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Systematic Review

Effectiveness of non-opioid interventions to reduce opioid withdrawal symptoms in patients with chronic pain: a systematic review

Annely I. Langejan MSc, Loes de Kleijn MSc*, Hanneke J.B.M. Rijkels-Otters PhD, Stan F.J. Chudy MSc, Alessandro Chiarotto PhD, Bart W. Koes PhD

Department of General Practice, Erasmus MC, University Medical Center, Rotterdam, the Netherlands

*Corresponding author: Loes de Kleijn, Department of General Practice, Erasmus MC, University Medical Center, Doctor Molewaterplein 40, Na-gebouw nr. 19, 3015 GD Rotterdam, the Netherlands. Email: l.dekleijn@erasmusmc.nl

Abstract

Background: Dealing with the opioid crisis, medical doctors are keen to learn how to best treat opioid dependency in patients with chronic non-cancer pain. Opioid replacement therapy is commonly used, but success rates vary widely. Since many patients still experience severe withdrawal symptoms, additional interventions are necessary.

Objective: To review the effectiveness of interventions in the treatment of withdrawal symptoms during opioid tapering or acute withdrawal in patients with long-term non-cancer pain.

Methods: A systematic review was conducted in Embase.com, MEDLINE, Web of Science, PsycINFO, and Cochrane CENTRAL register of trials. Studies eligible for inclusion were (non-)randomized controlled trials in adults with long-term opioid prescriptions for non-cancer pain. Included trials had to compare a non-opioid intervention to placebo, usual care, no treatment, or non-opioid drug and had to report on withdrawal symptoms as an outcome. Study quality was assessed with the 2.0 Cochrane risk of bias (RoB) tool. Evidence quality was rated following the GRADE approach.

Results: One trial (n = 21, some concerns regarding RoB) compared Varenicline to placebo. There was no statistically significant between-group reduction of withdrawal symptoms (moderate-quality evidence).

Conclusions: Evidence from clinical trials on interventions reducing withdrawal symptoms is scarce. Based on one trial with a small sample size, no firm conclusion can be drawn. Meanwhile, doctors are in dire need for therapeutic options to tackle withdrawal symptoms while tapering patients with prescription opioid dependence. We hope this review draws attention to this unfortunate research gap so that future research can provide doctors with answers.

Lay summary

There is a global increase of patients depended on opioids prescribed by a doctor for chronic non-cancer pain. Tapering these drugs is challenging, especially since treatment options for withdrawal symptoms are lacking. We conducted a systematic review of controlled studies on interventions aimed at reducing withdrawal symptoms during opioid tapering in patients with long term opioid treatment for chronic non-cancer pain. One trial could be included. No firm conclusions can be drawn from this one trial. Hence, this review demonstrates that to improve care for patients depended on opioids for chronic non-cancer pain, more high-quality research in this field is necessary.

Key words: chronic pain, interventions, non-opioid, opioid dependency, treatment, withdrawal symptoms

Background

Chronic non-cancer pain (CNCP) is one of the main causes for the increasing global non-fatal burden of disease and non-fatal health loss for nearly three decades.[1] Research shows that opioid prescribing for CNCP is common and has increased over time.[2] In the United States, this increase has led to the "opioid crisis" costing thousands of lives each year.[3] However, this opioid crisis is not limited to the United States alone. Last year, many European countries were ranked in the top-10 of countries with the highest prescription opioid use.[4] A retrospective observational study found an increase in overall opioid prescriptions by general practitioners (GPs) in the United Kingdom from 2010 to 2014.[5] Experts compare this increase to the starting point of the opioid crisis in the United States and worry about these trends.[6] Between 1993 and 2018, the mortality rates of opioid-related deaths have increased substantially, due to prescription opioids like codeine and tramadol.[5,7] Although a stabilization in the number of opioid prescriptions by GPs in the United Kingdom is visible since 2016 July, with a decline in some opioids such as fentanyl and tramadol since 2018 but an increase in others such as oxycodone, the overall number of opioid prescriptions by GPs is not declining.[8]

Long-term opioid use has several potential health risks and can lead to dependence,[9,10] addiction, overdose incidents, and

Key messages

- First review on interventions to reduce opioid withdrawal when tapering opioids.
- Only one trial could be included, demonstrating scarcity of evidence.
- To improve the treatment of opioid withdrawal symptoms, more trials are necessary.

death.[11] Over the last two decades, healthcare professionals have emphasized the problem of iatrogenic opioid dependence and its increase following the release of new opioids. A review from 2009 showed the surge of addiction and abuse of Oxycontin, after the launch and marketing of this new slow-release opioid.[12]

During a medically supervised opioid taper, pharmacological therapy with (partial) opioid receptor agonists has been one of the most used therapies.[13] The prescribed opioid is usually replaced by Methadone or Buprenorphine, followed by tapering until (near) abstinence is accomplished.[12] Previous studies published varying success rates ranging from 4% to 100%.[14,15] Patients trying to cease opioid use often fail due to withdrawal symptoms, such as craving, anxiety, restlessness, gastrointestinal distress, and tachycardia.[16] While opioid prescriptions have increased in general practice, tapering of opioids remains difficult due to the lack of guidelines on treating withdrawal symptoms. GPs are in need for further solutions to manage withdrawal symptoms.

Apart from opioid replacement therapy, recent research considers other interventions useful for opioid tapering and reducing withdrawal symptoms.[17] Some trials have pointed out the potential benefits of pharmacological treatments with α2-adrenergic agonists, benzodiazepines, and non-opioid analgesics on withdrawal symptoms during detoxification of opioids in general.[18,19] In addition, other studies have shown promising results for psychological and physical therapies in aiding opioid tapering or reducing withdrawal symptoms during heroin withdrawal.[20,21] These results suggest that these therapies might alleviate withdrawal symptoms during prescription opioid withdrawal as well.

These non-opioid therapies could be beneficial in a primary care setting as an adjunct to opioid tapering for patients on long-term prescription opioids. Although various interventions may have been investigated in clinical trials, a systematic review evaluating the effectiveness of these interventions is still missing. High-quality evidence would help GPs to manage opioid withdrawal symptoms thereby making opioid tapering more feasible.

The primary objective of this systematic review is to evaluate the effectiveness of non-opioid treatments for withdrawal symptoms during a tapered or acute opioid withdrawal in adult patients with long-term opioid therapy (LTOT) initially prescribed for CNCP. Secondary areas of interest are the influence of the treatments on the success rate of opioid tapering, patient safety, satisfaction, emotional functioning, and pain outcomes.

Methods

This systematic review was reported according to the PRISMA guidelines,[22] and its protocol was registered in PROSPERO (reference number: CRD42020200529) (see Supplementary data 1).

Eligibility criteria

Studies eligible for inclusion were (randomized) controlled trials on the effectiveness of different non-opioid treatments for withdrawal symptoms. Our main inclusion criteria were trials with adult participants undergoing medically supervised withdrawal from LTOT prescribed for CNCP. These trials had to compare any pharmacological, psychological, or physical treatment to a placebo, no treatment, usual care, or non-opioid drugs. Trials were excluded if they included pregnant women, participants with an oncological diagnosis or receiving palliative treatment, or participants with concomitant alcohol addiction or illicit substance abuse. Trials that were unpublished or for which a full text was unavailable were excluded. See Table 1 for full overview of inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Participants	Adults, meaning 18 years or older. Long-term opioid use (>3 months). Opioids initially prescribed for non-cancer pain. Opioids were prescribed by a doctor and legally obtained. Participants undergo acute or tapered opioid withdrawal under supervision of a health professional.	Pregnant participants. Participants with an oncological diagnosis. Participants receiving palliative treatment. Participants suffering from alcohol addiction or illicit substance abuse. Participants undergo detoxification treatment that involves general anaesthesia/treatment with heavy narcotics in an ICU.
Intervention	Pharmacological treatments, non-pharmacological treatments (e.g. physical, psychological), or other treatments.	Opioid drug treatment.
Comparison	Placebo, usual care, no treatment, non-opioid drug or non-drug-related treatment.	Opioid drug treatment (except 3 for armed trials with also a placebo group).
Study type	Randomized, non-randomized controlled trial. Intensity or frequency of withdrawal syndrome/symptoms as one of the outcomes.	Uncontrolled trial. Unpublished studies. No full-text articles available.

Search method for identification of studies

An extensive search from inception date up to 2020 July 24 was carried out in the following databases: Embase.com, MEDLINE ALL Ovid, Web of Science Core Collection, PsycINFO Ovid, and Cochrane CENTRAL register of trials. The full search strategies are listed in Supplementary data 2. Two reviewers (AIL and LdK) independently performed a primary selection on title and abstract. All included articles were read in full text and selected on inclusion and exclusion criteria by the same two reviewers independently. If necessary, trial authors were contacted for additional information regarding the inclusion or exclusion criteria or missing data. To ensure maximum retrieval, backward citation tracking of papers identified as potentially relevant was performed. The included articles of both reviewers were compared and discussed. If doubts regarding eligibility persisted, a third reviewer (BWK) was consulted.

Data collection and analysis

Two reviewers (AIL and LdK) independently scored the risk of bias (RoB) using version 2.0 of the Cochrane RoB tool for randomized trials.[23] A consensus meeting was held to discuss any disagreements between the reviewers. Afterwards, one reviewer (AIL) extracted the data of all included studies through a standardized extraction form in Excel. The data extracted were checked by a second reviewer (LdK). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence into "high," "moderate," "low," or "very low."[24] As stated in the review protocol the aim was to statistical pool primary effect measures if there would have been sufficient clinical and methodological homogeneity across included trials. Secondly, different subgroups of non-opioid drugs were meant to be investigated and subgroup analysis of specific drugs was meant to be performed. However, due to insufficient inclusions, we had to deviate from this intended method for data synthesis and subgroup analyses. Alternatively, a narrative description of included trials using the Synthesis Without Meta-analysis (SWiM), guideline,[25] was adopted. However, after realizing this systematic review could only include one study, the use of the SWiM guideline seemed meaningless, and we decided to present the result of the included study through a basic narrative description.

Results

After screening 2,084 article titles and abstracts, 91 full-text articles were selected by AIL and 90 by LdK. After a consensus meeting, 91 were included based on title and abstract. After applying the selection criteria, one study could be included. There were no disagreements between the reviewers when applying the inclusion criteria. Figure 1 shows the PRISMA flowchart of the database search.

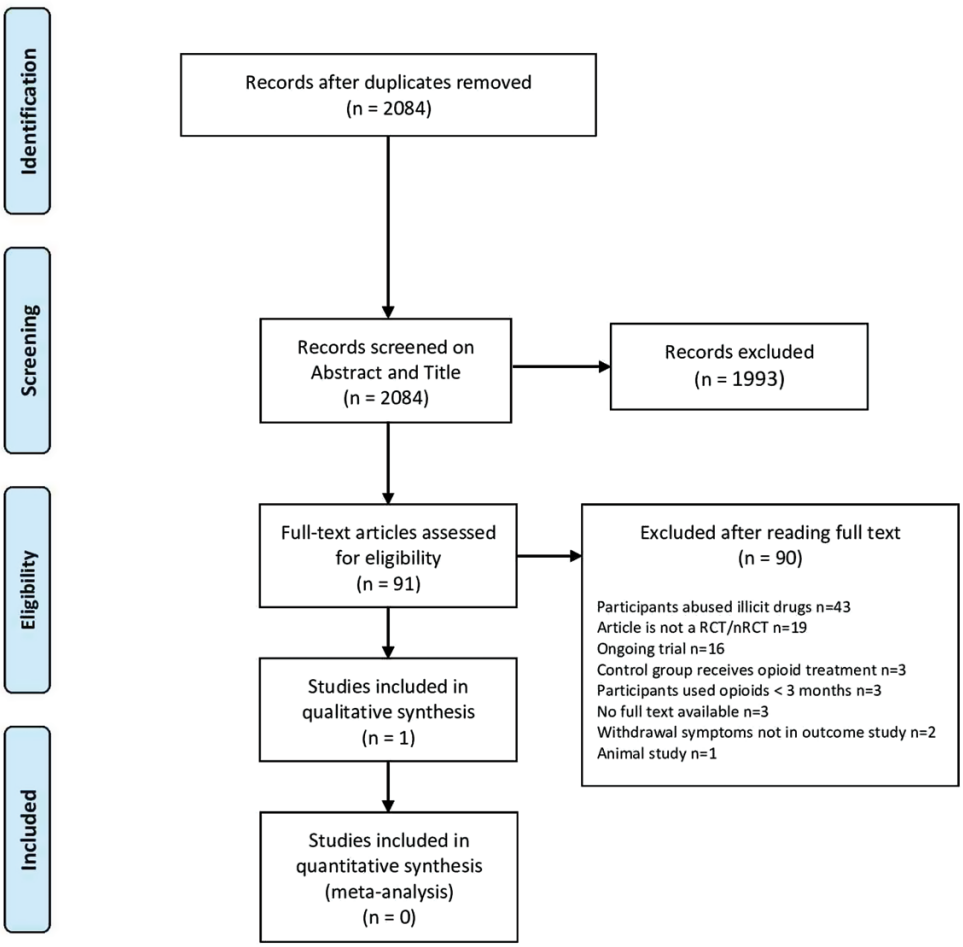

Fig. 1. PRISMA flowchart of inclusion.

Table 2. Study characteristics and outcome data of the included trial.

	Hooten and Warner[26], #1160
Objective and duration	Varenicline vs. placebo—effect on withdrawal symptoms. 21 days
Sample size and completion rate	21 pts, 10 (i), 11 (c), male 86% (i) to 64% (c), completion n = 7 (i), n = 11 (c)
Frequency/severity withdrawal symptoms	Median regression coefficients of COWS scores: (i) −0.116 (−0.264, −0.332), (c) 0.086 (−0.264,0.332), P = 0.258
Change in opioid use	All 7 and 11 patients successfully tapered opioids to complete cessation. Duration 18 (i) vs. 15 (c) days (P > 0.1)
Pain	MPI pain severity score: Baseline IQR: (i) 50.6 (45.3–55.9), (c) 53.3 (47.9–61.2) Dismissal IQR: (i) 34.6 (24.0–53.3), (c) 41.3 (34.0–43.9) Change IQR: (i) 16.0 (2.7–21.3), (c) 12.0 (6.6–23.3) Change from baseline to dismissal pain severity, P = 0.001
Emotional functioning	CES-D: Baseline IQR: (i) 31.0 (24.0–37.0), (c) 30.0 (17.0–35.0) Dismissal IQR: (i) 10.0 (6.0–14.0), (c) 12.0 (9.0–16.0) Change IQR: (i) 21.0 (10.0–32.0), (c)18.0 (0.0–28.0) Change from baseline to dismissal, P < 0.001
Participation rate of improvement	No information
Satisfaction with treatment	No information
Adverse effects	None reported

(i), intervention; (c), control; COWS; Clinical Opiate Withdrawal Scale; MPI, multidimensional pain inventory; CES-D; Center for Epidemiologic Studies for Depression Scale.

Table 3. Risk of bias for included trial.

RoB	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall risk of Bias
Hooten and Warner[26]	+	?	+	+	+	?

Legend
Low **risk** *of bias*
High risk **of** *bias*
Unclear risk of bias

Characteristics of trial

The characteristics and outcome data of the included trial are presented in Table 2. Supplementary data 3 includes the full data extraction form.

The trial of Hooten and Warner[26] assessed the effectiveness of Varenicline for opioid withdrawal in patients with chronic pain during a 21-day trial. Varenicline, a nicotinic acetylcholine-receptor agonist is commonly used to aid in smoking cessation. This study was a randomized, single-blinded, controlled pilot trial including 21 patients. The overall RoB (see Table 3), had some concerns, due to possible deviations from intended interventions. Severity of withdrawal symptoms was measured in COWS (Clinical Opiate Withdrawal Scale)-score for opiate withdrawal and calculated using median regression coefficients. The intervention group had a median regression coefficient of −0.116 (−0.264 to −0.332), the control group 0.086 (−0.264 to 0.332) with P = 0.258. The regression slope was negative, indicating a decrease in withdrawal symptoms over time, in 71% of the participants in the intervention group and 36% of the participants in the control group, P = 0.334, Fisher's exact test (moderate quality of evidence due to imprecision). Pain severity and depression scores changed in both groups but the between-group differences were not statistically significant (moderate quality of evidence due to imprecision).

Discussion

Summary

This systematic review evaluated the effectiveness of different pharmacological, physical, psychological, and other treatments for withdrawal symptoms that occur during a medically supervised opioid withdrawal in adult patients with long-term opioid treatment (LTOT) initially prescribed for CNCP. One study could be included and demonstrated no statistically significant between-group differences in withdrawal symptoms. There are some indications for a positive trend, but non-significant. More importantly, no firm conclusions on effectiveness of non-opioid interventions to tackle withdrawal symptoms in patients with LTOT can be drawn from just one small sample-sized trial with moderate-quality evidence.

Strengths and limitations

This is the first systematic review on the effectiveness of non-opioid interventions focusing on withdrawal symptoms during medically supervised opioid tapering or acute opioid withdrawal from prescription opioids. This work systematically searched multiple databases. When finding as little evidence as we did (i.e. only one RCT) one is compelled to ask whether the search was too narrow leading to missing out on important trials. We are convinced that this was not the

case since we have thoroughly conducted a wide database search and performed backward citation tracking. We did, however, identify several ongoing randomized controlled trials that are potentially eligible for inclusion in a future updated review.[27–29] Many trials were excluded because trial participants were dependent on illicit opioids, frequently heroin. Since there is a considerable difference in patient characteristics between illicit drug abusers and patients on prescription opioids,[30–32] we found these trials not eligible for inclusion. As stated in our protocol, we included only published (randomized) controlled trials. Yet, by limiting inclusion to controlled trials, possible evidence based on observational studies on this topic might have been missed.

Comparison with existing literature

We found a few recent systematic reviews on CNCP and LTOT. These reviews focused on interventions aimed to improve tapering success rates and not on treating withdrawal symptoms. The results from these articles show that different non-opioid-based interventions do improve opioid tapering success, lower the opioid dose and positively affect pain scores, physical functioning, and satisfaction.[33–35] A recent article from the Lancet discussed directions for the treatment of opioid withdrawal in patients with CNCP. They assessed different opioid and non-opioid treatment options for managing withdrawal symptoms.[36] They found promising results for opioid replacement therapy combined with a α2-receptor agonist and ancillary medications for treating sleeping issues or nausea. However, these results were mainly based on research that included mainly patients with illicit opioid use (i.e. Heroine), again demonstrating the lack of studies specifically focused on treating withdrawal symptoms in patients suffering from prescription opioid dependence. Finally, we identified new protocols registered for trials testing interventions for reducing withdrawal symptoms during medical opioid tapering.[27–29] It is promising to see these new trials as they suggest an increased awareness amongst doctors and researchers about the importance of addressing withdrawal symptoms in opioid reduction.

Implications for research and practice

Finding ourselves in the midst of a prescription opioid crisis, it is of utmost importance to help our patients to withdraw from these drugs. It is our task as researchers and physicians to do everything we can to help these patients and develop the most effective treatments in conquering their prescription opioid dependence. Reducing severe withdrawal symptoms that occur during opioid tapering, opioid replacement therapy, or abrupt withdrawal may lead to higher efficacy of these interventions and may help patients to pursue complete abstinence. This systematic review has clearly highlighted the lack of (randomized) controlled trials on this topic.

Therefore, it is no surprise that protocols on treating withdrawal in patient tapering off LTOT for GPs are scarce. Some guidelines and handbooks on tapering opioids in patients on LTOT for CNCP offer some examples of non-opioid pharmacological and non-pharmacological treatment options but these proposed interventions are based on expert opinion, anecdotal reports, and evidence from trials on treating withdrawal in heroin and methadone addiction.[37,38]

For now, GPs only have these recommendations when treating withdrawal symptoms in patients tapering LTOT. However, to improve our care and develop evidence-based protocols for treating opioid-dependent CNCP patients we need more research on prescription opioids. Not only on how to taper opioids or on opioid replacement therapy, but also on how to address withdrawal symptoms with non-opioid treatments that can be used in primary care.

Conclusion

The current shortage of well-conducted randomized controlled trials and the continuing rise of patients with prescription opioid dependence must be a stimulus for future research. To keep the problem attainable, expand treatment options and encourage more doctors to guide patients during an opioid taper more research is necessary.

Supplementary material

Supplementary material is available at *Family Practice* online.

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Conflict of interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

The original protocol for the study

The original protocol of this study can be viewed in the supplementary file or in PROSPERO with reference number: CRD42020200529.

Data availability

All data relevant to the study are included in the article or can be found in the supplementary files.

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