Title: Deprescribing opioids in chronic non-cancer pain; systematic review of randomised trials

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ABSTRACT

Background: Deprescribing, the process of reducing or discontinuing unnecessary or harmful medicines is an essential part of clinical practice.

Objective: To evaluate the efficacy of interventions designed to deprescribe opioid analgesics for pain relief in patients with chronic non-cancer pain.

Methods: We searched electronic databases including clinical trial registries from database inception to 13th January 2020 without restrictions, and conducted citation tracking. Our systematic review included randomised controlled trials (RCTs) evaluating interventions reducing the prescription, or use, of opioid analgesics in patients with chronic pain versus control. Inventions could be aimed at the patient, clinician or both. We excluded trials enrolling patients with cancer or illicit drug use. Two authors independently screened and extracted data. Outcome follow-up timepoints were short (≤ 3 months), intermediate (> 3 but < 12 months) or long (≥ 12 months) term. Primary outcome was the reduction in opioid dose (morphine milligram equivalent (MME) mg/day). Methodological quality was assessed using the Cochrane Risk of Bias Tool.

Results: We included 10 patient-focused RCT interventions (n = 835; median = 37 participants) and 2 testing clinician-focused interventions (n = 291 clinicians); none at low risk of bias. Patient-focused interventions did not reduce opioid dose at intermediate-term (e.g. dose reduction protocol, Mean Difference (MD) -19.9 MME, 95%CI -107.5 to 67.7), nor increased the number of participants who ceased their dose, nor increased 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) at long-term.

Limitations: Study heterogeneity prevented meta-analysis.

Conclusion: The small number of studies and heterogeneity prevented firm conclusions to recommend any one opioid analgesic deprescribing strategy in patients with chronic pain.

Systematic review registration number: PROSPERO CRD42017068422.

1. INTRODUCTION

Deprescribing is the process of reducing or discontinuing unnecessary or harmful medicines[1]. To address the 'opioid epidemic', clinical practice guidelines now discourage the initial prescription of opioid analgesics for chronic non-cancer pain[2] and strategies such as the introduction of Prescription Drug Monitoring Programs may reduce opioid prescribing[3, 4]. The management of people currently taking opioid analgesics requiring deprescribing can be a daunting task. There is no consensus on how to guide clinicians to deprescribe opioid analgesics. However, the overall concept of dose tapering involves the reduction of the dose slowly over time, such as 10% reduction per week, or longer if patients have been using their opioid analgesic for a prolonged time while monitoring side effects[5, 6]. Qualitative research has identified several obstacles that make deprescribing difficult including; clinician uncertainty around applying evidence-based medicine[7], and patient's fear of pain, withdrawal symptoms, the perceived lack of effectiveness of many non-opioid therapies and access of non-opioid options[8, 9].

Clinicians need to know which opioid dose reduction methods are most effective and safe for deprescribing opioid analgesics in patients with chronic pain[10]. Previous reviews of randomised trials assessing opioid analgesic deprescribing strategies in chronic pain have been inconclusive due to the limited number of studies[11] or focused on long-term opioid therapy (opioid use greater than one year)[12]. Since their publication, new randomised trials have emerged. Therefore, we aimed to review the current evidence of the efficacy of interventions designed to reduce/cease the prescription of, or the use of opioid analgesics in patients with chronic non-cancer pain.

2. METHODS

2.1 Data sources

This registered systematic review (PROSPERO: CRD42017068422) was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[13]. We searched PubMed (Legacy), MEDLINE, EMBASE, PsycINFO, Web of Science (Core Collection), Cochrane Central Register of Controlled Trials, International Pharmaceutical Abstracts, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform from database inception to 13th January 2020 with no language or publication date restrictions (SM). The database search strategy is presented in Appendix 1. We also conducted manual searching of reference list of included studies, and backward and forward citation

tracking of included papers using Scopus. We contacted authors by email with one follow up contact if relevant data were missing to determine eligibility (n = 11 studies).

2.2 Study selection

Two review authors from a panel (SM plus GF or MH) independently screened titles and the abstracts and full text of potentially eligible studies, and independently appraised eligibility. Disagreements were resolved by discussion first, then arbitration by a third author (CM). We included randomised controlled trials that evaluated an intervention to reduce or cease the prescription or use of prescription (non-illicit) opioids in adult (≥18 years) patients with chronic pain (i.e. three months' duration or longer) in a clinical setting compared to usual care (i.e. no intervention) or active control. The invention could be aimed at the patient, clinician or both. Interventions that were patient-focused aimed at reducing a patient's opioid dose, whereas clinician-focused interventions aimed at changing the clinician's behaviour. We excluded trials that exclusively enrolled patients with cancer, illicit drug users or women who were pregnant. We also excluded studies where opioid analgesics were not used for pain management.

2.3 Outcomes

The primary outcome was the mean reduction of daily dose (in morphine milligram equivalents) of opioid analgesic medication(s). Secondary outcomes were the reduction of opioid 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 pain intensity, disability and quality of life scores.

2.4 Data extraction and management

Two review authors from a panel (SM plus GF or MH) independently extracted data using piloted forms. Disagreements were resolved by discussion first, then arbitration by a third author (CM). Data extraction included bibliometric data (e.g. language, funding sources); study characteristics (e.g. setting, sample size); participants (e.g. age, gender, diagnosis, symptom duration); interventions and controls (type (i.e. medicine or therapy), dose, duration, mode of delivery); outcome data (e.g. proportion of participants who reduced or ceased their medication, serious adverse events including descriptors); and data completeness (i.e. percentage of missing data, how missing data were handled). Opioid analgesic medicines were defined as medicines listed as N02 according to the Anatomical Therapeutic Chemical (ATC) classification system[14] and were converted to

morphine milligram equivalent (MME)[2] dose if necessary to standardise for comparison. Follow-up time points of outcomes in individual studies were categorised as short (≤ 3 months), intermediate (> 3 but < 12 months) or long (≥ 12 months) term. If multiple time points fell within the same period, we used the time-point closest to seven weeks, six months and 12 months.

2.5 Risk of bias assessment

Methodological quality was independently assessed by two authors (the same authors who extracted the data on that study) using the Cochrane Risk of Bias Tool[15] (Appendix 2). Disagreements were resolved by discussion first, then arbitration by a third author (CM). A study was considered to have a low risk of bias if the study was scored low in six or more domains with no high risk of bias scores[15].

2.6 Data synthesis

The flow of studies was summarised in a study flow diagram following the PRISMA statement[13]. Study characteristics were reported descriptively. A narrative synthesis was used to present the results as clinical and statistical heterogeneity ($I^2 > 50\%$) prevented conducting a meta-analysis. Continuous outcomes are presented as mean differences between the intervention and control groups, and dichotomous outcomes are presented as absolute risk differences between the intervention and control groups. Heterogeneity prevented the assessment of the overall quality of evidence using a Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[16]. We were also unable to perform the pre-planned sensitivity analysis (i.e. explain potential sources of heterogeneity and differences in risk of bias) and subgroup (i.e. chronic low back pain population) analyses due to the low number of studies.

3. RESULTS

The search retrieved 37,406 records, of which 12 trials were included in this review plus ten ongoing clinical trials (NCT02737826, NCT03521960; NCT03743402, NCT03889418, NCT03916276, NCT03950791, NCT04013529, NCT04097743, NCT04184362, ISRCTN49470934) (Appendix 3). All studies were published from 2010 onwards, were published in English and were all conducted in the United States of America except one study from Australia[17] and one from Denmark[18].

3.1 Study characteristics

3.1.1 Patient-focused interventions

A total of 835 adult participants with chronic non-cancer pain were randomised with a mean age of 48.0 years (Standard Deviation (SD) 16.9). Most trials were of small size (median = 37 participants with chronic pain range 12 to 411) (Table 1). There were 10 studies of patient-focused interventions[17-26] including:

- Dose reduction protocols[18, 23, 24]. Two studies specifying dose reduction targets as part of the protocol such as starting with a 10% reduction of daily dose every week[18, 24]. One study initiated dose reduction by sending a letter to both patients and their community-based providers upon emergency department discharge[23].
- Opioid replacement with buprenorphine[19, 25] (e.g. gradual tapering versus steady dosing[19], tapering versus switching to morphine sulfate or oxycodone hydrochloride[25]) or varenicline[21] (titration up 1 mg twice daily versus placebo).
- Non-pharmacological therapies of mindfulness (versus active control of support group sessions)[20], Therapeutic Interactive Voice Response program (versus usual care)[22], meditation and cognitive behavioural therapy (versus usual care)[26], and electroacupuncture (versus sham)[17].

The most frequent comparator was usual care or no change in treatment[18, 22-24, 26].

3.1.1 Clinician-focused interventions

There were two clinician-focused interventions where the deprescribing intervention targeted changing clinician behaviour[27, 28] (Table 1) (n = 291 clinicians, 985 adults with chronic pain). Clinician-focused deprescribing interventions were an education-based multicomponent intervention in primary care consisting of training sessions plus decision tools to improve guideline adherence and decrease opioid misuse risk (e.g. early prescription refills) versus decision tools[27]; and online education of patient simulation plus case-based learning for safer prescribing to reduce prescribing behaviour (e.g. early prescription refills) versus existing online education[28].

3.2 Risk of bias

No study had an overall low risk of bias (Figure 1). Blinding was the most frequent domain not met; 66% of studies did not have participant blinding, 91% of studies did not blind intervention providers, and 50% of studies did not blind outcome assessors. Two studies were scored ‘high’ risk of bias due to high dropout rates

during follow-up [18, 20]. Industry sponsorship was scored within 'other bias'. We identified one industry-funded study[25], and two studies where the role of industry funding was unclear[19, 28].

3.3 Outcomes

3.3.1 Morphine equivalent daily dose reduction

The reduction in daily morphine equivalent dose due to deprescribing interventions was reported by three patient-focused intervention studies of dose reduction protocols[18, 24], non-pharmacological therapies[17] and one clinician-focused intervention of multicomponent training sessions and decision tools versus decision tools alone[27] (Figure 2). 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 to 275.5 MME/day). Considerable statistical (I^2 = 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[18] (Mean Difference -27.9 MME/day, 95%CI -41.1 to -14.7) (Figure 2), however, this study had a number of dropouts. One clinician-focused study (n = 985 participants with 53 physicians) did significantly reduce daily opioid dose compared to decision tools alone at long-term follow-up[27] (Mean Difference -5.3 MME/day, 95%CI -6.2 to -4.5).

3.3.2 Reduction of opioid prescriptions

The number of opioid analgesic prescriptions reduced by deprescribing interventions was reported in four studies; three patient-focused interventions [19, 23, 24] and one clinician-focused intervention[27] (Figure 3). Clinical heterogeneity prevented pooling of two patient-focused intervention studies at immediate-term (n = 47), however, one study showed a borderline significant effect of dose reduction protocol[24] (Risk Difference -0.3, 95%CI -0.6 to -0.0; 77.8% reduction of prescriptions in the intervention group versus 47.1% in the control group). At long-term follow-up, one patient-focused intervention of a dose reduction protocol (n = 406)[23] and one clinician-focused study[27] 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 versus 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 versus 35.8% in the control group respectively).

3.3.3 Number of participants who ceased using their opioid analgesic prescription

Five studies reported the number of participants who ceased using their opioid analgesics due to deprescribing interventions; four patient-focused intervention studies[19, 21, 22, 24] and one clinician-focused intervention[27] (Figure 3). 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 (Figure 3). One clinician-focused study[27] nearly showed statistical significance at long-term (Risk Difference -0.1, 95%CI -0.1 to 0.0; 21.3% ceased in the intervention group versus 16.8% in the control group).

3.3.4 Number of participants who reduced the dose of their opioid analgesic prescription

The proportion of participants who were able to reduce their opioid analgesic use was reported by six studies; five patient-focused interventions[17, 19, 21, 24, 25] and one clinician-focus intervention[27] (Figure 3). Clinical heterogeneity prevented pooling the patient-focused intervention studies. There were no significant effects of deprescribing interventions at short-term (n = 170) or at intermediate-term (n = 47) except a moderately large risk difference of borderline statistical significance favouring one patient-focused intervention of a dose reduction protocol[24] (Risk Difference -0.3, 95%CI -0.6 to 0.0; 72.2% reduced their opioid use in the intervention group versus 41.2% in the control group). One clinician-focused intervention did have a significant risk difference favouring the intervention[27] in reducing a patient's daily use at 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.

3.3.5 Adverse events

Serious adverse events were reported in four studies of patient-focused interventions[17, 21, 24, 25]. Serious adverse events were infrequent (at short-term, one event in 93 participants in the intervention group, and zero events in 77 participants in the control group. At 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 (Figure 4). Serious adverse events were chest pain and dyspnoea[25], and an allergic reaction[24]. Adverse events were reported in three studies of patient-focused interventions[17, 24, 25]. There was no risk difference between groups for the number of participants reporting adverse events at short-term (Risk Difference 0.1, 95%CI -0.1 to 0.3) or intermediate-term (Risk Difference 0.0, 95%CI -0.1 to 0.1) [24, 25] (Figure 4). 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)[17, 19, 25].

Five studies did not have any adverse event withdrawals [21-24,26], while two studies did not provide sufficient detail to determine if the reasons of the study withdrawal were adverse event related [18, 20].

3.3.6 Pain, disability and quality of life

Pain outcomes were reported in seven studies of patient-focused interventions [17, 18, 20, 21, 22, 24, 26] (Online Resource Appendix 4). Considerable statistical heterogeneity prevented pooling at short-term and intermediate-term (I^2 = 100%, I^2 = 95% respectively). Overall, two studies reported greater reduction in pain in the intervention group compared to controls[20, 24].

Disability outcomes were reported in six studies of patient-focused interventions[17, 18, 20, 22, 24, 26] (Online Resource Appendix 4). Statistical heterogeneity prevented pooling at short-term and intermediate-term (I^2 = 99%, I^2 = 57% respectively). Overall, two studies demonstrated a greater reduction in disability compared to controls[20, 24].

Quality of life outcomes were reported in three studies of patient-focused interventions[17, 18, 22] (Online Resource Appendix 4). Overall, one study had a small effect on quality of life mental and physical composite scores[17].

4. DISCUSSION

Our review updated the current body of evidence and found twelve eligible randomised controlled trials of which none were considered to have overall low risk of bias, and statistical and clinical heterogeneity prevented firm recommendations to support any opioid analgesic deprescribing strategy for chronic pain. Patient-focused deprescribing interventions were of dose reduction protocols, opioid replacement or a range of non-pharmacotherapies such as mindfulness. One deprescribing intervention (a dose reduction protocol) reduced the daily opioid dose at short-term. However, the other dose reduction protocol did not reduce the daily opioid dose at intermediate-term. Overall, patient-focused deprescribing interventions did not reduce the number of participants who ceased their opioid medicine or increased the risk of serious adverse events or adverse events. Clinician-focused deprescribing interventions that targeted changing clinician behaviour were education-based and showed a reduction in the daily opioid dose prescribed, opioid use and the number of prescriptions issued at long-term.

The strength of our review includes extending the previous small body of literature by incorporating five new randomised trials [18, 20, 23, 27, 28] plus identifying ten registered, ongoing randomised trials potentially eligible for inclusion in future reviews. Homogeneity was noted as most studies were published from the USA. The quality of the evidence may increase over time especially if new eligible studies are conducted with enhanced methodological rigour. The addition of new trials will also provide a greater evidence base to generalise the results across different types of chronic pain conditions and healthcare systems. An additional strength is that we included all studies regardless of publication language and length of opioid use when prescribed for the management of pain. However, clinical and statistical heterogeneity limited our findings of the review due to the range of deprescribing interventions across the small pool of eligible randomised trials and prevented any subgroup analyses of assessing deprescribing interventions in patients with chronic low back pain.

Previous reviews assessing deprescribing interventions to cease opioid analgesics in chronic pain were also unable to draw definite conclusions due to heterogeneity[11], and low methodological quality[12, 29]. Two of these previous reviews[11, 29] were small (i.e. including five randomised trials) while the other review was larger by including both controlled and uncontrolled observational studies as well as randomised controlled trials of patients on long-term opioid therapy (n = 67 studies). Our review is the first review to consider if industry support potentially influenced study findings by considering industry funding in the risk of bias assessment. We identified two studies where the role of industry funding was unclear[19, 28]. Similarly to the review by Frank et al[12], we noted that randomised trials often were inadequately powered due to the small number of participants and some studies having high dropout rates to the point of study discontinuation (e.g. Kurita 2018). However, we did not assess sample size within the risk of bias assessment like the review by Eccleston et al who rated studies as high risk of bias if there were fewer than 50 participants per treatment arm.

Our review highlights the urgent need for more research to identify evidence-based methods to decrease the use and prescription of opioid analgesics in chronic non-cancer pain. At present, the lack of evidence to support any particular deprescribing intervention creates uncertainty for clinicians on how they might best manage their patients with chronic pain taking opioid analgesics. Meanwhile, clinicians may reflect on individual studies for empirical evidence to guide their deprescribing in patients with chronic pain. For example, in two studies that reported positive conclusions, behavioural approaches were incorporated into the deprescribing process[20, 24].

However, patients may find access to behavioural programs via pain management programs costly or less accessibile; and sourcing behavioural treatments in another setting may be worthwhile.

Future research is needed to establish effective strategies for reducing the initial prescription of opioid analgesics, which in turn may prevent the potential need for future opioid cessation strategies. We found clinician-focused interventions could change clinician's prescribing behaviour, leading to the reduction of issuing early prescription refills. Future clinician-focused educational strategies may also consider methods to delay or reduce the number of initial prescription of opioids to patients with chronic pain. Opioid stewardship programs such as coordinated programs that promote appropriate use of opioid medication, may provide strategies to reduce long-term opioid use and to reduce the initial prescription of opioid analgesics. Research into reducing opioid use in patients with chronic pain could evaluate strategies of dose reduction protocols that include a patient support component such as pain management education. This strategy is similar to the small 35-participant pilot study by Sullivan et al. However, the effects of this strategy should be evaluated in a larger sample of randomised patients with chronic pain before making any strong clinical recommendations. Additionally, we did not find a larger scale version of the Sullivan et al study as a registered clinical trial. Future research into strategies to reduce the unnecessary prescription of opioids may further investigate clinician-focused deprescribing interventions.

5. CONCLUSION

Currently, the small number of randomised trials, and clinical and statistical heterogeneity prevent any firm conclusions on the recommendation of any specific opioid analgesic deprescribing strategy for people with chronic pain. Overall, patient-focused deprescribing interventions frequently did not provide a greater effect in the intervention group compared to controls. However, one clinician-focused deprescribing intervention did change clinician prescribing behaviour at long-term and may be an implementable deprescribing strategy upon further research.

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Figure legends

Fig 1 Summary of risk of bias

Fig 2 Daily morphine milligram equivalent dose reduction (mg/day)

Fig 3 The effect of deprescribing interventions on the reduction of opioid prescriptions, and the number of participants ceasing and reducing their opioid analgesic use.

Fig 4 The risk difference of opioid analgesic deprescribing interventions on serious adverse events and adverse events

Table captions

Table 1 Description of included studies

Online Resources

Appendix 1 Search strategy

Appendix 2 Risk of bias

Appendix 3 Study flow diagram

Appendix 4 Pain, disability and quality of life forest plots

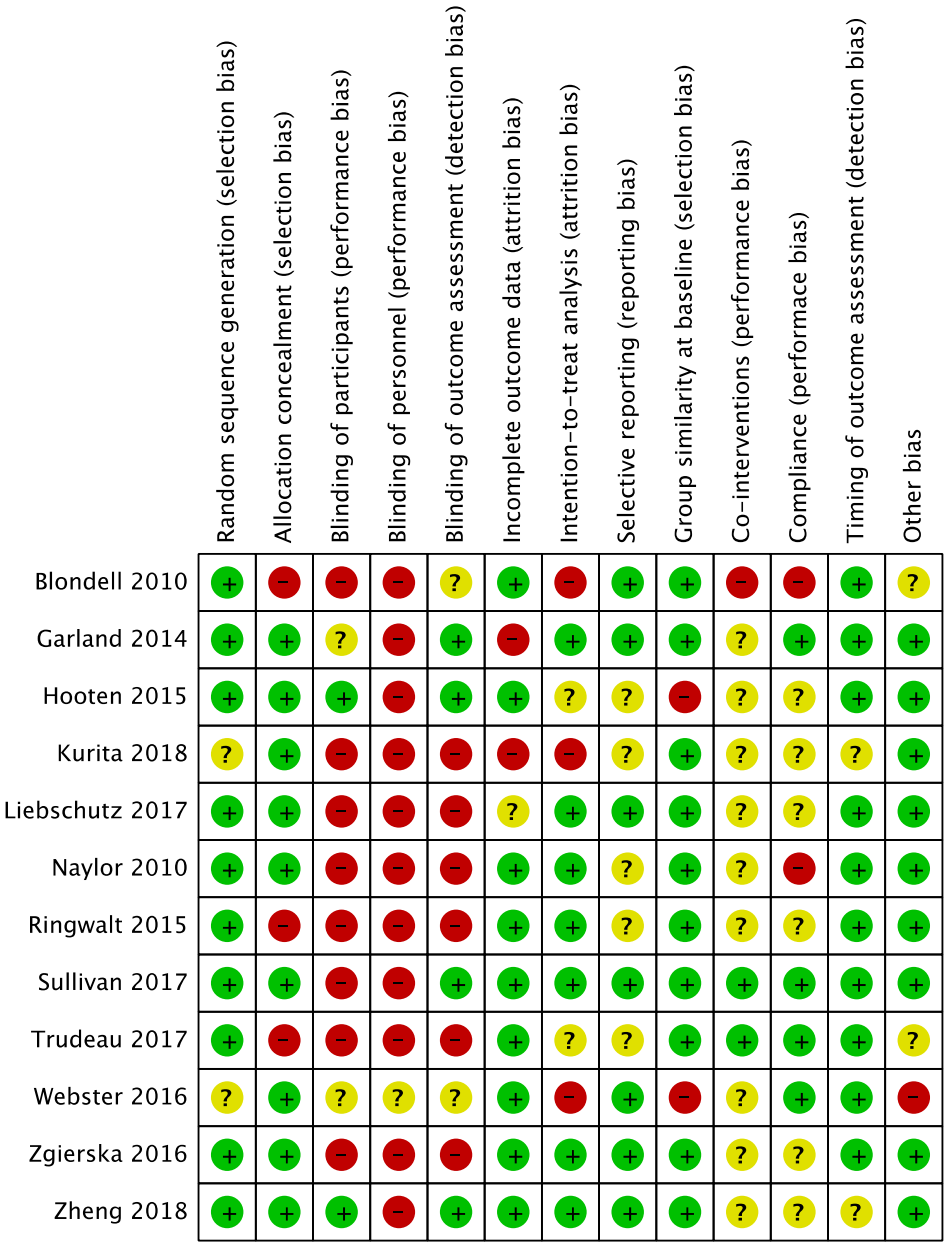

Fig 1 Summary of risk of bias

Each domain was scored as low risk of bias (+), unclear (?) or high (-) risk of bias.

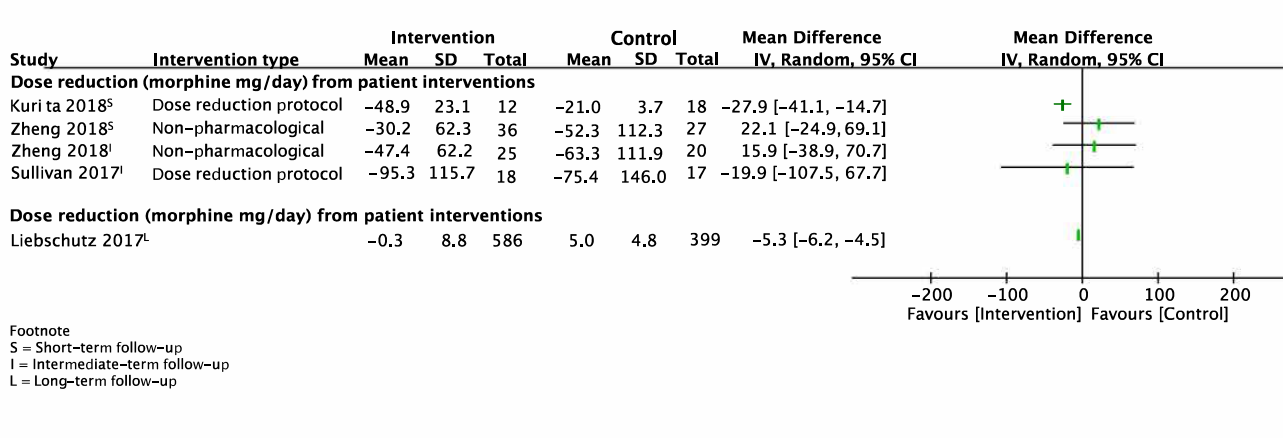

Fig 2 Daily morphine milligram equivalent dose reduction (mg/day)

Abbreviations: IV = Inverse Variance; CI = Confidence Interval; S = Short-term follow-up; I = Intermediate-term follow-up; L = Long-term follow-up.

Patient-focused interventions varied and included dose reduction protocols (Kurita 2018[18], Sullivan 2017[24]) and non-pharmacological interventions (Zheng 2018[17]). The clinician-focused study was of multicomponent training sessions and decision tools (Liebschutz 2017[27]). Other studies that reported dose reduction included Trudeau 2017[28] but reported as a categorical measure of reluctance prescribing opioids on a 1 to 5 Likert scale; individual group scores were unavailable in Zgierska 2016[26] and standard deviation unavailable in Blondell 2010[19] and Naylor 2010[22].

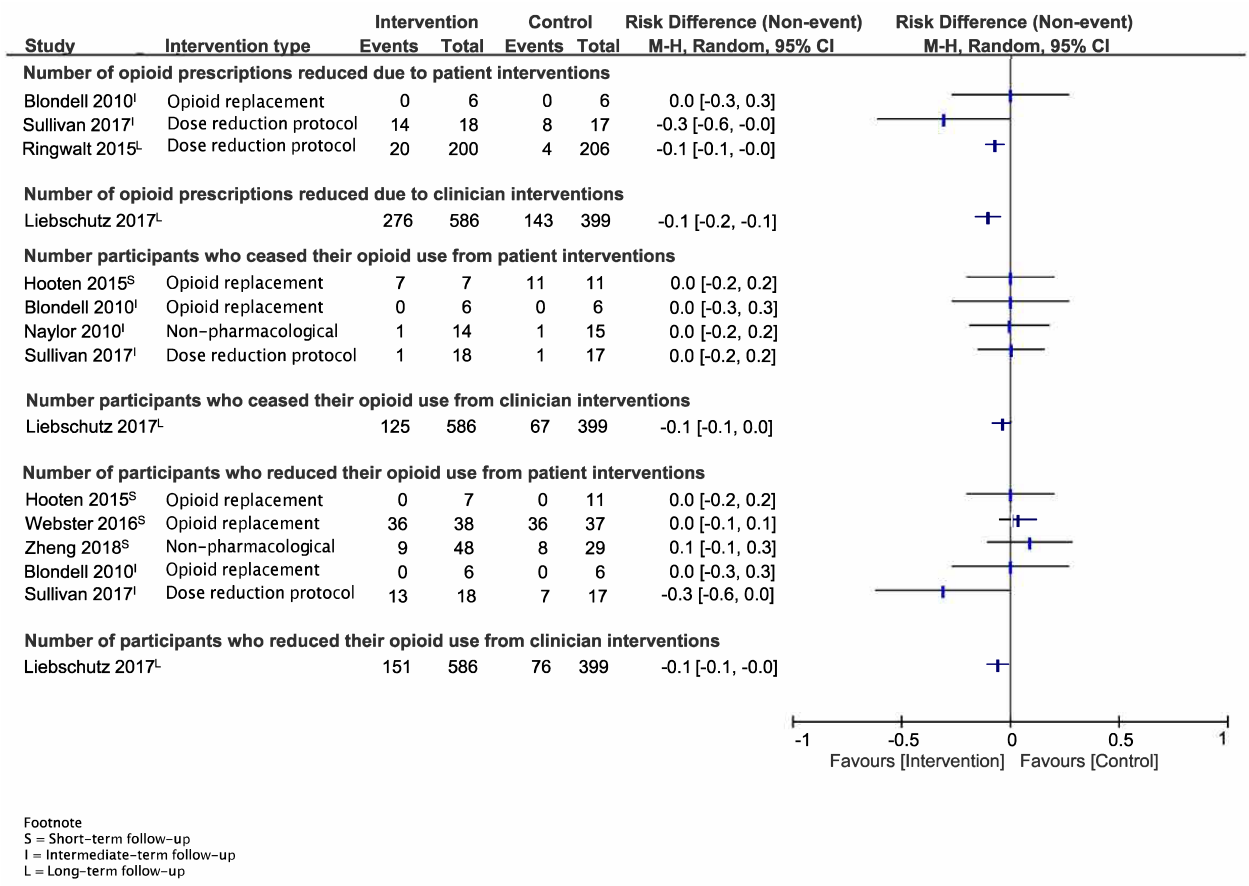

Fig 3 The effect of deprescribing interventions on the reduction of opioid prescriptions, and the number of participants ceasing and reducing their opioid analgesic use.

Abbreviations: M-H = Mantel-Haenszel; CI = Confidence Interval; S = Short-term follow-up; I = Intermediate-term follow-up; L = Long-term follow-up.

Patient-focused interventions varied and included opioid replacement therapy with varenicline (Hooten 2015[21]) or buprenorphine (Blondell 2010[19], Webster 2016[25]); non-pharmacological interventions (Naylor 2010[22], Zheng 2018[17]); and dose reduction protocols (Sullivan 2017[24], Ringwalt 2015[23]). The clinician-focused study was of multicomponent training sessions and decision tools (Liebschutz 2017[27]).

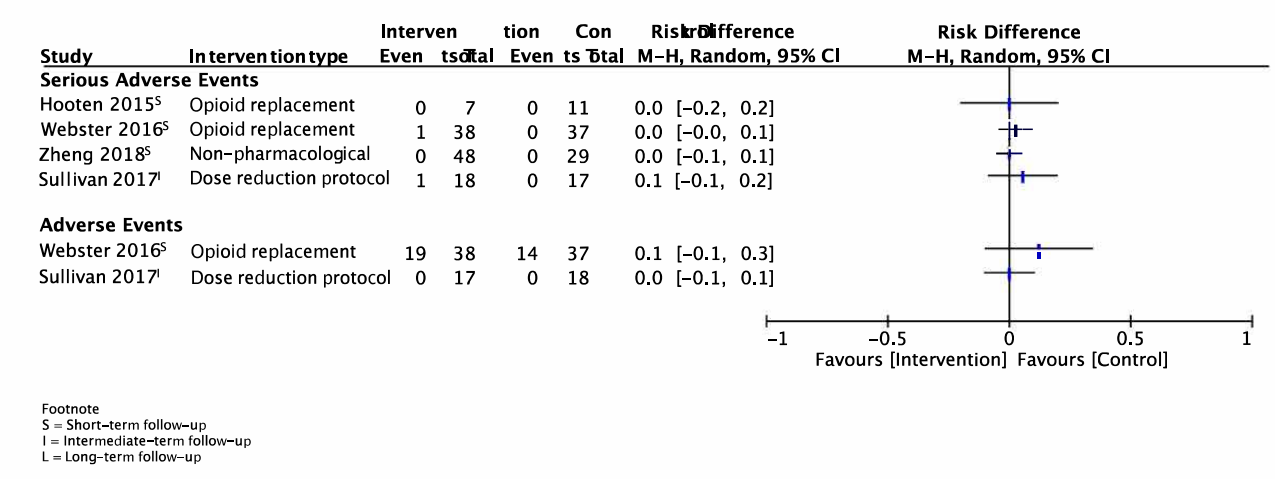

Fig 4 The risk difference of opioid analgesic deprescribing interventions on serious adverse events and adverse events

Abbreviations: M-H = Mantel-Haenszel; CI = Confidence Interval; I = Intermediate-term follow-up; L = Long-term follow-up.

All studies were patient-focused interventions and included opioid replacement therapy with varenicline (Hooten 2015[21]) or buprenorphine (Webster 2016[25]); a non-pharmacological intervention (Zheng 2018[17]); or dose reduction protocol (Sullivan 2017[24]). Events represent the number of participants with one or more (serious) adverse events. One study reported adverse events per the number of electroacupuncture sessions rather than participants (86 events/496 sessions in the electroacupuncture group, 70 events/329 sessions in the sham electroacupuncture group; Risk Difference 0.4, 95%CI 0.1 to 0.7)[17].

Study	Study population	Intervention	Outcomes	Conclusions
Patient interventions				
Blondell et al 2010[19]	12 chronic non-cancer patients from a multidisciplinary outpatient pain management clinic, USA	All participants were admitted to hospital to stabilise opioid dose (4 mg sublingual buprenorphine/naloxone tablet + 2mg dose every 2 hours until withdrawal symptoms and signs controlled, ~24-48 hours). At discharge participants were randomised (open label) to either: **Opioid discontinuation protocol** (gradual buprenorphine/naloxone tapering over 4 months (<16 mg/day), then discontinued for 2 months. Participants could opt out of the tapering protocol and initiate steady dose schedule) ***OR*** **Steady or regular buprenorphine/naloxone dosing** (<16 mg/day for 6 months). Rescue medicine and requested to continue usual care (at their expense).	Dose reduction, number prescriptions reduced, number patients ceased/reduced at intermediate-term.	"Participants with chronic non-cancer pain and coexistent opioid addiction were more likely to adhere to steady doses of buprenorphine for opioid replacement therapy than tapering doses of buprenorphine for opioid discontinuation therapy. None of the 6 participants in the tapering arm could successfully complete the 6-month protocol".
Garland et al 2014[20]	115 chronic non-cancer, arthritis or fibromyalgia patients from primary and tertiary care clinics, USA	**Mindfulness-Oriented Recovery Enhancement (MORE)** (8-session group intervention of 8-12 individuals of 2 hours duration including mindfulness training, positive reappraisal training, raining in favouring pleasant events and positive affectivity. Homework included CD guided 15 minute mindfulness practice session) ***Or*** **Active control (support group sessions)** (8 weekly, 2-hour conventional support group sessions of 8-12 individuals with facilitator led discussion topics pertinent to chronic pain and long-term opioid use, matched to MORE intervention themes).	Pain, disability at short and intermediate-term.	"MORE reduces pain severity and functional interference for up to 3 months following treatment, and decreases sympathetic stress arousal, desire for opioids, and disordered opioid use at the end of treatment"
Hooten et al 2015[21]	21 chronic non-cancer patients of interdisciplinary pain program, USA	Patients within interdisciplinary pain program were randomised to either: **Varenicline** (0.5 mg QD for 3 days, then 0.5 mg BID days 4 to 7, then 1 mg BID days 8 to 15). ***Or*** **Placebo** (identically appearing tablets).	Number ceased/reduced, pain and SAE at short-term.	The pilot study found "that opioid withdrawal scores tended to decrease over the course of opioid tapering in those receiving varenicline and increase in those receiving placebo. Varenicline was well-tolerated in this population, with no adverse drug effects (including nausea) observed and no effect on improvements in pain severity and depression."

Kurita et al 2018[18]	35 chronic non-cancer patients on a waiting list to a pain centre, Demark	**Taper off group** (10% reduction of the daily opioid dose every week (or 2 weeks if necessary) until discontinuation of opioid treatment for up to 6 months). Clonidine use (25–150 μg/day) permitted to manage withdrawal. Managed by a multidisciplinary team). ***Or*** **Control** (maintained same treatment for next 6 months. Offered intervention on study completion).	Dose reduction, pain, disability and quality of life at short-term.	"The opioid tapering-off program was not successful due to the vast number of dropouts". "However, improvements after opioid treatment stabilization were achieved and stable pain intensity in those tapered off may encourage the development of more refined programs."
Naylor et al 2010[22]	55 chronic musculoskeletal pain (back pain, osteoarthritis, fibromyalgia) patients at a university medical centre, USA	All participants completed group pain coping skills training of 90-minute weekly sessions over 11 weeks. Then randomised to either: **Therapeutic Interactive Voice Response (TIVR) program plus usual care** (4 months access to TIVR, where participants interact with a computer through the telephone keypad that aims to maintain treatment gains following their pain coping skills training. TIVR has four components: 1) 21-item daily self-monitoring questionnaire about pain, medication etc; 2) didactic review of skills, a verbal review of the 8 pain management skills learnt during skills training; 3) guided behavioural rehearsal of pain coping skills, pre-recorded voice of a therapist guiding them through behavioural rehearsals from skills training; 4) a monthly therapist feedback message, a personalised recorded message from the therapist). ***Or*** **Usual care** (per participants usual sources, unmeasured)	Dose reduction, number ceased, pain, disability and quality of life at intermediate-term.	"We have previously demonstrated the efficacy of Therapeutic IVR to decrease pain and improve coping; this analysis demonstrates that the use of TIVR may also result in concurrent reductions in opioid analgesic and NSAID medications use."
Ringwalt et al 2015[23]	411 chronic non-cancer patients from 13 Emergency Departments, USA	Patients identified in electronic medical records with frequent (>10) visits to the emergency department over a 12 month period were randomised to either: **Intervention** (1) advice to the patient's emergency department provider to advise the patient to visit a community-based primary care provider, pain clinic etc. on a supplied handout, and not to prescribe opioids; and 2) a letter sent to both patients and their community-based providers informing that a group of medical providers determined that they should no longer receive opioid pain medication). ***Or*** **Usual Care** (no intervention for 12 months).	Number prescriptions reduced at long-term.	"Our study has demonstrated the positive effects of our intervention on repeat visits and opioid analgesics prescribed to a population of very frequent visitors to a set of electronically linked EDs who are characterized by CNCP".

Sullivan et al 2017[24]	35 chronic non-cancer from self-referral, primary and tertiary clinics, USA	Non-blinded randomisation to either: **Opioid Taper Support intervention** (10% reduction of original dose per week until 30% of original dose reached. Then, 10% reduction recalculated, then proceeded by 10% of this new dose per week. Plus 17 weekly 30-minute support sessions containing pain self-management, pain education, behavioural techniques, sleep education. Homework included workbook, CD with relaxation exercises. ***Or*** **Usual Care** (for 34 weeks, only restriction was to avoid buprenorphine).	Dose reduction, number prescriptions reduced, number patients ceased/reduced, pain, disability, SAE, AE at intermediate-term.	The pilot study showed "lower opioid doses and pain severity ratings were observed at 22 weeks in both groups. The groups did not differ significantly at 22 weeks in opioid dose or pain severity, but the taper support group improved significantly more in pain interference, pain self-efficacy, and perceived opioid problems"
Webster et al 2016[25]	39 chronic pain patients in a clinic in USA	Patients receiving around-the-clock μ-opioid agonist therapy (confirmed opioid dependent by naloxone challenge), continued their opioid therapy and randomised (cross-over study, double-blind, double-dummy to either: **Treatment AB** (Treatment A of 2 doses of buccal buprenorphine. A subject's original dose was reduced to 50%, then given 2 doses of either 300 or 450 μg of buprenorphine (determined by original dose) for 24 hours duration, then received their normal opioid therapy. After returning to clinic 7-14 days later, participants received Treatment B of 2 doses of active full μ-opioid agonist, morphine sulfate or oxycodone hydrochloride, for 24 hours). ***Or*** **Treatment BA** (Treatment B ***then*** Treatment A, as detailed above).	Number patients reduced, SAE, AE at short-term.	"Chronic pain patients treated with around-the-clock full μ-opioid agonist therapy can be switched to buccal buprenorphine (a partial μ -opioid agonist) at approximately 50% of the full μ -opioid agonist dose without an increased risk of opioid withdrawal or loss of pain control".
Zgierska et al 2016[26]	35 chronic low back pain patients from a University outpatient clinic, USA	**Mediation-CBT group plus usual care** (2 hour sessions for 8 weeks of mindfulness meditation & cognitive behavioural therapy. Plus, homework of 30 minute mindfulness practice, ≥ 6 days per week). ***Or*** **Usual Care** (for 8 weeks duration. Participants could receive the intervention on study completion).	Dose reduction, pain, disability at short and intermediate-term.	The pilot study found that "meditation-CBT intervention reduced pain severity … in patients with opioid-treated CLBP". "We did not find a statistically significant decrease in the use of opioid medications during this study".
Zheng et al 2018[17]	77 chronic musculoskeletal pain patients from pain clinics, Australia	After a 5 week run-in period to stabilise all treatments, all patients received pain medication management (PMM) brochure in the 5th week. Participants were given individualised opioid medication reduction schedules and asked to reduce their dosage by 30% in week 8, 50% by week 11, and 75% to 100% by week 14, as long as their pain did not get worse). Then randomised to 10 week intervention of either:	Dose reduction, number patients reduced, pain, disability, QoL, SAE, and AE at short and intermediate-term.	There was "reduced opioid medication usage in the Short-term with no group difference either at the end of the treatment or the follow-up. Reduction of OM-related (opioid medications] adverse events and

		Electoacupuncture (EA) (≥ 12 needles per session, consisting of four formula points and eight supplementary points chosen according to the adverse effects of opioid medications participants experienced that week. Sessions were twice a week for 4 weeks, then once a week for 2 weeks, then every 2 weeks for 4 weeks. ***Or*** **Sham electoacupuncture (SEA)**; Sham electroacupuncture was simulated with a manufacturer-modified non-functioning stimulator to match a set of sham points. Same session schedule as EA group.		pain and improvement of function and depression were similar".
Clinician interventions				
Liebschutz et al 2017[27]	53 primary care clinicians from 4 urban primary care clinics, USA involving 985 chronic pain patients	Clinicians with patients receiving long-term opioid therapy with an active opioid prescription in the past 60 days were randomised to either: **Multicomponent primary care-based intervention (TOPCARE)** included 4 components; (1) Nurse care manager collected information e.g. pain, prepare prescriptions, opioid misuse risk; (2) web-based electronic registry to facilitate population management from electronic health record; (3) single 1-on-1 academic detailing session; and (4) orientation and access to electronic decision tools online platform. For 12 months duration; to improve guideline prescribing adherence and decrease misuse (e.g. reduce prescription of early refills). ***Or*** **Control intervention** (orientation and access to electronic decision tools online platform only).	Dose reduction, number prescriptions reduced, number patients ceased/reduced at long-term.	"A multicomponent intervention improved guideline-concordant care but did not decrease early opioid refills".
Trudeau et al 2017[28]	238 primary care clinicians, USA	Clinicians who provided treatment for chronic non-cancer pain patients in the last 90 days were randomised to either: **Online education** (Managing Addiction and Pain in Primary Care (MAP-PC) program, which is an immersive, standardised patient simulation–type, case based continuing education program about the management of chronic pain and addiction to reduce prescribing behaviour (e.g. early refills). ***Or*** **Active control** (existing online continuing education courses with text-based content).	Dose reduction at short and intermediate-term.	"Findings suggest online CE [continuing education] programs may positively impact PCPs' knowledge, attitudes, and pain practice behaviors". "Post hoc comparisons suggested that participants in the experimental condition were less likely to endorse use of opioid TRFs [tamper-resistant formulations] over time compared with the control".

Ongoing studies			
Identifier	**Status**	**Title**	**Outcomes reported**
NCT02741076	Active, not recruiting chronic low back pain patients	Structured discontinuation vs continued therapy in suboptimal and optimal responders to high-dose long-term opioids for chronic pain	Pain, disability, QoL.
NCT03521960	Recruiting patients	Buspirone for opioid tapering	Number patients ceased/reduced.
NCT03743402	Recruiting patients	Strategies to improve pain and enjoy life (STRIPE)	Dose reduction, pain.
NCT03889418	Recruiting patients	Opioid treatment and recovery through a safe pain management program	Dose reduction, pain, QoL
NCT03916276	Recruiting patients	Living In Full Even (LIFE) with pain study	Dose reduction, pain.
NCT03950791	Recruiting patients	Single session class to reduce opioid use in chronic pain	Dose reduction, pain.
NCT04013529	Recruiting patients	Connected health to decrease opioid use in patients with chronic pain	Dose reduction, pain.
NCT04097743	Not yet recruiting	Pain catastrophizing and prescription opioid craving	Dose reduction, pain
ISRCTN49470934	Ongoing, no longer recruiting	Improving the wellbeing of people living with opioid treated chronic pain	Dose reduction, number patients ceased/reduced, pain, QoL and AE.

Table 1 Description of included studies.

Abbreviations: USA = United States of America; SAE = Serious Adverse Event; AE = Adverse Event; QoL = Quality of Life; QD = *quaque die* (i.e. once daily); BID = *bis in die* (i.e. twice daily).