Efficacy of interventions to reduce long term opioid treatment for chronic non-cancer pain: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To review interventions to reduce long term opioid treatment in people with chronic non-cancer pain, considering efficacy on dose reduction and discontinuation, pain, function, quality of life, withdrawal symptoms, substance use, and adverse events.

DESIGN

Systematic review and meta-analysis of randomised controlled trials and non-randomised studies of interventions.

DATA SOURCES

Medline, Embase, PsycINFO, CINAHL, and the Cochrane Library searched from inception to July 2021. Reference lists and previous reviews were also searched and experts were contacted.

ELIGIBILITY CRITERIA FOR STUDY SELECTION

Original research in English. Case reports and cross sectional studies were excluded.

DATA EXTRACTION AND SYNTHESIS

Two authors independently selected studies, extracted data, and used the Cochrane risk-of-bias tools for randomised and non-randomised studies (RoB 2 and ROBINS-I). Authors grouped interventions into five categories (pain self-management, complementary and alternative medicine, pharmacological and biomedical devices and interventions, opioid replacement treatment, and deprescription methods), estimated pooled effects using random effects meta-analytical models, and appraised the certainty of evidence using GRADE (grading of recommendations, assessment, development, and evaluation).

RESULTS

Of 166 studies meeting inclusion criteria, 130 (78%) were considered at critical risk of bias and were excluded from the evidence synthesis. Of the 36 included studies, few had comparable treatment arms and sample sizes were generally small. Consequently, the certainty of the evidence was low or very low for more than 90% (41/44) of GRADE outcomes, including for all non-opioid patient outcomes. Despite these limitations, evidence of moderate certainty indicated that interventions to support prescribers' adherence to guidelines increased the likelihood of patients discontinuing opioid treatment (adjusted odds ratio 1.5, 95% confidence interval 1.0 to 2.1), and that these prescriber interventions as well as pain self-management programmes reduced opioid dose more than controls (intervention *v* control, mean difference −6.8 mg (standard error 1.6) daily oral morphine equivalent, P<0.001; pain programme *v* control, −14.31 mg daily oral morphine equivalent, 95% confidence interval −21.57 to −7.05).

CONCLUSIONS

Evidence on the reduction of long term opioid treatment for chronic pain continues to be constrained by poor study methodology. Of particular concern is the lack of evidence relating to possible harms. Agreed standards for designing and reporting studies on the reduction of opioid treatment are urgently needed.

REVIEW REGISTRATION

PROSPERO CRD42020140943.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Opioid tapering is the gradual reduction of opioid treatments with the goal of either reducing or discontinuing opioid use while limiting possible adverse effects, including withdrawal symptoms and increased pain

Guidelines recommend that people on long term opioid treatment for chronic non-cancer pain should consider opioid tapering when it is safe to do so and when the risks of opioid treatment outweigh the benefits

Reviews to date are inconclusive as to the most effective approach for tapering opioid treatment and the effect of such interventions on patient outcomes (eg, pain, function, and quality of life)

WHAT THIS STUDY ADDS

This review indicates that interventions supporting prescribers' adherence to opioid guidelines and participation in pain self-management programmes are probably effective in reducing opioid use by small and moderate amounts, respectively

Psychosocial support should be provided to patients tapering opioid use owing to the lack of evidence regarding the effect of opioid tapering interventions on adverse outcomes

Studies at critical risk of bias dominate this topic; agreed standards for designing and reporting studies on the reduction or discontinuation of opioids are urgently needed

Introduction

Opioid overprescribing for patients with chronic non-cancer pain, where the harms of opioid treatment outweigh the benefits, has led to the recent promulgation of guidelines recommending the reduction or discontinuation of long term opioid treatment.[1-4] The publication of these guidelines accords with the acceleration of a pre-existing downward trend in opioid prescribing.[5-7] Yet changing treatment in the context of chronic pain is not straightforward.[8-10] Tapering is the gradual reduction of opioid drug treatment with the goal to either reduce or discontinue opioids while limiting possible adverse effects such as withdrawal symptoms and increased pain. The US Centers for Disease Control

and Prevention recommends against the prescription of more than 90 mg oral morphine equivalent per day in most circumstances.[1] However, risks are involved even below this threshold, and perspectives differ as to what constitutes a safe dose.[4 11] Opioid tapering can be complicated by the onset of withdrawal symptoms as well as increased pain, suicidality, and substance use, and such risks could increase when undertaken rapidly or without patient consent.[12-14]

Previous reviews have considered the outcomes of clinical interventions to facilitate opioid tapering, including one Cochrane review and nine other systematic, scoping, and rapid reviews.[15-25] Included studies evaluate, among other things, pain management programmes, the drug management of withdrawal symptoms, and biomedical procedures. The variety of approaches to opioid tapering reflects the complexity of this process, the differing causes of chronic pain and approaches to treatment (biomedical, biopsychosocial, alternative medicine), and the presence of comorbidities such as substance use disorder. The most comprehensive review to date, published in 2017 by Frank and colleagues,[18] found very low quality evidence that several types of intervention might be effective in the reduction or discontinuation of opioid treatment, and that pain, pain related function, and quality of life could improve with opioid tapering. However, the researchers acknowledged a dearth of evidence, especially for adverse events such as overdose and suicide. Owing to a paucity of studies at low risk of bias and the difficulties associated with synthesising clinically heterogeneous interventions, prior reviews have been unable to recommend a particular intervention with better than low certainty (appendix 1).

Clinicians continue to make decisions without strong evidence. In the context of deprescription guidelines,[1-4] local and regional policy changes,[26] and attempts to reduce opioids becoming more common,[5-7] recently published studies could contribute some new evidence. However, effective supporting evidence needs to overcome the clinical heterogeneity that has mired previous systematic reviews by appropriately differentiating between treatment types. Therefore, this systematic review aims to provide a clinically relevant synthesis of up-to-date evidence on the efficacy of interventions to reduce or discontinue long term opioid treatment in patients with chronic non-cancer pain.

Methods

This review focuses on two key questions: how effective are the interventions to reduce or discontinue long term opioid treatment, and what are their effects on patient outcomes? We followed the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines[27] and registered the protocol in PROSPERO (CRD42020140943).

Data sources and searches

We developed a sensitive search strategy with the help of a research librarian based around the key concepts of "opioids," "tapering," and "pain" (appendix 2) and searched Medline, Embase, PsycINFO, the Cochrane Library, and CINAHL for articles published in English from inception to 28 July 2021. We also examined reference lists from all included studies, sourced studies from known reviews on the topic, and sought input from expert contacts.

Eligibility criteria and relevant outcomes

Included studies had to answer at least the first key question (regarding the effectiveness of interventions to reduce or discontinue long term opioid treatment) and report the experiences of adults (age ≥18 years) with chronic pain (defined as pain persisting for more than three months) who were prescribed opioid treatment for pain management in randomised controlled trials, non-randomised controlled trials, and uncontrolled studies. Outcomes for the first key question were the number of people who discontinued opioids as a result of treatment and change in opioid dose (in oral morphine equivalent per day). Outcomes for the second key question (regarding the effects of these interventions on patient outcomes) were pain intensity, pain related function, quality of life, opioid withdrawal symptoms, substance use, and adverse events.

Included studies reported original research, clearly described a clinical intervention, and were in the English language. To capture the broad field of literature, interventions were not required to have an explicit goal of opioid tapering. For instance, we included studies in which the intervention might have an auxiliary effect on opioid use. Studies were excluded if they included patients with only acute, surgical, or postoperative pain; patients in hospice or palliative care only; people using opioids for non-medical reasons only; or non-human participants. Studies of patients with cancer and HIV pain were excluded. We included uncontrolled studies alongside controlled studies in order to capture more evidence on infrequent outcomes such as substance use and adverse events. However, case reports and cross sectional studies were excluded.

Study selection

Titles and abstracts were double screened (by NA, AGM, AG, and PG), with a random sample screened by a third reviewer (NA or PG) to check for inter-rater reliability. Two reviewers (of NA, AGM, AG, or PG) checked full texts against eligibility criteria. Disagreements were resolved by discussion or, if unresolved, through arbitration with a third reviewer selected from the authors.

Data extraction, risk of bias, and certainty of evidence

Two reviewers (of NA, AGM, AGh, or PG) independently extracted data on design, sample, setting, baseline dose, intervention, outcome measures, and results from included studies. Two reviewers (of NA, AM, AGh, PG, CAJ, FS, or FB) appraised the risk of bias of the results

of all studies that met inclusion criteria. We used the Cochrane risk-of-bias tools for randomised controlled trials (RoB 2) and for non-randomised studies of interventions (ROBINS-I).[28 29] For randomised controlled trials with crossover or cluster designs, we used the additional RoB 2 questions.[30 31] Agreement by consensus was reached on the risk of bias for the results of each study. Disagreements were resolved by discussion with a third reviewer (NA or FS). We applied the GRADE (grading of recommendations assessment, development and evaluation) framework to assess the certainty of evidence on outcomes, using the terms "we are uncertain" to refer to very low certainty, "may" for low certainty, "probably" or "likely" for moderate certainty, and "very likely" or simply the absence of qualification when referring to high level certainty on the effect of an intervention on a particular outcome (eg, improves, reduces).[32 33]

Data synthesis and analysis

To reduce clinical heterogeneity, we grouped interventions into five categories based on their clinical approach to the problem of long term opioid treatment: pain self-management[34 35]; complementary and alternative medicine[36]; pharmacological and biomedical devices and interventions[37 38]; opioid replacement treatment[39-41]; and deprescription methods[42] (table 1). Where interventions included elements from multiple categories, we assigned the study to the category deemed most applicable to its principal mechanism.

For the non-randomised controlled trials and uncontrolled studies appraised with ROBINS-I, those judged at critical risk of bias for all their included outcomes were deemed too problematic to be included in the evidence synthesis.[29] Study results at low, moderate, or serious risk of bias using ROBINS-I and the results of all randomised controlled trials were included in the syntheses.

Controlled studies (that is, randomised and non-randomised controlled trials) and uncontrolled studies are presented separately in the results below. Controlled studies were synthesised in GRADE summary of findings tables for each intervention group. Randomised controlled trials with sufficient clinical homogeneity were synthesised in meta-analyses, and the remaining randomised controlled trials plus non-randomised controlled trials were synthesised narratively. Uncontrolled studies were synthesised narratively.

Within each category, random effects meta-analysis using Review Manager 5.4 software (Cochrane) was undertaken on groups of randomised controlled trials where interventions, comparator groups, and measures were deemed to be sufficiently similar to enable meaningful meta-analysis.[43-45] At least two studies were required for each meta-analysis.

When studies included more than two intervention arms, we excluded irrelevant groups or combined relevant groups as recommended in the Cochrane Handbook in order to avoid arbitrary decisions.[45] For example, a study comparing inpatient and outpatient versions of the same pain management programme included an additional control group on a waiting list.[46] Multiple studies included in the synthesis compare outpatient pain management programmes with a control group without pain management, and as such the inpatient group of this study[46] was considered irrelevant in two meta-analyses. In another study, electro-acupuncture was compared with sham electro-acupuncture and no electro-acupuncture.[47] Using the formula provided for combining two treatment arms (Cochrane Handbook 6.5.2.10, 23.3.4), we calculated the combined mean difference and standard deviation for sham electro-acupuncture and no electro-acupuncture as a single no acupuncture treatment group.

Effect estimates used included risk ratios for the proportion of people discontinuing opioids, substance use, and adverse events; mean differences for opioid dose; and standardised mean differences (Hedges' adjusted g) for pain, function, quality of life, and

Table 1 | Interventions to reduce long term opioid treatment in people with chronic non-cancer pain

Category	Explanation	Examples
Pain self-management	Aims to reduce over-reliance on prescription opioids through behaviour change by increasing tolerance to pain and withdrawal symptoms; usually adopts a bio-psychosocial framework for pain management or has a focus on improving function	A three week outpatient multidisciplinary pain management programme based on cognitive behavioural therapy principles and including exercise, goal setting, pain education, and opioid discontinuation
Complementary and alternative medicine	Complementary and or alternative to mainstream medicine; seeks to decrease pain intensity or withdrawal symptoms through different mechanisms that might include biomedical and psychosocial elements	Acupuncture as an additional treatment to opioid discontinuation in an outpatient pain clinic; medical cannabis; herbal medicine
Pharmacological and biomedical devices and interventions	Aims to reduce over-reliance on prescription opioids by decreasing the intensity of pain or withdrawal symptoms through drug treatments, implantation of medical devices, or provision of interventional procedures	Clonidine for the management of withdrawal symptoms; spinal cord stimulation; total knee arthroplasty
Opioid replacement treatment	Also known as opioid maintenance treatment; patients are transitioned from long term opioid treatment to methadone or buprenorphine; most often recommended for patients with chronic pain and comorbid opioid use disorder or other substance use disorder	Transition to methadone maintenance; transition and stabilisation on buprenorphine or buprenorphine/naloxone, and then weaning off these substances
Deprescription methods	An emphasis on drug treatment management that might occur alongside or in the absence of alternative pain management techniques; these include patient focused and prescriber focused interventions	Treatment in primary care where opioids are reduced by 10% per week; an electronic decision tool that helps prescribers adhere to a new opioid prescription safety policy

withdrawal symptoms. Standardised mean differences were calculated for the above patient outcomes because we anticipated that multiple different scales would be used to measure the same outcomes. Small, moderate, and large differences between groups were indicated by standardised mean differences of 0.20, 0.50, and 0.80, respectively.[48]

Study authors were contacted for data if none could be found in the publication and for clarification. If studies included the outcomes of patients who did not receive long term opioid treatment alongside those of patients who did receive long term treatment, we isolated the outcomes of the second group. To obtain these data, we extracted published data and, in one case, used original data supplied by the authors.[46] In the case where the original data were supplied, mean differences and standard deviations for each treatment group were calculated in SPSS (IBM). Long term opioid treatment was considered distinct from the opioid treatment used when needed.

Confidence intervals were converted to standard deviations using Review Manager 5.4. When measures of variation were missing for mean differences within each treatment arm of a given study and a test of difference between treatment arms was reported, we converted F statistics, t statistics, and P values to standard errors and standard deviations using the tool in Review Manager 5.4 (Cochrane Handbook 6.5.2.3). Here, t was taken as the square root of F, and it was assumed that the standard deviations of the mean differences in each treatment arm were equal (6.5.2.3). When measures of variation were missing for mean differences within each treatment arm of a given study and the study had no test of difference between groups, we used the highest standard deviation recorded in the same meta-analysis for each treatment arm instead of the study's own data (6.5.2.7).

We assessed heterogeneity by using τ^2 and I^2 statistics. We also conducted post hoc sensitivity analyses when measures of variance were imputed and when a study reported a clear outlier effect. In each case, the relevant trials were excluded and the meta-analysis was repeated.

Patient and public involvement

Despite no direct patient or public involvement in the development or completion of this review owing to time and funding constraints, the research question was formed as a result of conversations about opioid tapering between clinician authors and patients attending the pain clinic at Royal North Shore Hospital, Sydney, Australia. We have asked a member of the public to read our manuscript after submission in order to solicit feedback on the best way to communicate our findings to the community.

Results

Search results, study designs, participants, and study characteristics

Our search identified 11 420 records from five databases. Another 168 records were identified in systematic reviews, reference lists, and through expert contacts. After removing duplicates, 9999 unique records were screened and the full text of 490 records were reviewed. In total, 166 studies met inclusion criteria and were appraised for risk of bias, including 27 randomised controlled trials,[46 47 49 50-73 212 213] 13 non-randomised controlled trials[74-86] and 126 uncontrolled studies.[87-211] Data were not synthesised for eight non-randomised controlled trials and 122 uncontrolled studies because of critical risk of bias. The remaining 36 studies contributing to the evidence synthesis included 27 randomised controlled trials,[46 47 49 50-73 212 213] five non-randomised controlled trials,[79 82-84 86] and four uncontrolled studies.[126 146 182 203] Meta-analysis was conducted on 11 randomised controlled trials[46 47 53 54 5657 59 65 68 72 73] (fig 1 and appendices 3-5).

The 36 studies contributing to the evidence synthesis were conducted in the following settings: outpatient (n=17), primary care (n=6), inpatient (n=5), unclear (n=5), outpatient and community (n=2), and community only (n=1). The baseline opioid dose for participants on long term opioid treatment was reported in 24 studies, with participants taking a mean daily dose of ≤100 mg oral morphine equivalents in 14 studies (58%) and >100 mg oral morphine equivalents in 10 studies (42%). Twenty six studies reported a programme goal of opioid dose reduction or discontinuation for all or some patients. Studies often reported that patients had chronic non-cancer pain without providing more detail. Otherwise, studies reported patients with diverse chronic pain syndromes including various back, spine, and neck disorders; musculoskeletal pain; sacroiliac joint pain; osteoarthritis; headaches; neuropathy; and fibromyalgia. In 12 studies, some or all patients had chronic pain and comorbid prescription opioid use disorder, opioid dependence, or previous substance use.[49 55 60 61 64 67 70 71 79 146 182 203]

Controlled clinical trials

The 27 randomised controlled trials and five non-randomised controlled trials contributing to the evidence synthesis are described in table 2. Two articles[212 213] were secondary analyses of a randomised controlled trial,[71] and thus the three articles were considered together as one study. Most randomised controlled trials had a high risk of bias overall, with only two studies appraised as have a low risk of bias overall (fig 2 and appendix 4). Meta-analysis was possible in three categories (pain self-management, complementary and alternative medicine interventions, and pharmacological and biomedical devices and interventions) where multiple studies were found with comparable treatment arms (fig 3, fig 4, and appendix 6). In the pain self-management group, meta-analysis was possible for opioid discontinuation, opioid dose, pain intensity, and function from six studies.[46 54 56 65 68 72] In the complementary and alternative medicine group, meta-analysis was possible for three studies on acupuncture for opioid dose and pain intensity.[47 57 73]

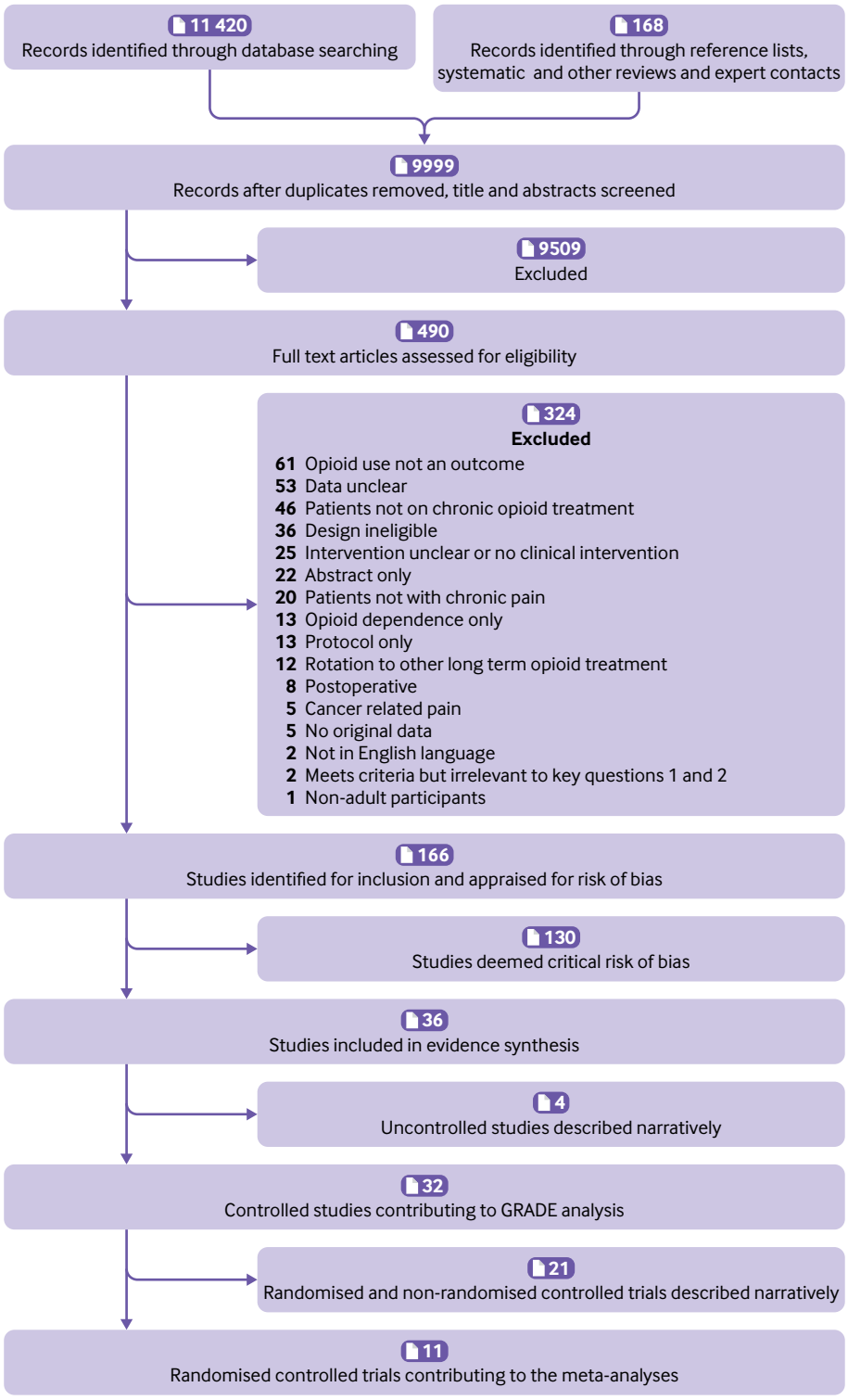

Fig 1 | Literature flowchart. Key questions refer to (1) how effective interventions are to reduce or discontinue long term opioid treatment, and (2) what their effects are on patient outcomes

In the pharmacological and biomedical group, meta-analysis was possible for two studies of spinal cord stimulation on opioid discontinuation.[53 59] The remaining outcomes and studies in the above three groups and all studies in the opioid replacement treatment and deprescription groups were too clinically heterogenous to allow meaningful meta-analysis and so were described narratively. GRADE analysis of the 32 controlled studies showed that none of the outcomes had a high level certainty, with three outcomes of moderate certainty and the remainder of low and very low certainty (table 3 and appendix 7).

Table 2 | Characteristics of randomised and non-randomised controlled trials investigating interventions to taper long term opioid treatment for chronic non-cancer pain

Intervention group, study, and design	Intervention (No of patients on long term opioid treatment at baseline)	Comparator(s)
Pain self-management		
Williams et al, 1996; RCT[46†]	4 weeks; inpatient, CBT based programme with exercise, goal setting, education, and opioid discontinuation (n=27*)	8 weeks; outpatient, CBT based programme with exercise, goal setting, education, and opioid discontinuation (n=30*); or third arm (wait list control; n=16*)
Thieme et al, 2003; RCT[69]	5 weeks; inpatient, group based programme of operant pain treatment consisting of drug treatment reduction and education (n=unclear)	5 weeks; inpatient, physical therapy programme plus antidepressant drug treatment (n=unclear)
Naylor et al, 2010; RCT[63]	4 months; therapeutic interactive voice response to support CBT maintenance after 11 weeks of CBT (n=14)	Standard care after 11 weeks of CBT (n=15)
Zgierska et al, 2016; RCT[72†]	26 weeks; individual and group mindfulness and CBT plus usual care (n=21)	Wait list control receiving usual care (n=14)
Sullivan et al, 2017; RCT[68†]	22 weeks; taper support intervention (psychiatric consultation, opioid tapering, 18 weekly meetings with physician assistant regarding motivations and pain management; n=18)	Usual care (n=17)
Nielssen et al, 2018; RCT with post hoc analysis[65†]	8 weeks; online pain management programme, based on CBT (n=161)	Wait list control (n=42)
Garland et al, 2020; RCT with post hoc analysis[54†]	8 weeks; mindfulness oriented recovery enhancement based on mindfulness, CBT, and positive psychology (n=50)	8 weeks; support group without mindfulness component (n=45)
Matthias et al, 2020; RCT[62]	6 months; one-on-one pain self-management programme delivered by peer coaches, including relaxation, activity pacing, and cognitive behavioural skills (n=not reported)	One 2 hour class of pain self-management (n=not reported)
Hudak et al, 2021, RCT[56†]	8 weeks; mindfulness oriented recovery enhancement based on mindfulness, CBT, and positive psychology (n=34)	8 weeks; support group without mindfulness component (n=28)
Raiszadeh et al, 2021; NRCT[83]	In-clinic rehabilitation based on multidisciplinary exercise, including use of exercise machines (n=130)	Online rehabilitation based on multidisciplinary exercise, in patients' homes (n=14)
Complementary and alternative medicine interventions		
Zheng et al, 2008; RCT[73†]	Electro-acupuncture (n=17)	Sham electro-acupuncture (n=18)
Oohata et al, 2017; NRCT[82]	Kampo herbal medicine (n=74)	No Kampo (n=28)
Zheng et al, 2019; RCT[47†]	Electro-acupuncture plus education on pain and drug treatment management (n=48)	Sham electro-acupuncture plus education on pain and drug treatment management (n=29); or third arm (education on pain and drug treament management; n=31)
Jackson et al, 2021; RCT[57†]	Outpatient management of drug treatment with opioid weaning plus auricular acupuncture (n=9)	Outpatient management of drug treatment with opioid weaning (n=7)
Pharmacological and biomedical devices and interventions		
Kumar et al, 2007; RCT[59†]	Spinal cord stimulation (n=36)	Conventional medical treatment (n=32)
Kapural et al, 2010; NRCT[79]	Intravenous ketamine infusions (n=18)	Control (no ketamine; n=18)
Zhao et al, 2010; NRCT[86]	Duloxetine (n=341)	Other standard-of-care drug treatments, including tricyclic antidepressants, venlafaxine, gabapentin, and pregabalin (n=940)
Raphael et al, 2013; RCT[66]	Intrathecal morphine with 20% dose reduction for 10 weeks (n=10)	Intrathecal morphine stable dose (n=5)
de Vos et al, 2014; RCT[53†]	Spinal cord stimulation (n=18)	Conventional medical treatment (n=11)
Hooten and Warner, 2015; RCT[55]	15 day course of varenicline plus 3 week intensive programme of multidisciplinary pain rehabilitation (n=10)	Placebo plus 3 week intensive programme of multidisciplinary pain rehabilitation (n=11)
Johnson et al, 2015; RCT[58]	Ibudilast 40 mg twice daily for 8 weeks (n=15)	Placebo twice daily for 8 weeks (n=19)
Cherian et al, 2016; RCT[50]	Transcutaneous electrical nerve stimulation (n=8)	Standard-of-care treatment including corticosteroid injections, physical therapy, and pharmaceutical management (n=10)
Dengler et al, 2019; RCT[52]	Sacroiliac joint arthrodesis with triangular titanium implants (n=29)	Conservative management (n=24*)
Opioid replacement treatment		
Blondell et al, 2010; RCT[49]	Buprenorphine/naloxone taper (n=6)	Buprenorphine/naloxone maintenance (n=6)
Weiss et al, 2011; Worley et al, 2015; and Worley et al, 2017; RCT with post hoc analyses[71 212 213]	Phase 1: 2 weeks, buprenorphine/naloxone stabilisation; and 2 weeks, taper plus counselling (n=139)	Phase 1: 2 weeks, buprenorphine/naloxone stabilisation; and 2 weeks, taper (n=135)
	Phase 2 (for those unsuccessful in phase 1): 12 weeks, buprenorphine/naloxone stabilisation; and 4 weeks, taper plus counselling (n=unclear)	Phase 2 (for those unsuccessful in phase 1): 12 weeks, buprenorphine/naloxone stabilisation; and 4 weeks, taper (n=unclear)
Roux et al, 2013; RCT[67]	Buprenorphine/naloxone (2/0.5 mg) maintenance dose (n=25, crossover)	Buprenorphine/naloxone (8/2 mg) maintenance dose (n=25, crossover); and third arm (buprenorphine/naloxone (16/4 mg) maintenance dose; n=25, crossover)
Webster et al, 2016; RCT[70]	Two doses of buccal buprenorphine at about 50% of prescribed total opioid daily dose (n=39, crossover)	Two doses of full μ opioid agonist at about 50% of prescribed total opioid daily dose (n=39, crossover)
Neumann et al, 2020; RCT[64]	6 months; methadone maintenance (n=9)	6 months; buprenorphine/naloxone m intenance (n=10)
Deprescription methods		
Ralphs et al, 1994; NRCT[84]	Patient controlled reduction of opioids plus 4 weeks of residential multidisciplinary pain programme (n=63)	Clinician controlled reduction method plus 4 weeks of residential multidisciplinary pain programme (n=45)
Cowan et al, 2005; RCT[51]	60 hours; morphine placebo (abrupt cessation of opioids; n=10, crossover)	Morphine maintenance (n=10, crossover)
Liebschutz et al, 2017; RCT[61]	Nurse care management, electronic registry, one-on-one academic detailing, and electronic decision tool for safe prescribing (n=570)	Control intervention of electronic decision tools only (n=394)
Kurita et al, 2018; RCT[60]	Opioid dose reduction; 10% per week up to 6 months (n=15)	Stable opioid dose (n=20)

For results see appendix 3. CBT=cognitive behavioural therapy; NRCT=non-randomised controlled trial; OME=oral morphine equivalent; RCT=randomised controlled trial.
*These numbers are estimates—the number of people on opioid treatment was not clearly reported.
†Included in meta-analyses.

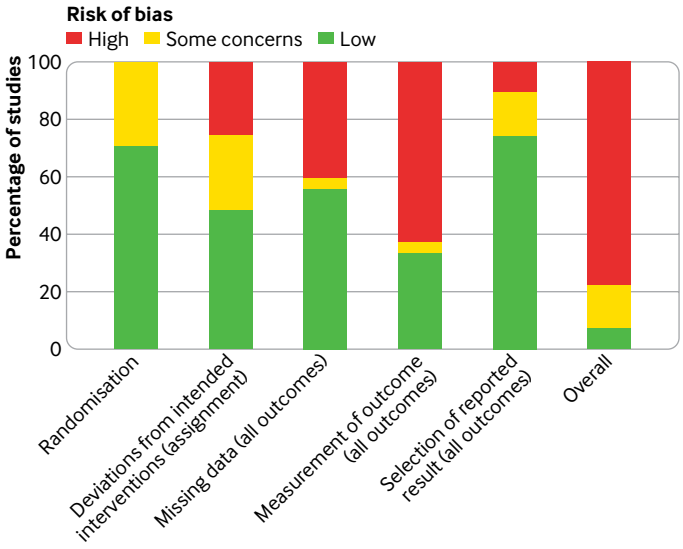

Fig 2 | Risk-of-bias summary for randomised controlled trials included in evidence synthesis, using Cochrane risk-of-bias tool RoB 2

Meta-analyses

Pain self-management versus no pain self-management

Meta-analyses were possible for six studies in which patients in the intervention arm were provided with non-pharmacological techniques to manage their pain.[46 54 56 65 68 72] Techniques were based on the principles of cognitive behavioural therapy (CBT) and mindfulness, and primarily took place within an outpatient multidisciplinary pain programme. In one study, the programme was delivered online.[65] Control groups included patients on waiting lists receiving usual care, which typically involved opioid treatment management with patients' regular clinicians and limited restrictions for other treatment.[46 65 68 72] In two instances, the control groups participated in a support group and discussed their experiences of pain and opioids (without receiving pain self-management training).[54 56] Each study evaluated pain self-management versus no pain self-management.

Pain self-management programmes compared to no pain self-management probably moderately reduced opioid dose (mean difference −14.31 mg oral morphine equivalent, 95% confidence interval −21.57 to −7.05, τ^2=0.00, I^2=0%, moderate level certainty), based on five studies of 428 participants. Pain self-management might have had a moderate effect on pain intensity (standardised mean difference −0.59, 95% confidence interval −1.02 to −0.16, τ^2=0.00, I^2=0%, low level certainty) and might have had no effect on function (−0.27, −0.69 to 0.15, τ^2=0.00, I^2=0%, low level certainty), based on three studies of 92 participants. We were uncertain with the estimate of participants being twice as likely to discontinue opioids than controls (risk ratio 2.15, 95% confidence interval 1.02 to 4.53, τ^2=0.00, I^2=0%, very low level certainty), based on two studies of 238 participants.

Acupuncture versus no acupuncture

Meta-analyses were possible for three studies involving a total of 158 participants that evaluated the efficacy of either electro-acupuncture or general acupuncture compared to no acupuncture in the context of opioid tapering in an outpatient pain clinic.[47 57 73] In one study, two control arms were combined into one group of no acupuncture (appendix 6). We were uncertain in the estimate that, in the context of clinician guided opioid reduction, additional acupuncture had little or no effect on opioid dose compared to no additional acupuncture (mean difference −1.56 mg oral morphine equivalent per day, 95% confidence interval −19.03 to 15.92, τ^2=155.05, I^2=69%, very low level certainty), and had no effect on pain intensity (standardised mean difference 0.02, −0.29 to 0.34, τ^2=0.00, I^2=0%, very low level certainty).

Spinal cord stimulation versus conventional medical treatment

Meta-analyses were possible for two studies involving 97 participants that evaluated the efficacy of spinal cord stimulation compared to conventional medical treatment.[53 59] We were uncertain in the estimate that those individuals who received spinal cord stimulation were six times more likely to discontinue opioids than those who received conventional medical treatment (risk ratio 6.07, 95% confidence interval 1.16 to 31.77, τ^2=0.00, I^2=0%, very low level certainty).

Narrative synthesis of studies and outcomes not included in the meta-analyses

Pain self-management

Nine randomised controlled trials and one non-randomised controlled trial evaluated inpatient and outpatient programmes comprising CBT or mindfulness combined with exercise, education, and management of drug treatment.[46 54 56 62 63 65 68 69 72 83] Certainty of evidence for all outcomes not included in meta-analyses was low or very low.

In two studies, patients who undertook three and four week pain management programmes incorporating opioid discontinuation achieved greater improvements in pain, function, and opioid use than those who undertook physical therapy in one study (all P<0.001)[69] and wait listed controls in the other study.[46] Less intensive programmes were also successful. Patients who undertook eight sessions of group mindfulness achieved greater reductions in opioid dose at three and four month follow-ups than patients who undertook eight sessions of support group therapy (P=0.006, P=0.02).[54 56] However, six months of peer delivered pain management training did not achieve significant differences in opioid dose, pain, and quality of life compared with one session of training.[62]

Three studies evaluated pain self-management programmes delivered online or by telephone.[63 65 83] A post hoc analysis[65] of a randomised controlled trial[215] reported that eight weeks of online pain self-management increased rates of opioid discontinuation

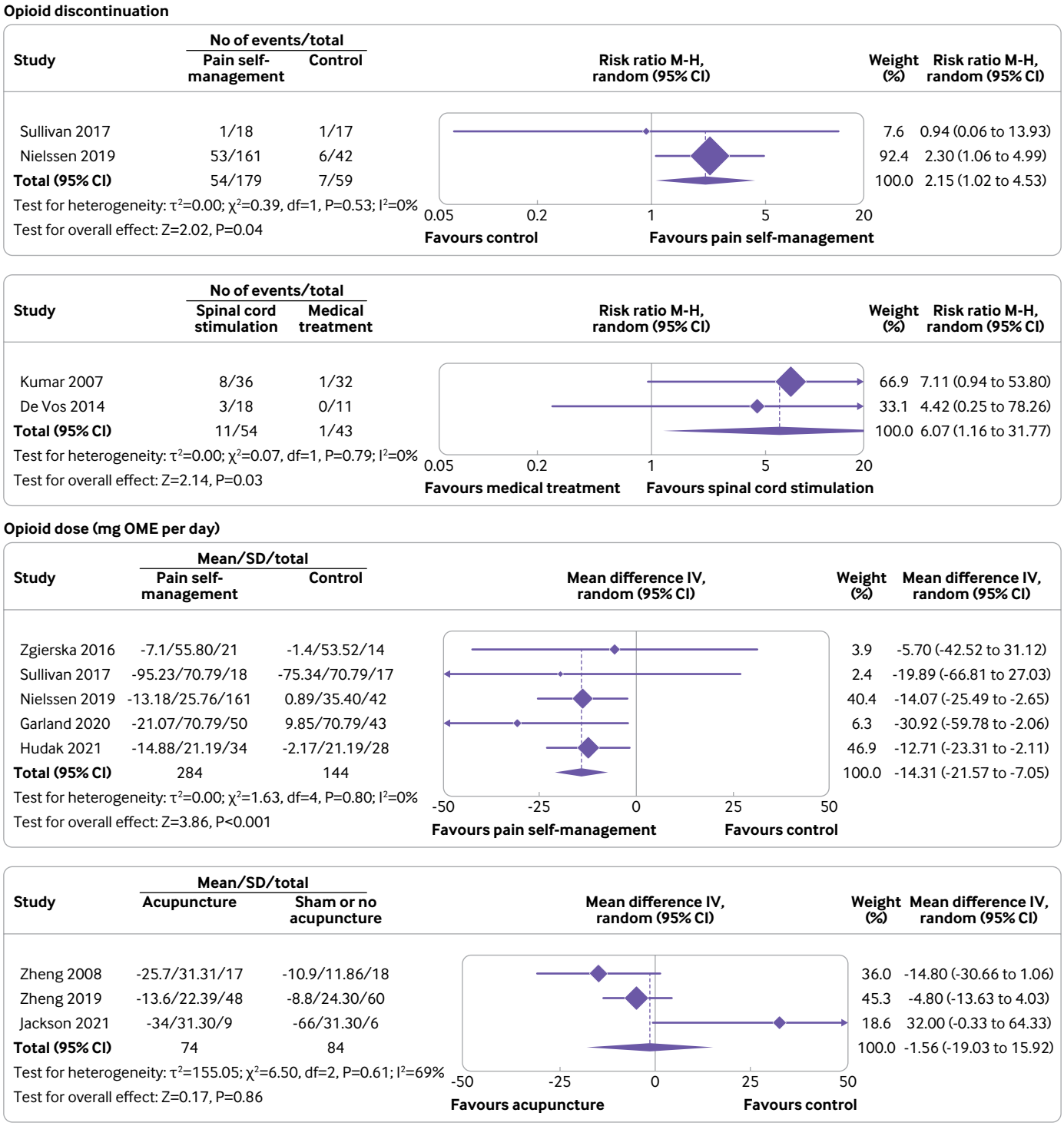

Fig 3 | Meta-analyses of randomised controlled trials investigating interventions to taper long term opioid treatment for chronic non-cancer pain, according to opioid discontinuation and opioid dose. IV=inverse variance; M-H=Mantel Haenszel test; SD=standard deviation; df=degrees of freedom; OME= oral morphine equivalent

(33% *v* 14%, P=0.27) and led to greater dose reduction (46% *v* −3%, P=0.003) than wait listed controls. No difference in opioid discontinuation rates was observed in a comparison of in-clinic versus web delivered programmes of pain self-management .[83] Both groups achieved clinically significant improvements, while the in-clinic group had significantly greater improvement in pain and disability.[83] Another study found that patients who received CBT reminders by an automated telephone service had better opioid discontinuation, dose, pain, and function outcomes than control participants.[63]

Complementary and alternative medicine interventions

We had low or very low certainty in the evidence on the outcomes of the four controlled studies that did

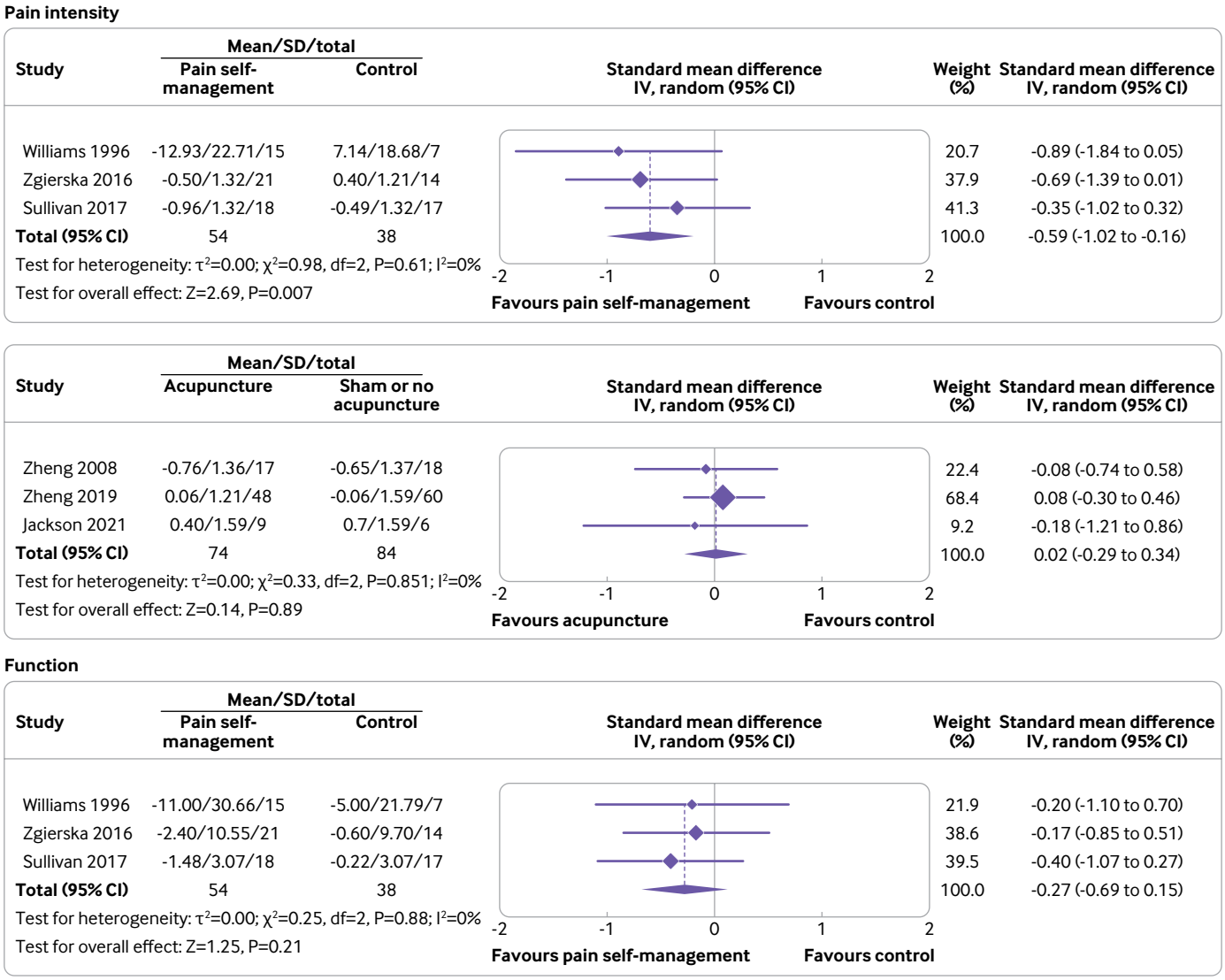

Fig 4 | Meta-analyses of randomised controlled trials investigating interventions to taper long term opioid treatment for non-cancer chronic pain, according to pain intensity and function. IV=inverse variance; SD=standard deviation; df=degrees of freedom

not contribute to the meta-analyses in this group. Of the three acupuncture studies, one reported no effect on function,[47] another reported no difference between groups for withdrawal symptoms,[57] and two reported no effect on quality of life and serious adverse events, with few mild adverse events due to electro-acupuncture.[47 73] A non-randomised controlled trial evaluating a herbal medicine, Kampo, found significant differences favouring the treatment group over controls who did not receive Kampo on opioid discontinuation and dose.[82] Substance use was not measured.

Pharmacological and biomedical devices and interventions

Two main biomedical approaches were evaluated in controlled trials: the pharmacological management of pain and withdrawal symptoms and invasive procedures (eg, surgery, device implantation). For all outcomes not included in the meta-analysis, certainty in the evidence was low. Substance use was not measured.

Regarding pharmacological interventions, no significant difference on withdrawal symptoms was reported between groups treated with varenicline (primarily used to treat nicotine withdrawal) and placebo in the context of an outpatient pain programme.[55] No significant difference in pain scores and opioid use at six months was observed between patients receiving intravenous ketamine infusions and those not receiving ketamine, and two adverse events occurred (supraventricular arrhythmia and anxiety).[79] In a placebo controlled study of ibudilast for patients with headache from the overuse of drug treatment, researchers found that opioid use and quality of life did not differ between groups throughout follow-up, whereas patients in the intervention group reported significantly more adverse events, including nausea, pruritis, and diarrhoea (P=0.02).[58]

Table 3 | Certainty of evidence and summary effect estimates assessed by GRADE (grading of recommendations, assessment, development, and evaluation) of controlled trials investigating interventions to taper long term opioid treatment for non-cancer chronic pain

Outcome	Intervention group				
	Pain self-management	Complementary and alternative medicine	Pharmacological and biomedical devices and interventions	Opioid replacement treatment	Deprescription
Opioid discontinuation (positive effect favours intervention over control)	Very low certainty (RR 2.15 (95% CI 1.02 to 4.53), τ^2=0.00, I^2=0%); subgroup: pain self-management *v* no pain self-management	Very low certainty (moderate positive effect)	Very low certainty (RR 6.07 (95% CI 1.16 to 31.77), τ^2=0.00, I^2=0%); subgroup: SCS *v* conventional medical treatment	Low certainty (no effect)	Low certainty (no effect); subgroup: patient focused
	Low certainty (nil or small positive effect); subgroup: other	—	Low certainty (nil or moderate positive effect); subgroup: other	—	Moderate certainty (aOR 1.5 (95% CI 1.0 to 2.1)*); subgroup: prescriber focused
Opioid dose (negative effect favours intervention over control)	Moderate certainty (MD −14.31 mg daily OME (95% CI −21.57 to−7.05), τ^2=0.00, I^2=0%); subgroup: pain self-management *v* no pain self-management	Very low certainty (MD −1.56 mg daily OME (95% CI −19.03 to 15.92), τ^2=155.05, I^2=69%); subgroup: acupuncture *v* no acupuncture	Low certainty (nil or small negative effect)	Very low certainty (no effect)	Low certainty (no effect); subgroup: patient focused
	Low certainty (small negative effect); subgroup: other	Very low certainty (moderate negative effect); subgroup: other	—	—	Moderate certainty (MD −6.8 (SE 1.6) mg daily OME*); subgroup: prescriber focused
Pain intensity (negative effect favours intervention over control)	Low certainty (SMD −0.59 (95% CI −1.02 to −0.16), τ^2=0.00, I^2=0%); subgroup: pain self-management *v* no pain self-management	Very low certainty (SMD 0.02 (95% CI −0.29 to 0.34), τ^2=0.00, I^2=0%); subgroup: acupuncture *v* no acupuncture	Low certainty (nil or small negative effect)	Very low certainty (no effect)	Low certainty (nil or small positive effect); subgroup: patient focused
	Low certainty (small negative effect); subgroup: other	—	—	—	—
Pain related function (negative effect favours intervention over control)	Low certainty (SMD −0.27 (95% CI −0.69 to 0.15), τ^2=0.00, I^2=0%); subgroup: pain self-management *v* no pain self-management	Low certainty (no effect)	Low certainty (nil or small negative effect)	Very low certainty (no effect)	Low certainty (nil or small positive effect) subgroup: patient focused
	Low certainty (small negative effect); subgroup: other	—	—	—	—
Quality of life (positive effect favours intervention over control)	Very low certainty (small positive effect)	Low certainty (no effect)	Low certainty (nil or small positive effect)	—	Very low certainty (no effect); subgroup: patient focused
Withdrawal symptoms (negative effect favours intervention over control)	—	Very low certainty (no effect)	Low certainty (no effect)	Low certainty (no effect)	Low certainty (small positive or negative effect); subgroup: patient focused
Substance use (negative effect favours intervention over control)	Low certainty (no effect)	—	—	Very low certainty (multiple events†)	Low certainty (no effect); subgroup: patient focused
Adverse events (negative effect favours intervention over control)	Low certainty (1 event†)	Low certainty (few minor events†)	Low certainty (multiple events†)	Low certainty (multiple events†)	Low certainty (no effect); subgroup: patient focused

aOR=adjusted odds ratio; MD=mean difference; OME=oral morphine equivalent; RR=risk ratio; SCS=spinal cord stimulation; SE=standard error; SMD=standardised mean difference.
*Statistics were the findings from one study of 985 participants.
†Differences between intervention and control groups on this outcome were not reported in this group of studies.

Regarding invasive procedures, studies of sacroiliac joint arthrodesis[52] and spinal cord stimulation[53 59] versus conventional treatment reported better outcomes in opioid dose,[52] pain,[52 53 59] disability,[52] and quality of life[52 53 59] in the intervention group. Patients with knee osteoarthritis who received transcutaneous electrical nerve stimulation reported better opioid discontinuation rates, pain, function, and quality of life than controls at follow-up.[50] Adverse events were common in patients receiving sacroiliac joint arthrodesis[52] and spinal cord stimulation (electrode migration, wound infection),[53 59] and were not observed in patients receiving electrical nerve stimulation.[50] Lastly, a double blinded trial of patients on intrathecal morphine comparing stable dose with 20% weekly dose reduction found that 70% (7/10) of the tapering group dropped out due to worsening pain.[66]

Opioid replacement treatment

Five randomised controlled trials compared various protocols of opioid maintenance treatment using buprenorphine/naloxone and methadone. Certainty in the evidence was either low or very low for all outcomes, with quality of life not measured. Each study showed no significant difference between treatment groups reported for opioid dose,[64] function,[64] and withdrawal symptoms.[64 67] Withdrawal symptoms including headache, nausea, and diarrhoea, were reported in both treatments of a crossover trial comparing the tolerability of full μ opioid agonist dose

at 50% of participants' usual doses versus a similar dose of buccal buprenorphine.[70] This study reported no differences between treatments on pain scores,[70] however, another study reported greater analgesic effects for participants receiving higher doses of buprenorphine/naloxone.[67] Two studies reported use of heroin, benzodiazepine, and alcohol.[49 64] Two of 43 participants trialling various buprenorphine/naloxone doses dropped out owing to nausea and heavy sedation,[67] and a comparison of buprenorphine/naloxone tapering (n=6) with maintenance (n=6) failed to retain any participants in the tapering arm.[49] Counselling did not affect the completion rate of those individuals tapering use of buprenorphine/naloxone.[71 212 213]

Deprescription methods

We included one randomised controlled trial of a prescriber focused deprescription intervention and three trials of patient focused deprescription interventions. Certainty in the trial outcomes was moderate for the prescriber focused intervention, and low or very low for the patient focused interventions.

The randomised controlled trial of a prescriber focused intervention evaluated changes to primary care practices in relation to opioid prescribing, including nurse care management, one-to-one academic detailing, and an electronic decision tool for clinicians.[61] Based on this study (n=964), prescriber focused deprescription interventions probably had a small effect on opioid dose (mean difference −6.8 mg (standard error 1.6) oral morphine equivalent, P<0.001; adjusted odds ratio for dose reduction 1.6, 95% confidence interval 1.1 to 2.4; moderate level certainty) and probably had no effect to small effects on opioid discontinuation (adjusted odds ratio 1.5, 95% confidence interval 1.0 to 2.1; moderate level certainty). This study did not measure non-opioid patient outcomes.

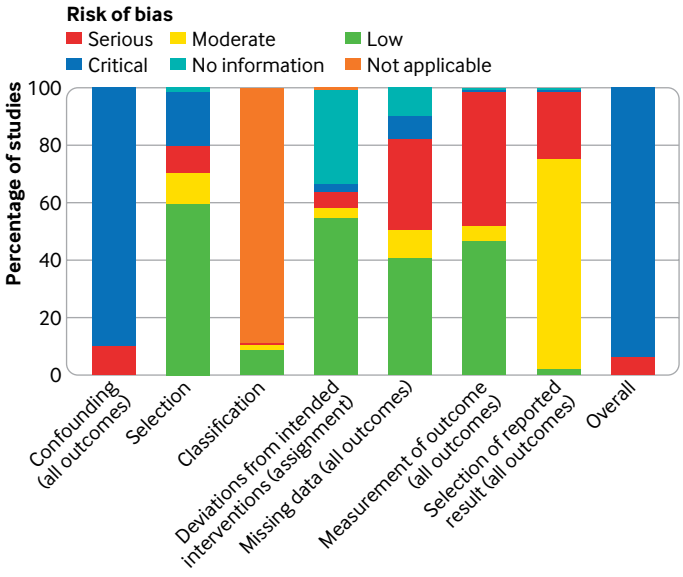

Fig 5 | Risk-of-bias summary for non-randomised studies investigating interventions to taper long term opioid treatment for non-cancer chronic pain, using Cochrane risk-of-bias tool ROBINS-I

Of the patient focused trials, one compared patient controlled with clinician controlled opioid reduction during a four week pain management programme.[84] Researchers found no differences between groups on opioid discontinuation, dose, pain, function, quality of life, and benzodiazepine use at six months. The second trial found that periods of abrupt opioid cessation caused significant increases in pain, disability, and withdrawal symptoms (including diarrhoea, anxiety, muscle twitching, and rhinorrhoea) when compared to opioid maintenance.[51] The third trial compared six months of a weekly dose reduction by 10% of baseline dose with six months of a stable dose, and results were inconclusive owing to high a dropout rate.[60]

Uncontrolled studies

Of 126 uncontrolled studies meeting inclusion criteria, four were at serious risk of bias and thus were eligible for narrative synthesis (fig 5 and appendix 4). Primary care prescriber education and an opioid tapering referral programme was associated with a mean dose reduction of 111 mg oral morphine equivalent (P value not reported) over 12 months.[146] Prescriber education and a dose reduction policy was associated with a mean dose reduction of 64 mg oral morphine equivalent (95% confidence interval 32 to 96, P<0.001) over 16 months.[203] For patients with a new diagnosis of depression, adherence to antidepressants increased the odds of opioid cessation (hazard ratio 1.24, P=0.007).[182] Lastly, patients experienced a 16% reduction in opioid dose after total knee arthroplasty (adjusted incidence rate ratio 0.84, 95% confidence interval 0.78 to 0.90, P<0.001) and 7.2% (52/720) discontinued long term opioid treatment.[126]

The remaining 122 uncontrolled studies were at critical risk of bias, including studies from all five intervention categories. Risk of bias varied between low, moderate, serious, and critical across all ROBINS-I domains except for confounding where the risk of bias was uniformly critical.

Discussion

Principal findings

This review evaluated 166 studies on the efficacy of interventions to reduce or discontinue long term opioid treatment in people with chronic non-cancer pain and the effect of these interventions on patient outcomes: pain, function, quality of life, withdrawal symptoms, substance use, and adverse events. Only 36 studies were at lower than critical risk of bias, including 27 randomised controlled trials, five non-randomised controlled trials, and four uncontrolled studies. Meta-analyses were conducted on 11 randomised controlled trials, and the remaining 25 randomised controlled trials, non-randomised controlled trials, and uncontrolled studies were narratively synthesised. For the 32 controlled studies contributing to the GRADE summary of findings tables, certainty in the evidence was low or very low for all outcomes aside from three which were moderate.

Many uncontrolled before-and-after studies met inclusion criteria but were at critical risk of bias because they were unable to deal with confounding. Studies that accounted for underlying trends in opioid use before the intervention and observed changes during and after the intervention were deemed at serious risk of bias.[126 146 203] Their results were synthesised, but because these studies did not perform time series comparisons of projected versus actual observations, they could not be considered equivalent to randomised controlled trials. One study with serious risk of bias that did not assign patients to intervention and control groups was considered to approximate a non-randomised controlled trial.[182]

Opioid outcomes

We had moderate certainty in the efficacy of interventions to support prescriber adherence to opioid reduction guidelines and pain self-management programmes in the reduction or discontinuation of opioids. The 6.8 mg oral morphine equivalent per day difference found in a multi-component intervention encouraging prescribers to follow guidelines recommending against high dose opioids was probably a true effect, and the higher opioid discontinuation rate associated with this intervention was also probably a true effect.[61] Pain self-management programmes probably achieved a moderate reduction in dose (14.31 mg oral morphine equivalent per day) when compared to no training in pain self-management, but we were uncertain in the evidence that participants are twice as likely to discontinue opioids. According with previous evidence,[21 22] the pooled results for studies of acupuncture found no effect on opioid dose when compared to no acupuncture, and the pooled results for studies of spinal cord stimulation found that intervention patients were six times more likely to discontinue opioids than patients receiving conventional care. However, owing to blinding issues, small samples, statistical heterogeneity, and confidence intervals of effect estimates spanning contradictory clinical decisions, we were uncertain in the evidence for both outcomes.

Patient outcomes

The certainty of evidence for the effect of interventions on patient outcomes was uniformly low or very low. The pooled data on the effect of pain self-management programmes on pain and function accorded with previous evidence that pain self-management might be an effective alternative to opioids;[19 216 217] however, certainty in our evidence was low. Nearly all randomised controlled trials were at high risk of bias in their reporting of patient outcomes, owing to the use of self-report measures. Thus, we were not able to evaluate the effect of interventions on pain, function, quality of life, and withdrawal symptoms. In a subset of studies, researchers blinded participants to sham, placebo, or other interventions,[51 55 58 67 70 73] but small samples precluded us from assessing their findings with anything other than low or very low certainty.

The lack of evidence on adverse events and substance use was a concern, and capturing their occurrence is outside the scope of most trials, which are usually brief. However, adverse events were reported by patients receiving electro-acupuncture,[47 73] ketamine,[79] ibudilast,[58] sacroiliac joint arthrodesis,[52] and spinal cord stimulation.[53 59] Two studies of opioid replacement treatment reported instances of alcohol, heroin, and benzodiazepine use,[49 64] although these findings did not contribute to evidence on outcomes at anything better than low certainty. One observational study reported the hazard ratio for death of patients who discontinued long term opioid treatment in primary care, but it was excluded from the evidence synthesis owing to critical risk of bias.[142]

Several studies that were ineligible for this review have considered the association of adverse events with opioid discontinuation. Their findings were mixed. One study found that opioid discontinuation was associated with fewer overdoses and injuries than maintenance.[218] Another study found that a significant increase in the risk for overdose death in patients on opioids for longer periods before discontinuing,[219] indicating that tapering should not be delayed. Yet evidence also suggests that changes in opioid treatment might be dangerous. High rates of suicidal ideation and self-harm have been found in US veterans with and without substance use disorder who discontinued opioids.[220] Moreover, the initiation of opioids, tapering, and the three months after discontinuation have been associated with higher risk of overdose, suicide, mental health crises, and heroin use.[219 221 222 223]

Limitations

A lack of good quality evidence remains a barrier to more conclusive findings. While some randomised controlled trials were at low risk of bias, imprecision because of small samples was the main reason for reducing our certainty in the outcomes. Meta-analyses included the few studies where pooling results was clinically meaningful but were limited by the exclusion of studies where event rates were zero in each group, by missing data, and by the necessity to impute missing measures of variance. Effect sizes might have been overestimated owing to the small-study effect.[224 225] Funnel plots and meta-regression were not performed because of the small number of studies contributing to the meta-analyses. Lastly, while the outcomes synthesised in the present study reflect standard practice in the literature, their applicability and meaningfulness to patients' lived experiences needs further consideration. For any protocol deviations, see appendix 8.

Implications

The clinical implications of this review are modest. No intervention stands out for recommendation. Nevertheless, owing to the risks associated with long term opioid treatment, clinicians should discuss with patients the prospect of opioid tapering when it is

safe to do so. Close follow-up is important given the possibility that severe adverse events are associated with changes in treatment.[226] Comorbidities such as depression and substance use disorder need specific attention, and the risks involved with forced tapers (that is, when patients are not involved in decision making) are substantial and must not be ignored.[182] For patients at increased risks when tapering because of complex persistent opioid dependence, transition to buprenorphine should be considered, although the evidence for this approach, like others, remains limited.[23 227] Multidisciplinary pain management programmes are probably effective at helping to reduce opioid dose. However, access remains an issue for people who are unable to take time off work, in regional areas where services are limited, and for people from culturally and linguistically diverse communities.

Researchers should design studies with replicability in mind,[225] deal with the problem of dropout rates,[132 211 228] place a stronger emphasis on outcomes relevant to both clinical practice and patients' lived experiences,[229 230] and use longer follow-up periods to reflect the scale of patients' experiences in treatment.[229]

Systematic reviewers and guideline authors must consider the clinical heterogeneity of interventions in this field, as well as variation in risk of bias. Future reviews should consider the limited value of including uncontrolled studies, and perhaps exclude in the first pass those clearly at critical risk of bias. Refined research questions and eligibility criteria are required to isolate uncontrolled studies at lower than critical risk of bias.

Conclusion

The evidence to guide patients and clinicians on the efficacy of interventions to reduce or discontinue long term opioid treatment in patients with chronic non-cancer pain continues to be constrained by poor study methodology. Of particular concern is the lack of evidence regarding possible harms associated with these interventions and the reduction of opioids. Agreed standards for designing and reporting studies on the reduction or discontinuation of opioids are urgently needed.

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Contributors: NA, PG, and CEA-J conceived the study idea and designed the search strategy. NA, AGM, AG, and PG screened studies for eligibility and extracted data. NA, AGM, AG, CEA-J, FS, FMB, and PG double appraised the results of studies for risk of bias. NA, PG, AGM, FS, and FMB undertook the data synthesis and analysis. NA wrote the first drafts of the figures, tables, and appendices. NA wrote the first draft of the manuscript with PG. PG, AGM, CEA-J, FS, FMB, RM, and AG interpreted the data analysis and critically revised the manuscript. NA and PG are guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Not applicable.

Data sharing: See appendices 1-8 for all data available.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: We plan to disseminate the findings of this review to relevant patient and clinician groups at conferences and other meetings.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix 1: Existing reviews of clinical interventions for the reduction or discontinuation of long term opioid therapy prescribed for chronic pain and the effect of interventions on patient outcomes
Web appendix 2: Search strategy
Web appendix 3: Characteristics of included studies (n=166)
Web appendix 4: Risk of bias appraisal of included studies
Web appendix 5: Excluded studies (n=324)
Web appendix 6: Meta-analyses
Web appendix 7: Summary of findings tables
Web appendix 9: Protocol deviations