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Review Article

Does Opioid Tapering in Chronic Pain Patients Result in Improved Pain or Same Pain vs Increased Pain at Taper Completion? A Structured Evidence-Based Systematic Review

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Abstract

Objective. To support or refute the hypothesis that opioid tapering in chronic pain patients (CPPs) improves pain or maintains the same pain level by taper completion but does not increase pain. **Methods**. Of 364 references, 20 fulfilled inclusion/exclusion criteria. These studies were type 3 and 4 (not controlled) but reported pre/post-taper pain levels. Characteristics of the studies were abstracted into tabular form for numerical analysis. Studies were rated independently by two reviewers for quality. The percentage of studies supporting the above hypothesis was determined. **Results**. No studies had a rejection quality score. Combining all studies, 2,109 CPPs were tapered. Eighty percent of the studies reported that by taper completion pain had improved. Of these, 81.25% demonstrated this statistically. In 15% of the studies, pain was the same by taper completion. One study reported that by taper completion, 97% of the CPPs had improved or the same pain, but CPPs had worse pain in 3%. As such, 100% of the studies supported the hypothesis. Applying the Agency for Health Care Policy and Research Levels of Evidence Guidelines to this result produced an A consistency rating. **Conclusions**. There is consistent type 3 and 4 study evidence that opioid tapering in CPPs reduces pain or maintains the same level of pain. However, these studies represented lower levels of evidence and were not designed to test the hypothesis, with the evidence being marginal in quality with large amounts of missing data. These results then primarily reveal the need for controlled studies (type 2) to address this hypothesis.

Key Words: Chronic Pain; Opioids; Tapering; Pain Improvement; Opioid-Induced Hyperalgesia

Introduction

With the recognition of the "opioid epidemic," there has been significant pressure on physicians not to place chronic pain patients (CPPs) on opioids and to taper some CPPs from opioids. Part of the difficulty in tapering CPPs from opioids is the CPPs' fear and that of the clinician that tapering the opioid will increase the CPPs' pain. However, there are a couple of lines of literature evidence that indicate that this may not necessarily be the case.

The first of these is the concept of opioid-induced hyperalgesia (OIH) and reports relating to OIH. Early authors have pointed out that OIH could add to the pain perceived by CPPs treated with opioids [1]. One of the suggested approaches for treatment of OIH is tapering the opioid. There have been case reports of OIH where complete pain relief or improved analgesia was achieved by complete elimination or significant reduction in the opioid dose by opioid tapering [2–5]. Although the prevalence of OIH in CPPs maintained on opioids is unknown, some authors have suggested that the prevalence of OIH in CPPs on opioids could be high [6]. These observations point to the possibility that in some patients, opioid tapering could lead to pain relief.

The second line of evidence comes from multidisciplinary pain centers. Comprehensive pain rehabilitation programs have a long history of including opioid tapering as part of their program package [7]. Historically,

these centers have observed that when CPPs are tapered from opioids, in most cases pain remains the same or is improved [8].

If these lines of evidence are correct, then this could ease the fear that CPPs and clinicians have that opioid tapering will necessarily lead to increased pain. This in turn would make it easier for clinicians to suggest tapering as an approach to potential opioid addiction and/or suspected OIH.

It has not been *definitely* established that opioid tapering does indeed result in the CPPs' pain being the same or improved. As such, the objective of this evidence-based structured systematic review is to gather any studies that have tapered CPPs from opioids and to tabulate their results according to the Levels of Evidence Guidelines developed by the Agency for Health Care Policy and Research (Table 1) [9]. The hypothesis of this systematic review, described below, was that a greater number of studies would support the finding that opioid tapering decreased or maintained the same pain levels vs increasing pain levels.

It is to be noted that to our knowledge this is the first such systematic review to address this specific question. However, there has been a recent systematic review that has addressed patient outcomes in dose reduction and discontinuation of long-term opioid therapy [10]. This review, however, did not focus specifically on whether opioid tapering increases, decreases, or maintains the same level of pain and did not select studies to address this specific question with appropriate inclusion/exclusion criteria. In addition, the above review did not utilize the levels of evidence developed by the Agency for Health Care Policy and Research [9]. In addition, there has been one recent narrative review that has addressed opioid reduction following interventional procedures [11]. This was also not the objective of the present systematic review, which focused on opioid tapering without interventional procedures to assist the taper.

Methods

Relevant references were located as follows: subject headings were queried within Embas, Medline, Psychological Abstracts, PsycINFO, CINAHL, Science Citation Index, and the National Library of Medicine Physician Data Query database. Subject headings were the following: opioid detoxification, opioid tapering, opioid reduction, opioid stoppage, opioid withdrawal, opioid removal, and opioid cessation. Each of these was exploded with the terms chronic pain, chronic pain patients, chronic widespread pain, fibromyalgia, opioid dependence, and opioid addiction. Searches were conducted back to 1966 and were not restricted to the English language. Science Citation index was conducted back to 1974, and the upper index of each search was 2017. In addition, abstracts of the following pain meetings were reviewed: International Association of Pain (1981–2017) and American Pain Society (1982–2017).

Three hundred sixty-four case reports/studies/reviews fulfilled search criteria. These were reviewed by DF in a cursory fashion for selection for detailed review utilizing the following inclusion criteria only: 1) the study had to deal with CPPs on opioids or with opioid addicts with chronic pain; 2) the study group had to have undergone an opioid tapering procedure at a multidisciplinary facility, pain facility, outpatient pain treatment clinic, medical hospital or clinic, or addiction facility or clinic; and 3) CPP pain levels had to be documented for the tapering pain group before the taper and immediately post–taper completion. Exclusion criteria were the following, with examples of studies that were excluded as a result of the abovementioned criteria: 1) papers that were case reports [2–5]; 2) taper was not controlled but was self-stop [12–17]; abrupt opioid cessation with no taper support [18]; a small proportion of CPPs in the treatment group were tapered, with no report on pain values for that subgroup [19–21]; no pain change results reported at end of taper for the tapered group, but for all patients in the study [22–26]; outcome not reported at program completion, but at a time period after, during follow-up [27,28]; no pain results reported at end of taper at all [29–41]; buprenorphine substitution utilized and buprenorphine not tapered by end of program [26,42–50]; no patients tapered [51]; no taper but ketamine substitution utilized [52–55]; no taper but THC substitution utilized [56]; no taper but substitution of implantation of an intrathecal delivery system [57]; and a significant percentage of patients received blocks during the taper period (Appendix Figure A1) [58–60].

Study selection for detailed data abstraction was performed independently by DF and AP. Details of the agreed-upon studies were then abstracted into tabular form by DF. Abstracted information was independently checked by AP. This abstracted information is presented in Appendix Table A1. This table contains the following information: author/year/reference number, study question, design/type of study, prospective vs retrospective, type of chronic pain, opioid tapered from, type of tapering, number of patients tapered, types of treatments besides tapering, number of days tapering, pain intensity pretaper, pain intensity post-tapering, how pain was measured, statistical analysis type, statistical analysis results, type of facility, type of evidence by Agency for Health Care Policy and Research (AHCPR) criteria, quality score, pain increased or decreased or the same after tapering, and comment/problems with study.

The quality of the studies was calculated by the system reported by Hoogendoorn et al. [61] and De Vet et al. [62]. In this system, there are 23 criteria used to evaluate the methodological quality of prospective, historical cohort, case-control, and controlled studies [61,62]. All 20 studies were either type 3 or type 4 (Table 1), and none

Table 1. Levels of evidence, as developed by the Agency for Health Care Policy and Research for guideline development [9]

Type of Evidence and Strength/Consistency of the Evidence Guidelines According to the AHCPR
Type of evidence guidelines:
I. Meta-analysis of multiple well-designed controlled studies
II. At least one well-designed experimental study
III. Well-designed, quasi-experimental studies such as nonrandomized controlled, single group pre-post, cohorts, time series, or matched case-controlled studies
IV. Well-designed nonexperimental studies, e.g., comparative, correlational, descriptive, case-control
Case reports and clinical examples
I is considered highest level of evidence, with V being lowest level of evidence
Strength and consistency of evidence guidelines:
A. There is evidence of type I or consistent findings from multiple studies of type II, III, or IV
B. There is evidence of type II, III, or IV, and findings are generally consistent
C. There is evidence of type II, III, or IV, but findings are inconsistent
D. There is little or no evidence, or there is type V evidence only
E. Panel consensus: practice recommended on the basis of opinion of experts

AHCPR = Agency for Health Care Policy and Research.

were type 2 (well-designed experimental studies, controlled). Of the 27 criteria, seven could be applied to type 3 and 4 studies and were selected as appropriate quality characteristics for type 3 and 4 studies. In addition, two criteria were added that were appropriate to this review (positive if pain level data were collected by means of a standardized instrument for pain level, positive if prospective study), for a total of nine criteria.

The nine criteria were the following:

1. positive if the study had a clearly defined objective;
2. positive if the main features of the study population were described;
3. positive if the participation rate at baseline was at least 80%;
4. positive if data were collected by means of standardized methods of acceptable quality for pain;
5. positive if the method used for the statistical analysis was appropriate for the study;
6. restriction to a homogenous study population;
7. allocation procedure not leading to bias;
8. smallest group bigger than 50 participants;
9. positive if prospective study.

Each study was rated for each criterion independently by two raters (DF and AP) as either fulfilling the criterion (positive), not fulfilling the criterion (negative), or not applicable to the criterion (not applicable). The ratings for each criterion were then compared in a consensus meeting, and any differences were resolved by mutual agreement. For each criterion, the number of positives was the added together, divided by 9, and multiplied by 100 to generate a consensus % quality rating for that study for that criterion. Additionally, the % agreement between raters for each criterion was calculated, as well as Kappa for inter-rater reliability. The actual individual rater criterion ratings are not presented but are available on request.

In some reviews [63], studies having quality scores of less than 50% are considered "low quality" and are usually not utilized. In this systematic review, a score less than 60% was deemed low quality. These studies were not utilized.

A number of years ago, the AHCPR developed guidelines to categorize the type of evidence a study represented [9]. In addition, it developed strength and consistency of evidence guidelines in order to allow researchers to weigh the evidence that the overall number of studies represented [9]. These guidelines are presented in Table 1. They allow the researcher to categorize the reviewed evidence as being consistent, generally consistent, inconsistent, or demonstrating little or no evidence for supporting the hypothesis under study. Appendix Table A1 therefore contains a column identifying the type of study each included study represented according to these guidelines. In addition, and most importantly, Appendix Tables A1–3 contain a column for whether each study supported or did not support the hypothesis. Studies reporting that pain decreased or stayed the same after tapering were counted as supporting the hypothesis. Studies reporting that the pain was worse after taper were counted as not supporting the hypothesis. The total number of studies supporting the hypothesis was divided by the total number of studies and multiplied by 100. This gave the percentage of studies supporting the hypothesis. The AHCPR strength and consistency of evidence guidelines were then applied to the derived percentage, along with type of evidence the studies represented, to derive an overall rating for the consistency of the evidence: either A, B, C, D, or F (Table 2).

As a final step, the data derived from Appendix Tables A1–3 were tabulated and formatted into a summary table (Table 2).

Results

Twenty studies [6,64–82] fulfilled inclusion and exclusion criteria. The details of these are presented in Appendix Tables A1–3. A numerical summary of the relevant observations from Tables 1–3 is detailed in Table 2. The lowest consensus quality score within the 20 studies was 66.6%, and therefore none of the 20 studies were eliminated from analyses because of a low-quality score. The consensus average overall quality score for the 20 studies was 83.1%. The percent agreement of the two raters for each of the nine criteria for the 20 studies was as follows: criterion 1, 20/20, or 100%; criterion 2, 14/20, or 70%; criterion 3, 19/20, or 95%; criterion 4, 19/20, or 95%; criterion 5, 17/17 (in three studies, this criterion was not applicable), or 100%; criterion 6, 16/20, or 80%; criterion 7, 19/20, or 95%; criterion 8, 20/20, or 100%; and criterion 9, 20/20, or 100%. For all

Table 2. Summary of relevant findings from 20 studies (Appendix Tables A1–3) that addressed opioid tapering in chronic pain patients

Percentage of studies by type of study according to AHCPR criteria (Table 1)	1. Group pre and post cohort (type 3) = 75% 2. Comparative (type 4) = 25%
Prospective vs retrospective	1. Retrospective = 45.0% 2. Prospective = 40% 3. Unclear = 15%
Types of chronic pain	1. More than one type = 60% 2. One type of pain such as fibromyalgia = 15% 3. Not stated = 25%
Was a tapering procedure described?	1. Described = 40% 2. Not described = 60%
Was the opioid range tapered from reported in MEQ?	1. Reported = 80% 2. Not reported = 20% Opioid range tapered from, in those studies that reported it, was 5 mg to 1,250 mg
Percentage of the 20 studies where CPPs tapered entirely from starting dose?	45%
Percentage of 20 studies where CPPs were tapered only partially to a lower dose than their starting dose?	55%
Was number of days of tapering reported?	1. Reported in 60% of the studies 2. Not reported in 35% 3. Tapered on first day in 5% 4. Time tapering in the studies reporting days tapering ranged from 2 to 180 days, with an average of 45 days
Total number patients tapered in the 20 studies?	1. Total all studies combined = 2,109 2. Study range of patients tapered = 7 – 596
Additional treatments received in the 20 studies besides tapering	1. Information not provided = 20% 2. Information provided = 80% 3. No other treatments provided = 5% 4. Counseling only for addiction or pain or physical therapy = 20% 5. Only adjuvants such as antidepressants = 5% 6. Full range of treatments as per multidisciplinary or interdisciplinary model (physical therapy/occupational therapy/counseling/groups/biofeedback/etc.) = 45%
In what type of facility was tapering performed for the 20 studies?	1. Not stated = 10% 2. Medical = 5% 3. Detoxification facility = 5% 4. Psychiatry inpatient = 5% 5. Pain clinic = 10% 6. Multidisciplinary/interdisciplinary/functional restoration = 65%—this represented 1,878 CPPs or 89.0% of the 2,109 CPPs tapered in all the studies combined
Overall quality score of the 20 studies	83.1% (range from low of 66.6% to a high of 100%)
How pain intensity measured	1. Visual analog scale = 50% 2. Not stated = 20% 3. Numerical rating scale = 20% 4. Multidimensional pain inventory = 10%
Number of studies reporting pain had improved?	16/20 or 80%
Of the improved studies, what percentage had demonstrated improvement in pain statistically?	1. 13/16 or 81.25% 2. This represented 62.8% of all CPPs tapered in the 20 studies
Of the improved studies, what percentage had reported that pain had improved but not demonstrated this statistically?	1. 3/20 or 15% 2. This represented 32.6% of all CPPs tapered in the 20 studies
What percentage of the studies demonstrated that the pain remained the same at taper completion by statistical analysis?	1. 3/20 of 15% 2. This represented 1.9% of all CPPs tapered in the 20 studies
Were there any studies that reported that some CPPs were worse at taper completion?	1. 1/20 or 5% reported that in 3% of the tapered CPPs pain had worsened whereas in 97% pain had stayed the same or improved at taper completion 2. The worsened CPPs represented only 0.09% of the 2,109 CPPs tapered in the 20 studies
Percentage of studies supporting the hypothesis (opioid tapering is associated with pain being the same or decreasing on taper completion)?	100%
What is the strength and consistency of the evidence from the 20 studies for supporting the hypothesis according to the AHCPR guidelines in Table 1, based on 100% of the studies supporting the hypothesis?	There is consistence evidence (100%) from multiple studies [9] of type 3 and 4 giving an A rating

CPP = chronic pain patients; AHCPR = Agency for Health Care Policy and Research.

criteria combined for the 20 studies, percent agreement between the two raters was 92.6%. Cohen's Kappa for inter-rater reliability for the two raters was calculated at 0.73 (substantial agreement).

The following observations were derived from Appendix Tables A1–3. Of the 20 studies, 75% were type 3, the rest being type 4. Forty-five percent of the studies were retrospective, 40% prospective, and 15% of unclear status. Most of the studies (60%) involved more than one type of pain in the tapering group. Fifteen percent were of one type of pain, and in 25% of the studies, the type of pain under treatment was not stated. The taper procedure was not described in 60% of the studies but was described in the remaining 40%. Studies varied widely. In 80% of the studies, the opioid range of morphine equivalents (MEQ) tapered from was reported, and in 20% it was not. All the CPPs were tapered entirely from their starting opioid dose in 45% of the studies, and in 55% the opioid dose had been reduced by the end of the taper. The number of days of tapering was not stated in 35% of the studies, and in 5% tapering was performed

on the first day. In 60%, the number of days of tapering was provided and ranged from two days to a maximum of 180 days, with an average of 45 days.

The numbers of CPPs tapered in the 20 studies ranged from seven to 596, and for all studies combined, the total number of CPPs tapered was 2,109. Besides opioid tapering, the studies provided the following information as to additional treatments the CPPs received during tapering: in 20% this information was not provided; in 5% no other treatments were provided; in 20% the treatments were counseling for addiction or for pain or physical therapy; in 5% only adjuvants, such as antidepressants, were provided; and in 45% the full range of treatments was provided as per multidisciplinary/interdisciplinary centers (physical therapy/occupational therapy/counseling/groups, biofeedback/etc.). Pain was measured in 50% of the CPPs via the visual analog scale, in 20% via the numeric rating scale, and in 10% via the multidimensional pain inventory. In 20% it was not stated how pain was measured. Tapering was performed in the following types of facilities for the 20 studies: facility not stated 10%, medical 5%, detoxification/addiction 5%, psychiatry inpatient 5%, pain clinic 10%, and multidisciplinary/interdisciplinary/functional restoration 65%.

By the end of the taper period, 16 studies or 80% reported that the tapered CPPs' pain had improved. In 13 of 16 studies, or 81.2%, a statistical analysis had been done demonstrating that the drop in pain was statistically significant. Overall, this represented 62.8% of all the CPPs tapered in the 20 studies. In addition, three studies, or 15%, demonstrated that pain had improved but did not perform a statistical analysis. This represented 32.6% of all the CPPs tapered in the 20 studies. Three studies, or 15%, reported doing a statistical analysis that demonstrated that on tapering the pain had remained the same. These three studies represented 1.9% of all the CPPs in the 20 studies. Finally, there was one study representing 5% of all the studies that reported that in 97% of the CPPs, the pain dropped or was the same by the end of the taper but was worse in 3% or two CPPs. The two CPPs whose pain was worse on tapering only represented 0.09% of all the 2,109 CPPs in the 20 studies. It was therefore concluded that this study also supported the hypothesis. Overall then, 100% of the 20 studies supported the hypothesis (on tapering, pain would drop or remain the same). Applying AHCPR strength and consistency guidelines to this result, it was concluded that there is consistent evidence (100%) from multiple studies [18] for supporting the hypothesis that opioid tapering will decrease pain or maintain the same level of pain.

Discussion

According to the reviewed studies, the results of this systematic review confirm the hypothesis that opioid tapering can lead to decreased pain or the same pain and not necessarily to increased pain at tapering completion. However, it is to be noted that this information was generated from type 3 and 4 studies, which are considered lower levels of evidence vs type 2 studies (higher level of evidence; controlled, randomized, prospective, etc.). According to the quality criteria for type 3 and 4 studies, the reviewed studies were acceptable evidence. Nevertheless, because they represent lower levels of evidence, these results only allow for speculation that a subset of CPPs can undergo opioid tapering with less pain or the same pain by taper completion. Thus, these results primarily reveal the need for more studies to address his hypothesis.

Currently, a meta-analysis was not possible secondary to lack of data and types of studies found. However, if prospective studies were specifically performed to address this hypothesis, then a meta-analysis could be performed in order to determine if changes in pain scores post-tapering are clinically meaningful. In addition, future studies should be designed to answer the following additional questions: does tapering lead to/not lead to adverse consequences (e.g., decreased functional status, disability, anxiety, depression, suicidality, etc.)?; what is the effect of opioid tapering on long-term pain and opioid use outcomes?; what types of tapering protocols lead to the best outcomes?; and who are the best and worst patients for consideration for tapering? It is to be noted that none of the reviewed studies addressed any of these questions, as they were not designed to do so.

If opioid tapering does indeed lead to decreased or the same pain, by what mechanism does this occur? A potential answer is OIH. Some clinicians have claimed that OIH can be observed not only with high doses of opioids, but also with low doses, [83] which would be the majority of the CPPs involved in these studies. Conversely, there is some research that indicates that opioid tapering in CPPs leads to acute increases in pain sensitivity [77]. Also, detoxified methadone patients appear to demonstrate abnormal heat/pain perception months after detoxification [84]. But there is other research that indicates that opioid tapering may induce brief hyperalgesia that can be normalized over a longer period [41]. Additionally, there are three systematic reviews [1,85,86] that have questioned the evidence for the existence of this phenomenon in humans. There are currently no diagnostic criteria for OIH, and in addition, none of the included studies addressed this issue. As such, whether OIH is the answer to these results remains to be determined.

Another potential answer to the above question is multidisciplinary treatment. In one systematic review, strong evidence was detected in favor of multidisciplinary treatments vs no treatments or standard medical treatment [87]. Sixty-five percent of the studies in this review, or 89.0% of all the CPPs tapered in all the studies combined, were from multidisciplinary centers and thereby received *other* treatments besides opioid tapering that could have had a significant impact on the CPPs' pain. These studies did not control for the effects of this

treatment. It is possible that the drop in pain was the result of those treatments rather than opioid reduction.

Another potential answer to the above question is that of adjuvant medication treatments for pain. There is significant evidence that drugs such as antidepressants (e.g., Cymbalta) or anticonvulsants (e.g., Neurontin) have pain efficacy. In five of the studies, or 25.0% of the studies in this review, adjuvants were utilized during tapering, and the use of these drugs was not controlled for. However, it is likely that adjuvants were utilized in the majority of the studies, but this information was not provided. This is likely as the majority of the patients were tapered in multidisciplinary facilities, where such treatments would normally be utilized.

As seen in Appendix Tables A1–3, there was a lot of missing data in the reports, which is important to issues surrounding tapering. We did not make any efforts to contact these researchers to obtain this information as our main focus was on pain levels, and all studies provided this information. This could be considered a fault in our methods.

What is the current clinical relevance of the results of this review? In general, physicians believe that any decrease in opioid dose could increase pain. As a consequence of the results of this review, clinicians may wish to consider that in some CPPs this may not be the case. As a consequence, they may consider tapering some CPPs from opioids if indicated. Additionally, clinicians wishing to taper their CPPs from opioids may wish to impart this information to the CPP as increased pain is a significant fear of CPPs facing tapering [87,88]. This would decrease the CPPs' anxiety over tapering and may make the tapering process easier. In addition, they may wish to consider referring these CPPs to a multidisciplinary center where tapering is provided. This is because most of the studies in this review involved centers where additional multidisciplinary treatments may have a positive impact on the tapering process. In addition, the clinician should keep in mind that there is the following ancillary evidence. Depression predicts dropout from tapering [25]. Therefore, depression should be treated in CPPs who are depressed and are undergoing tapering. In addition, greater volatility in subjective pain [89], greater pain [90], and persistent pain [85] predict relapse after tapering. Therefore, these CPPs should be monitored closely after taper completion or perhaps tapered more slowly.

What are the potential confounders/limitations to the results of this systematic review? The first, discussed above, is that the results of this review are based on type 3 and 4 studies, which are considered lower-level evidence vs type 2 studies (experimental [randomized, controlled, etc.]).The second is the lack of controls for other treatments during opioid tapering. This potential confounder is present because none of the reviewed studies were specifically designed to address the problem of this review and only provided the required information for this review as ancillary data. Third, 45% of the studies were retrospective, and in 15% this issue was not reported. Retrospective studies are subject to more bias errors vs prospectively designed studies. The fourth potential confounder relates to the taper process. There was great variability in the studies in whether the tapering procedure was described, the type of taper, the opioid range tapered from, the percentage of patients tapered entirely, the number of days tapering, etc. All of these factors could affect the success of the taper and potentially the pain levels perceived. Additionally, this does not help the clinician who wishes to taper his/her CPP from opioids. He/she wishes to know what is the best tapering regimen and how it should proceed and over what time period. This review does not provide an answer to these questions. The final potential confounder is that in 45% of the studies CPPs were completely tapered, and in 55% they were only partially tapered. This leads to the possibility that in the partially tapered group the remaining opioid dose was adequate enough to control the CPPs' pain, giving them the perception that their pain was improved or the same and not actually taper related.

Conclusions and Future Directions

The results of this systematic review support the clinical observation that opioid tapering in some CPPs does not necessarily increase pain. However, as the reviewed studies were type 3 and 4 (low level of evidence) and the focus of this review was not their primary question, further research is required to answer this question in a definitive manner. These studies should be prospective, type 2 studies specifically designed to address the hypothesis of this systematic review.

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Apendix

Table A1. Details of studies that have reported on opioid tapering and effects on pain levels pre/post taper in chronic pain patients [64–68]

Author(Year) Reference Number	Study Question	Design, Type of Study	Prospective vs Retrospective	Type of Chronic Pain	Opioid Tapered from	Type of Tapering	Number of Patients Tapered	Types of Treatments Besides Tapering	Number of Days Tapering	Pain Intensity Pretapering	Pain Intensity Post-tapering
Di Benedetto et al. (2014) [64]	What is the impact of opioid tapering?	Single group pre-and postcohort	Prospective	Not stated	Average 508 MEQ tapered to 305–508 MEQ	Not stated	60	Not stated	Not stated	Average 6/10	Average 5.4/10
Robinson et al. (2008)[65]	Does tapering increase pain?	Single group pre- and postcohort	Not stated	Not stated	Not stated	Not stated	89	Not stated	Not stated	Mean not stated (statistic given)	Mean not stated (statistic given)
Sullivan et al. (2017) [66]	Does a taper support intervention group work?	Two groups pre- and postcohort (taper support and usual care)	Prospective	Not stated	Range from <50 mg to ≥1,000 mg MEQ	Self or with guidance from taper support staff	18 in taper support; 17 in usual care (also tapered), 35 total	Adjustment of antidepressants	22 weeks	Mean 5.68 ±1.36 taper support group; 6.26±1.49 usual care group	Mean 4.72±1.62 taper support group; 5.77±1.9 usual care group
Cunningham et al. (2016) [67]	Does opioid tapering lead to differences in withdrawal symptoms in low opioid users vs high users?	Comparison (Type 4)	Retrospective	Fibromyalgia	From 100 morphine mg equivalents to >200 mg morphine equivalents	• Same med as taking • Reduction 0–20% • Clonidine used	55	Interdisciplinary	Mean of 10 days or 28 days (for higher doses)	Mean 7.2±1.6	Mean 5.2±2.2
Miller et al. (2016) [68]	Do opioids improve or worsen pain in patients with an opioid dependence diagnosis?	Single group pre- and postcohort (Type 3)	Retrospective	Various	Various	• Immediate cessation • Withdrawal symptom control w/ benzos & clonidine over 3–5 days	33	Addiction counseling	Immediate cessation	Mean 5.5 (no SD given)	Mean 3.4 (no SD given)

(continued)

Table A1. continued

Author (Year) Reference Number	How Pain Was Measured	Statistical Analysis Type	Statistical Analysis Results	Type of Facility	Type of Evidence by AHCPR Criteria	Consensus Quality Score	Pain Increased, Decreased, or Same After Tapering	Comments Including Problems with Study	Supports the Hypothesis?
Di Benedetto et al. (2014) [64]	VAS	Not done	NA	Pain clinic	Type 3	100%	Pain decreased	• Adjuvants not stated • Not totally tapered • Other treatments not stated • Period of taper not stated	Yes
Robinson et al. (2008) [65]	Not stated	Not stated	Statistically significant drop in pain ($P = 0.001$)	Multidisciplinary pain center	Type 3	77.7%	Pain decreased	• Adjuvants not stated • Other treatments not stated • Period of taper not stated	Yes
Sullivan et al. (2017) [66]	VAS	Not stated	Not stated	Multidisciplinarypain center	Type 3	77.7%	Pain decreased	• Adjuvants utilized • Neither group totally tapered	Yes
Cunningham et al. (2016) [67]	Not stated	Chi-square	Statistically significant difference pre to post in pain ($P < 0.001$)	Three-week interdisciplinary pain rehabilitation program (PT, OT, cognitive treatment groups, relaxation, biofeedback; functional restoration)	Type 4	88.8%	Pain decreased	• Use of adjuvant analgesics not reported • How pain score was determined not reported • Retrospective • Pts totally tapered (100%)	Yes
Miller et al. (2016) [68]	VAS	Chi-square ANOVA	Statically significant drop in pain ($P < 0.01$)	Detoxification facility	Type 3	77.7%	Pain decreased	• Use of adjuvant analgesics not reported • Benzo use during detox period could have decreased pain • Patients totally withdrawn • Study included only pts on opioids	Yes

(continued)

Table A1. continued

Author (Year) Reference Number	Study Question	Design, Type of Study	Prospective vs Retrospective	Type of Chronic Pain	Opioid Tapered from	Type of Tapering	Number of Patients Tapered	Types of Treatments Besides Tapering	Number of Days Tapering	Pain Intensity Pretapering	Pain Intensity Post-tapering
Kidner et al. (2009) [69]	What is the functional recovery of opioid users?	Group comparison (type 4)	Retrospective	All types of occupation-al musculo-skeletal disorders	<30 mg MEQ to >120 mg MEQ	Not stated	596	Interdisciplinary	Not stated	Mean 6.6±1.7	Mean 4.9±2.1
Baron and McDonald PW (2006) [70]	Do opioids cause hyperalgesia?	Single group pre- and postcohort (type 3)	Retrospective	Various	High-dose opioids	Cessation then buprenorphine, later tapered over 14–180 days	23	Not stated	Max 180	Average 8	Average 3.3
Krumova et al. (2013) [71]	To gauge pain intensity after opioid withdrawal	Single group pre- & postcohort (type 3)	Prospective	Chronic non-cancer pain (various)	>240 mg MEQ some patients	With oral controlled morphine, 30% reduction first step; also clonidine and benzos utilized; adjuvants also utilized	Total opioid withdrawal N = 78; opioid reduction N = 24 Total = 102	PT, cognitive	7–14, 3-week program	Mean 7.1±1.8	Mean 5.4±2.1
Taylor et al. (1980) [72]	What is the effect of detoxification?	Single group pre- & postcohort	Retrospective	Mostly abdominal, unknown etiology	Not stated	Own opioid	7	Counseling, relaxation	1–6 days	Average 3.2	Average 2.1
Rome et al. (2004) [73]	What are the differences between patients taking/not taking opioids?	Group comparison (type 4)	Retrospective	Mostly low back pain and fibromyalgia	Not stated	3-week program	135	PT, biofeedback, relaxation training, stress management, OT, functional restoration	Not stated	Mean not stated (statistic given)	Mean not stated (statistic given)
Townsend et al. (2008) [74]	Are there differences between patients who do and do not use opioids?	Group comparison	Unclear	Mostly low back pain and fibromyalgia (various)	Mean daily morphine dose of 99 mg with range of 1–1,060 mg	Not stated	190, of which 176 completely tapered and 14 partially tapered	PT, OT, counseling groups, biofeedback, functional restoration, 3-week program	Not stated	Mean 49.3±8.6	Mean 40±12.9

(continued)

Table A1. continued

Author (Year) Reference Number	How Pain Measured	Statistical Analysis Type	Statistical Analysis Results	Type of Facility	Type of Evidence by AHCPR Criteria	Consensus Quality Score	Pain Increased, Decreased, or Same After Tapering	Comments Including Problems with Study	Supports Hypothesis?
Kidner et al.(2009) [69]	VAS	Not done	Functional restoration (PT, OT, counseling, group, stress training, vocational reintegration)		Type 4	87.5%	Pain decreased	• Retrospective • Adjuvant medications not stated • Tapering protocol not stated • Of opioid group, 74% D/C opioids	Yes
Baron and McDonald (2006) [70]	NRS	*t* test	Statistically significant drop in pain ($P < 0.001$)	Psychiatric inpatient	Type 3	77.7%	Pain decreased	• Retrospective • Adjuvant meds not stated • Buprenorphine taper but 100% D/C opioids eventually	Yes
Krumova et al. (2013)[71]	VAS	Chi-square	Pain drop significant ($P < 0.001$)	Pain facility in Germany	Type 3	100%	Pain decreased	• Adjuvant med used • All pts either completely tapered or opioid lowered	Yes
Taylor et al. (1980) [72]	Not stated	*t* test	Significant drop in pain for group ($P < 0.001$)	Pain clinic	Type 4	66.6%	Pain decreased	• Retrospective • Adjuvants not stated • 100% D/C opioids	Yes
Rome et al. (2004) [73]	VAS	Mean difference	Statistically significant drop in pain ($P < 0.001$)	Multidisciplinary pain center	Type 4	77.7%	Pain decreased	• Retrospective • Tapering not described • Adjuvants utilized • Pain measurements reported at program completion • 132/135 off opioids at program completion (98%)	Yes
Townsend et al. (2008) [74]	VAS	Chi-square	Significant improvement in pain severity ($P < 0.001$)	Multidisciplinary functional restoration pain center 3-week program	Type 4	88.8%	Pain decreased	• Unclear if prospective vs retrospective • Adjuvants utilized • Detox procedure not described • Pain measurements taken at discharge • Not all patients off opioids	Yes

ANOVA = analysis of variance; D/C = decreased; MEQ = morphine equivalents; NRS = numberic rating scale; OT = occupations therapy; PT = physical therapy; VAS = visual analog scale.

Table A2. Details of studies that have reported on opioid tapering and effects on pain levels pre/post-taper in chronic pain patients [75–79]

Author (Year) Reference Number	Study Question	Design, Type of Study	Prospective vs Retrospective	Type of Chronic Pain	Opioid Tapered from	Type of Tapering	Number of Patients Tapered	Types of Treatments Besides Tapering	Number of Days Tapering	Pain Intensity Pretapering	Pain Intensity Post-tapering
Nilsen et al. (2010) [75]	Can patients be tapered without pain escalation?	Single group, pre- and postcohort	Unclear	Nonmalignant chronic pain >6 mm (various)	Codeine, mean 237.3 mg	Not stated	11	Cognitive behavior counseling	8 weeks	Mean 6.2±1.4	Mean 5.8±1.3
Murphy et al. (2013) [76]	Investigate relationship between opioid cessation and treatment outcome	Single group, pre- and postcohort	Retrospective	Not stated	8–360 MEQ, mean 61.14 mg	Hydro-morphone cocktail	221	Physical therapy, occupational therapy, aquatic therapy, walking, relaxation, occupational therapy, recreational therapy, individual psychotherapy, educational classes, family intervention, cognitive behavioral model	Up to 7, 3-week program	Mean 7.01±1.77	Mean 6.46±1.74
Younger et al. (2008) [77]	What's the effect of opioid tapering on pain sensitivity?	Single group pre- and postcohort	Prospective	Various	MEQ range 5–1,250 mg	Blended cocktail	12	Unclear	Not stated	Mean 6.9±2.3	Mean 6.4±2.2
Drossman et al. (2012) [78]	What is the response of patients with narcotic bowel syndrome to opioid tapering?	Single group pre- and postcohort	Prospective	Mainly abdominal	75.3 mg morphine	Clonidine utilized	35	None	7.3 days inpatient 39.4 days outpatient	Mean 52.9±28.8	Mean 34.3±28.4
Hooten and Warner (2015) [79]	What is the effect of varenicline on opioid withdrawal?	Double-blind placebo-controlled study, but for this review only placebo arm utilized, so it is a single group pre/postcohort (N = 11)	Prospective	Various	75 mg/d	Not stated	11	PT, OT, counseling groups	3 weeks	Mean 53.3±13.3	Mean 41.3±9.9

(continued)

Table A2. continued

Author (Year) Reference Number	How Pain Measured	Statistical Analysis Type	Statistical Analysis Results	Type of Facility	Type of Evidence by AHCPR Criteria	Consensus Quality Score	Pain Increased, Decreased, or Same After Tapering	Comments Including Problems with Study	Supports Hypothesis?
Nilsen et al. (2010) [75]	NRS	ANOVA	No statistical effect for pain	Multidisciplinary pain center	Type 3	77.7%	Pain stayed same	• Detox procedure not described • Adjuvant use not stated • 55% D/C opioids • 27% lowered dose • To report of pain at completion of program	Yes
Murphy et al. (2013) [76]	NRS	*t* test & chi-square	Statistically significant reduction in pain ($P < 0.001$)	Multidisciplinary pain center 3-week program	Type 3	77.7%	Pain decreased	• Adjuvants utilized • Retrospective • 100% of patients (221) D/C opioids at program completion	Yes
Younger et al. (2008) [77]	VAS	*t* test	No drop or increase in pain NS	Pain center not described	Type 3	88.8%	Pain stayed same	• Adjuvants use not stated • Pharmacological treatments not described • 50% D/C opioids by completion of program, 25% same dose of opioids, 25% greatly reduced opioid dose	Yes
Drossman et al. (2012) [78]	VAS	Chi-square	Statistically significant drop in pain ($P < 0.003$)	GI inpatient	Type 3	77.7%	Pain decreased	• 89.7% tapered off completely • Adjuvants utilized	Yes
Hooten and Warner (2015) [79]	Multidimensional pain inventory	Linear regression	Significant improvement in pain ($P < 0.001$)	Multidisciplinary	Type 3	88.8%	Pain decreased	• 100% of pts [9] off opioids	Yes

ANOVA = analysis of variance; D/C = decreased; MEQ = morphine equivalents; NRS = numberic rating scale; NS = not significant; OT = occupations therapy; PT = physical therapy; VAS = visual analog scale.

Table A3. Details of studies that have reported on opioid tapering and effects on pain levels pre/post-taper in chronic pain patients [6, 80–82]

Author (Year) Reference Number	Study Question	Design, Type of Study	Prospective vs Retrospective	Type of Chronic Pain	Opioid Tapered from	Type of Tapering	Number Patients Tapered	Types of Treatments Besides Tapering	Number of Days Tapering	Pain Intensity Pretapering	Pain Intensity Post-tapering
Hooten et al. (2010) [80]	What is the association between baseline opioid dose and heat pain perception?	Single group pre- and postcohort	Prospective	Various	Various mean 192 mg	Not stated	91 completed data collection	• PT • OT • Counseling groups • Psychotherapy	3 weeks	Mean 50.62±7.72	Mean 41.0±11.32
Murphy et al. (2016) [81]	What are the differences between male and female vets engaged in chronic pain management?	Two groups pre- and postcohort	Retrospective	Various	Various mean 63 mg	Not stated	324	• PT • OT • Aquatic therapy • Relaxation • Recreational therapy • Psychotherapy • Education groups • Family therapy	1. weeks	Mean Females 6.94±1.57 Males 6.88±1.73	Mean Females 6.07±1.93 Males 6.19±1.80
Schwarzer et al. (2015) [82]	What is the prevalence of sleep disordered breathing in CPPs before and after opioid tapering?	Single group pre- and postcohort	Prospective	Various	Mean 175 mg	Clonidine, (controlled-release) morphine, benzos	18	• Groups • Psychotherapy • Co-analgesics	3 weeks	Mean 7.2±1.5	Mean 6.6±1.9
Belkin et al. (2017) [6]	What is the pain tolerance of opioid addicts recently tapered from opioids?	Single group pre- and postcohort	Retrospective	Not stated	Not stated	Not stated	61	Not stated	Not stated	Not reported	At 1-month post-taper: 51% pts improved pain; 46% same pain; 3% worse pain

(continued)

Table A3. continued

Author (Year) Reference Number	How Pain Was Measured	Statistical Analysis Type	Statistical Analysis Results	Type of Facility	Type of Evidence by AHCPR Criteria	Consensus Quality Score	Pain Increased, Decreased, or Same After Tapering	Comments Including Problems with Study	Supports Hypothesis?
Hooten et al. (2010) [80]	Multidimensional pain inventory	T-scores	Statistically significant improvement in pain scores ($P < 0.002$)	Multidisciplinary	Type 3	88.8%	Decreased	• Of 101 who completed program, 99 (98%) D/C opioids, but data was available only in 91 • Adjuvants are not stated	Yes
Murphy et al. (2016) [81]	VAS	T-scores	Statistically significantly improved pain scores for both females and males ($P < 0.05$)	Multidisciplinary	Type 3	77.7%	Decreased	• 100% of pts tapered	Yes
Schwarzer et al. (2015) [82]	NRS	Chi-square	Nonsignificant difference in average pain	Interdisciplinary	Type 3	88.8%	Decreased but not significant	• Received co-analgesics • 100% tapered off	Yes
Belkin et al. (2017) [6]	Not stated	None	None	NA	Type 3	75.0%	97% improved or no change	• Pain report derived from self-report • Not all tapered	Yes

ANOVA = analysis of variance; D/C = decreased; MEQ = morphine equivalents; NRS = numberic rating scale; OT = occupations therapy; PT = physical therapy; VAS = visual analog scale.

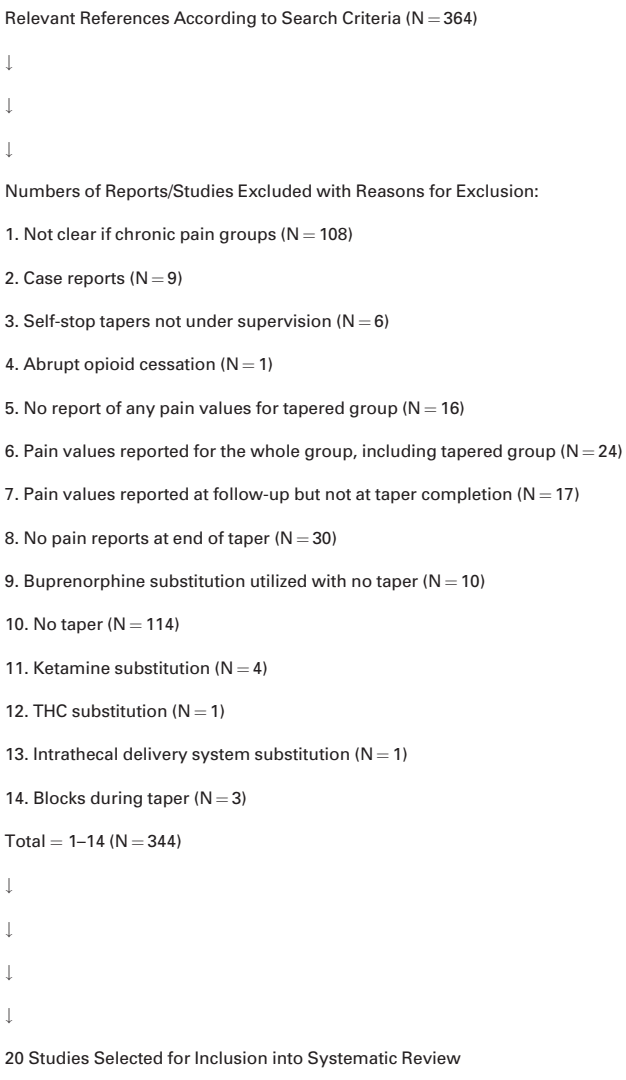

Figure A1. Flow diagram for study selection for this systematic review