescribing would want to minimise adverse outcomes and maximise the chance of successful deprescribing.

**Source of values and preferences:** Two qualitative studies were conducted with key stakeholder groups (healthcare professionals and persons taking opioids) regarding opioid deprescribing and the development of opioid deprescribing guidelines.

**Source of variability, if any:** There was variability in values and preferences. Sources of variability may include pain category (e.g. acute pain, chronic pain), pain and function scores, duration of opioid use, opioid dose, education levels and health literacy, previous attempts at deprescribing and relationships with healthcare professionals.

**Method for determining values satisfactory for this recommendation?**

additional resources and information to inform decision making about opioid use. Yes  No

**All critical outcomes measured?**

The desire to deprescribe opioids and one's belief in the ability to achieve opioid reduction was significantly influenced by relationships with healthcare professionals. A consideration for individual circumstances was believed to be beneficial when broaching the topic of opioid deprescribing. Tailoring recommendations to individuals was requested, rather than reiterating population-level benefits of opioid deprescribing. Furthermore, it was reinforced that guidelines would need to be flexible to account for individual circumstances and only be used if the person taking opioids was willing to have opioids deprescribed. Yes  No

Most persons taking opioids stated that they had not actively raised the topic of deprescribing with their prescriber and felt that if they agreed to deprescribing, their prescriber would be reluctant to allow re-initiation or dose increases in the future. Consumers felt that the power lay with the prescriber and that they were not equal partners in decision making.

**Healthcare professionals:**

Some participants saw deprescribing as an essential component of prescribing and advocated for a treatment agreement to be made between each patient and prescriber at the point of initiation regarding how opioids are going to be used, when to assess efficacy and when to withdraw. Planned opioid reduction at the point of prescribing was thought to create an expectation to

deprescribe, minimising potential disruptions to therapeutic relationships during therapy withdrawal. A structured and holistic approach to deprescribing was considered optimal, with adjunct or alternate analgesic agents, non-pharmacological pain management strategies and involvement of multidisciplinary healthcare members. There was some concern about guidelines and their ability to be applicable to the heterogeneous group of individuals who consume opioids. As such, it was thought that opioid deprescribing guidelines would require a multi-target, multimodal intervention strategy. Healthcare professionals suggested that functional measures, quality of life measures and overall risk reduction should be considered when assessing the effectiveness of opioid deprescribing in addition to pain outcome measures.

Is the intervention acceptable to patients, their caregivers and healthcare providers?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

It is likely that the deprescribing of opioids, if guided by an explicit and mutually agreed management plan, may be acceptable to both patients and healthcare professionals.

**Persons taking opioids:** It is likely that a gradual and individualised deprescribing approach which is modified based on an individual's clinical progress and needs would be acceptable to persons taking opioids. There may be acceptability concerns if opioid deprescribing is involuntary or occurs without the consent of the person taking opioids. In our qualitative study, persons taking opioids requested increased communication between healthcare professionals and consumers about the deprescribing process, including potential benefits, expectations surrounding tapering, and assurance

**Perspective taken:** Persons engaging in opioid deprescribing would want to minimise adverse outcomes and maximise the chance of successful deprescribing.

**Source of values and preferences:** Two qualitative studies were conducted with key stakeholder groups (healthcare professionals and persons taking opioids) regarding opioid deprescribing and the development of opioid deprescribing guidelines.

**Source of variability, if any:** There may be variability in acceptability. Sources of variability may include pain category (e.g. acute pain, chronic pain), pain and function scores, duration

regarding continued support throughout deprescribing. Addressing these factors may increase the acceptability of opioid deprescribing.

of opioid use, education levels and health literacy.

The association between opioid deprescribing and retention in healthcare is unclear and as such our overview of reviews does not provide significant insight into the acceptability of opioid deprescribing.

**Method for determining values satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

**Healthcare professionals:**

Planned opioid reduction at the point of prescribing was thought to create an expectation to deprescribe, minimising potential disruptions to therapeutic relationships during therapy withdrawal and may increase healthcare professional's acceptability.

Gradual opioid deprescribing may require close monitoring and engagement with between person and healthcare professional. As such, this may have implications for acceptability for primary healthcare professionals (general practitioners) due to increased workload in the form of additional time and effort spent engaging in opioid deprescribing.

**Opioid deprescribing:** Opioid deprescribing may involve regular clinician follow up which may be difficult for persons to access. This may particularly be the case in rural or remote areas, among socially-disadvantaged individuals, or in primary care settings where appointment times and bookings are limited. In such cases the barriers to opioid deprescribing may make a recommendation difficult to implement without additional resources.

**Is opioid deprescribing generally available?**

Yes  No

Yes, however regular monitoring and follow-up with clinicians may impact upon intervention feasibility.

Is the intervention feasible for patients, their caregivers and healthcare providers?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

How large are the resource requirements (costs)?

- Large
- Moderate
- Neutral
- Moderate savings
- Large savings
- Varies
- Don't know

Medicare and the public hospital system provide free or low-cost access for all Australians to many healthcare services. Private health insurance provides choice outside the public system and requires individuals to contribute toward the cost of healthcare. Approximately 53% of the Australian population has some form of private health insurance. People living in major cities are the most likely to have private health insurance. Those with private health insurance may still incur out-of-pocket costs for 'medical gaps'.

Transitions of care have been identified as a target area to implement a deprescribing plan (E.g. when persons are discharged from hospital on opioids). Targeting of transitions of care may be a feasible intervention strategy.

**Opioid continuation:** Direct costs of prescription opioid analgesics to individuals are generally relatively low, although prescribing rules in Australia require frequent visits to healthcare providers for ongoing prescriptions which may result in higher out-of-pocket costs or may have an impact on work.

The societal costs of chronic non-cancer pain are significant. Potential costs to society of widespread use of opioids for chronic non-cancer pain include direct and indirect costs relating to overdose, misuse, dependence and altered productivity. The societal costs of opioid misuse and abuse are also considerable. Indirect costs include the economic burden of untreated opioid

**Opportunity cost:** Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?

Yes  No

Gradual and individualised deprescribing may increase resource requirements but may also improve patient outcomes and minimise withdrawal effects and harms of abrupt opioid cessation.

**Is there lots of variability in resource requirements across settings?**

Yes  No

Deprescribing in isolation is a low resource intervention, feasible for primary and long term care. Additional monitoring required during deprescribing may increase resource requirements.

The addition of co-interventions to support deprescribing would increase the cost but may provide benefits in terms of efficacy, and clinical outcomes. (See EtD Question 3 for further detail).

- What would be the impact on health equity?
- Large
  - Moderate
  - Negligible
  - Varies
  - Don't know

dependence, drug-related crime, illicit opioid use and loss of productivity.

It is possible that gradual opioid tapering which requires regular follow up with healthcare professionals may not be as accessible for individuals who have limited access to healthcare. This may be the case for those who live in rural or remote areas or are socioeconomically disadvantaged.

**Perspective taken:** Gradual opioid deprescribing with regular clinician follow up may have moderate impacts on health equity.

**Source of equity:**

Equity implications discussed amongst guideline development group.

**Source of variability, if any:** We anticipate substantial variability in equity implications across population groups.

**Method for determining equity satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

**Appendix Table 4. Evidence-to-decision Framework for Key Clinical Question 3**

<b>Question</b>	Which interventions are effective to facilitate opioid deprescribing?		
<b>Population</b>	Adult (>18) taking opioids for any duration and for any pain condition		
<b>Intervention</b>	Opioid Deprescribing		
<b>Comparison</b>	Opioid Continuation		
<b>Main Outcomes</b>	Pain Physical Function Quality of life Adverse events		
<b>Settings</b>	No setting restrictions		
<b>Assessment</b>			
<b>Criteria</b>	<b>Judgement</b>	<b>Summary of evidence</b>	<b>Additional considerations</b>
Does the balance between desirable and undesirable effects favour the intervention or the comparison?	<input type="checkbox"/> Favour comparator <input type="checkbox"/> Probably favours comparator <input checked="" type="checkbox"/> Probably favours the intervention <input type="checkbox"/> Favour the intervention <input type="checkbox"/> Varies <input type="checkbox"/> Don't know	<p>Opioid deprescribing is clinically challenging, and may be difficult to achieve and maintain. Co-interventions may assist in opioid reduction and pain management when deprescribing. Evidence for the effectiveness of different methods designed to achieve reduction or cessation of prescribed opioids for the management of chronic non-cancer pain is inconclusive and varies substantially across interventions and reviews examined. Our overview of reviews identified pharmacological, physical, interventional and psychological or behavioural interventions. Additional reviews examined multiple intervention types. Across interventions rates of opioid reduction varied widely across reviews and examined interventions (12.43 – 101.00 OMEDD)</p> <p>Persons on long term opioid therapy who voluntarily participate in intensive pain management interventions that incorporate opioid tapering may experience improvements in pain severity and pain-related function, while those who taper opioids with less intensive</p>	<p>Is the baseline risk for benefit of deprescribing interventions similar across subgroups?            Yes <input checked="" type="checkbox"/> No <input type="checkbox"/></p> <p>There is no evidence to suggest different subgroups would benefit from specific deprescribing interventions at this time.</p> <p>Should there be separate recommendations for subgroups based on risk levels?            Yes <input type="checkbox"/> No <input checked="" type="checkbox"/></p> <p>No – no evidence of benefit for any risk level.</p>

co-interventions may have unchanged pain and function. Although the best evidence for opioid deprescribing effectiveness relates to multidisciplinary interventions, the direct evidence for the effect of multidisciplinary care on the outcome of opioid dose reduction is generally low certainty. Consistent low quality evidence suggests that regardless of intervention used, mean pain scores and functional measures improved or did not significantly change for most persons who reduced or discontinued opioids. Intensive outpatient multimodal pain management programs saw greater improvements in pain related function compared to less intensive interventions.

What is the overall certainty of the evidence of effects?

Very low  
 Low  
 Moderate  
 High  
 Very high

The certainty of evidence for the effectiveness of opioid deprescribing interventions ranged from **very low** to **low**.

**Key reasons for downgrading:** Study design, risk of bias, indirectness.

Certainty of evidence was downgraded due to study design with systematic reviews including both RCTs and non-randomised studies. The panel had concerns about attrition bias in the intervention groups and the selective reporting of outcomes. Many studies examined pain as the primary outcome rather than opioid reduction and as such, this secondary outcome was poorly reported. Strict inclusion and exclusion criteria across studies limited generalisability. Populations examined in reviews and primary studies were relatively homogenous (predominantly middle aged, Caucasian women) with limited co-morbidities which may not be reflective of the general population using opioids. Outcomes were often measured in the short term and maintenance was not assessed.

**Certainty of evidence:** Very low to low from overview of systematic reviews containing both randomized controlled trials (RCTs) and non-randomised studies.

Given the benefits and harms, what choice do you

Favour comparator  
 Probably favours comparator

**Persons taking opioids:** Persons taking opioids expressed a desire to discontinue opioids because of negative physiological feedback in the form of opioid-induced side effects. Constipation, fatigue, nausea, and impaired cognition were reported. Similarly, concerns

**Perspective taken:** Evidence suggests there are patients who wish to discontinue opioids to avoid the harms of long terms use. There are others who may be hesitant and may fail due to increased pain

expect patients to make?

- Probably favours the intervention
- Favour the intervention
- Varies
- Don't know

about long-term use and the development of physical dependence were voiced. Perceived failures of the healthcare system undermined beliefs about the feasibility of opioid deprescribing. Difficulties in accessing care, limited appointment times, travel, and significant costs associated with co-interventions and alternative pain management therapies such as physiotherapy, hydrotherapy and psychotherapy were described. Waiting times to see specialists, pain clinics, or undergo surgeries were described as significant and many participants spoke of a need to continue opioids due to a lack of alternative supports.

Persons taking opioids advocated for additional resources, interventions and information to inform decision making about opioid use.

**Healthcare professionals:** A structured and holistic approach to deprescribing was considered optimal, with adjunct or alternate analgesic agents, non-pharmacological pain management strategies and involvement of multidisciplinary healthcare members. There was some concern about guidelines and their ability to be applicable to the heterogeneous group of individuals who consume opioids. As such, it was thought that prospective opioid deprescribing guidelines would require a multitarget, multimodal intervention strategy.

A lack of alternative pharmacotherapy options was deemed a contributing factor for opioid continuation. Paracetamol and non-steroidal anti-inflammatory agents were identified as possible alternative analgesics; however, participants saw limited clinical utility of these agents as opioid substitutes due to a perceived lack of efficacy, clinical contraindications in specific patient cohorts and concerns about long-term use. As such healthcare professionals

and/or decreased function after dose reduction or cessation. Co-interventions may help to facilitate opioid deprescribing,

**Source of values and preferences:** Two qualitative studies were conducted with key stakeholder groups (healthcare professionals and persons taking opioids) regarding opioid deprescribing and the development of opioid deprescribing guidelines.

**Source of variability, if any:** There was substantial variability in values and preferences. Sources of variability may include pain category (e.g. acute pain, chronic pain), pain and function scores, duration of opioid use, education levels and health literacy and access to care.

**Method for determining values satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

requested further information about additional co-interventions to support opioid deprescribing.

Workload pressures, inadequate remuneration for healthcare professionals and insufficient resources for clinicians and patients were viewed as barriers to opioid deprescribing. Specialist and multidisciplinary care were largely seen as enablers to opioid deprescribing; however, effectiveness of a multidisciplinary approach was thought to be limited by accessibility and lengthy wait times for referrals to pain clinics. Significant costs associated with alternate pain management strategies such as pain psychoeducation and physiotherapy which were thought to accompany successful opioid deprescribing, limited their applicability.

Is the intervention acceptable to patients, their caregivers and healthcare providers?

- No
- Probably no
- Probably yes
- Yes
- Varies
- Don't know

**Persons taking opioids:** It is likely that the use of appropriate co-interventions to facilitate deprescribing of opioids, may be acceptable to both patients and healthcare professionals.

Co-interventions for opioid deprescribing may take substantial time and effort to engage in (e.g. cognitive behavioural therapy) and may come with higher costs to individuals, limiting acceptability. Further, some proposed co-interventions may be invasive such as spinal cord stimulation or acupuncture which may not be acceptable.

**Healthcare professionals:**

It may not be acceptable for healthcare professionals to continue to prescribe opioids due to the nature of Australia's current regulatory framework. Opioid deprescribing may be more acceptable to healthcare professionals than ongoing opioid prescribing.

**Perspective taken:** Persons taking opioids may require additional support and interventions to engage and persevere with opioid deprescribing. The effectiveness of opioid deprescribing and clinical outcomes may improve using co-interventions.

**Source of acceptability:** Two qualitative studies were conducted with key stakeholder groups (healthcare professionals and persons taking opioids) regarding opioid deprescribing and the development of opioid deprescribing guidelines. Additional acceptability considerations have been proposed by guideline development group members.

**Source of variability, if any:** There is likely some variability between acceptability of opioid

Is the intervention feasible for patients, their caregivers and healthcare providers?

No  
 Probably no  
 Probably yes  
 Yes  
 Varies  
 Don't know

How large are the resource requirements (costs)?

Large  
 Moderate  
 Neutral  
 Moderate savings  
 Large savings  
 Varies  
 Don't know

Some healthcare professionals expressed concern that specialised and multidisciplinary services, once engaged, decrease general practitioner agency to deprescribe opioids. As such, recommendation of co-interventions for opioid deprescribing may not be acceptable to all healthcare professionals.

**Opioid deprescribing interventions:** The guideline development group acknowledges that multidisciplinary and multimodal pain management services may be difficult to access or implement. This may particularly be the case in rural or remote areas, among socially-disadvantaged individuals, or in primary care settings where resources or access to multidisciplinary or specialist services are limited. In such cases the barriers to opioid deprescribing may make a recommendation difficult to implement without additional resources.

Opioid deprescribing may involve intensive co-interventions such as multidisciplinary and multimodal pain management services. Such interventions may be difficult to access or implement. This may particularly be the case in rural or remote areas, among socially-disadvantaged individuals, or in primary care settings where resources or access to multidisciplinary or specialist services are limited. In such cases the barriers to opioid deprescribing may make a recommendation difficult to implement without additional resources.

Medicare and the public hospital system provide free or low-cost access for all Australians to many healthcare services. Private health

deprescribing interventions across the cohorts of persons taking opioids and healthcare professionals.

**Method for determining acceptability satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

**Are opioid deprescribing interventions generally available?**

Yes  No

No, co-interventions to support opioid deprescribing may be difficult to access due to cost and accessibility barriers.

**Opportunity cost:** Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?

Yes  No

Economic and preventive benefits for harms at an individual and societal level.

**Is there lots of variability in resource requirements across settings?**

Yes  No

insurance provides choice outside the public system and requires individuals to contribute toward the cost of healthcare. Approximately 53% of the Australian population has some form of private health insurance. People living in major cities are the most likely to have private health insurance. Those with private health insurance may still incur out-of-pocket costs for 'medical gaps'.

Many allied health services are provided in the community, often by practitioners operating in private practices. Allied health services can usually be accessed directly by any patient paying privately without a referral. A range of national and state-based funding schemes and programs are available to help people access allied health services such as services provided by community or aboriginal health services, Medicare funded services, and allied health services provided by aged care or disability providers. In these cases, patients may need a referral, typically from a general practitioner. Access to these services can be limited by lengthy waiting times. Additional individual costs of accessing such treatment may include transport to and from appointments.

**Opioid continuation:** Opioids are a widely-available and feasible treatment option. Direct costs of prescription opioid analgesics to individuals are generally relatively low, although prescribing rules in Australia require frequent visits to healthcare providers for ongoing prescriptions which may result in higher out-of-pocket costs or may have an impact on work.

The societal costs of chronic non-cancer pain are significant. Potential costs to society of widespread use of opioids for chronic non-cancer pain include direct and indirect costs relating to overdose, misuse, dependence and altered productivity. The societal costs of opioid misuse and abuse are also considerable.

Deprescribing in isolation is a low resource intervention, feasible for primary and long term care.

The addition of co-interventions to support deprescribing would increase the cost but may provide benefits in terms of efficacy, and clinical outcomes.

What would be the impact on health equity?

- Large
- Moderate
- Negligible
- Varies
- Don't know

Indirect costs include the economic burden of untreated opioid dependence, drug-related crime, illicit opioid use and loss of productivity.

Socioeconomic factors are important determinants of chronic pain, opioid use and opioid-related adverse outcomes. Variation in access to health professionals may delay surgical treatment or alternatives to opioid analgesics.

Populations which may require additional support or consideration when implementing opioid deprescribing co-interventions include: culturally and linguistically diverse populations, Aboriginal and Torres Strait Islander populations, Aged Care Facility residents, Individuals with co-morbidities such as dementia, those in the forensic system and those with a severe opioid use disorder.

Access to comprehensive and multidisciplinary chronic pain management services varies within Australia. Access may be limited for socially-disadvantaged people and those in regional and remote areas.

**Perspective taken:** Opioid deprescribing interventions may have moderate impacts on health equity.

**Source of equity:** Equity implications discussed amongst guideline development group.

**Source of variability, if any:** We anticipate substantial variability in equity implications across population groups.

**Method for determining equity satisfactory for this recommendation?**

Yes  No

**All critical outcomes measured?**

Yes  No

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