
Evidence Brief: Benefits and Harms of Long-term Opioid Dose Reduction or Discontinuation in Patients with Chronic Pain

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PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of four ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the [program website](#).

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EXECUTIVE SUMMARY

Key Findings

- Evidence comprised mostly of observational studies in VHA and non-VHA settings is inadequate to fully weigh the balance of the benefits and harms of long-term opioid therapy (LTOT) for chronic pain against the benefits and harms of opioid tapering, primarily due to limited information on tapering harms.
- Patients on LTOT who voluntarily participate in intensive pain management interventions that incorporate opioid tapering may experience improvements in pain severity and pain-related function, while those who taper opioids with less intensive co-interventions may have unchanged pain and function. However, our confidence in these findings is low and additional evidence is needed before drawing stronger conclusions.
- Findings are inconclusive for other patient outcomes following opioid tapers, including serious harms such as overdose and suicide, as these outcomes have not been sufficiently studied.
- Inability to compare outcomes among groups due to study heterogeneity and limited subgroup analyses is an important gap in terms of understanding how outcomes may differ by patient or tapering characteristics.

Background

The ESP Coordinating Center (ESP CC) is responding to a request from VA Health Services Research and Development Service (HSR&D) for an evidence brief on patient outcomes following long-term opioid dose reduction or discontinuation. Findings from this evidence brief will be used to inform prioritization of questions for a State-of-the-Art conference in September 2019.

Methods

To identify studies, we searched MEDLINE®, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, and other sources up to March 2019. We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods.

In response to the evolving public health crisis related to opioid use, many providers, health systems, and payers are changing their approach to opioid prescribing for patients with chronic pain. Guidelines from the Centers for Disease Control & Prevention (CDC) and Department of Veterans Affairs/Department of Defense (VA/DoD) recommend using the lowest effective opioid doses for chronic pain and considering dose reduction when opioid risks exceed benefits. Patients with chronic pain currently on LTOT, who are sometimes referred to as “legacy patients,” and the providers who care for them, are at the center of a difficult balance between 2 necessary roles of the health care system – reducing suffering due to chronic pain and reducing harms associated with opioid use. Maintaining this balance not only requires providers to consider the risks and benefits of LTOT, but also the potential risks and benefits of the tapering process itself. Anecdotal evidence is accumulating that patients may be exposed to harms when tapering is conducted without patient buy-in and without additional pain management and psychosocial supports. Given the urgent need for continued action to reduce opioid overdose deaths and other potential harms associated with long-term opioid use, improved understanding of patient outcomes following opioid tapers is necessary to inform best practices.

A good-quality 2017 systematic review by Frank et al found inconclusive evidence on the impact of LTOT tapers on pain severity, pain-related function, quality of life, withdrawal symptoms, substance abuse, and adverse effects. The aim of the current review was to synthesize the studies of tapering included in Frank et al and those published more recently for a broader range of outcomes, including overdose and suicide, and with an emphasis on evidence most relevant and applicable to VHA populations.

We included 34 of 40 studies from Frank et al as well as 10 new studies for a total of 44 primary studies – 5 randomized controlled trials (RCTs), 6 controlled observational studies, and 33 uncontrolled observational studies. After prioritizing studies that are the most highly applicable and informative for VHA: 1) studies conducted in VHA settings, 2) studies conducted in non-VHA outpatient settings with sufficiently described patient populations and tapering interventions to assess their applicability to VHA, and 3) studies that evaluated serious harms of tapering (*ie*, suicide and overdose), we synthesized evidence from 15 studies.

Evidence from these 15 prioritized studies (including 5 VHA studies) suggests that pain severity and pain-related function may improve for some patients with chronic pain on LTOT who participate in intensive pain management interventions that incorporate opioid tapering, such as functional rehabilitation programs that require daily participation and include physical and occupational therapy as well as psychotherapy. For patients who taper opioids with lower intensity co-interventions or no co-intervention, pain severity and pain-related function may not change. However, our confidence in these findings is low and additional evidence is needed before drawing stronger conclusions. Importantly, while findings of improvement or nonsignificant changes in mean pain scores are encouraging, these types of outcome assessments are of lower utility as they provide insufficient information to determine how clinically meaningful the changes were to individual patients.

We were not able to evaluate which patient or tapering characteristics are associated with greater benefits and harms. Patient baseline characteristics were not sufficiently described and interventions were too nonspecific to draw meaningful conclusions about the comparative effectiveness of different tapering approaches, although results of 1 retrospective study based on Medicaid claims data in Vermont suggests that reductions in LTOT over more than 3 weeks are associated with lower rates of ED visits and hospitalizations due to opioid-related adverse events compared to abrupt discontinuation of opioids or tapering in less than 3 weeks.

The biggest gaps in the evidence for patient outcomes following LTOT tapers are related to serious harms, including the role of LTOT tapers in increased or new substance use, overdose, and suicide. Subgroup analysis from a retrospective study of VHA patients suggests that opioid tapers are associated with suicidal ideation and suicidal self-directed violence for Veterans with post-traumatic stress disorder (PTSD) and psychotic disorders, but studies have not identified additional risk factors for suicide or other serious harms following LTOT tapers. Characterizing these potential harms should be a priority of future research, as understanding the risks of LTOT tapering is critical to support patients and providers with shared decision-making and inform health system policy changes. Just as risk assessment tools are being developed for opioid prescribing, clinicians would benefit from a risk assessment tool to evaluate opioid tapers to weigh the balance of potential undesirable outcomes from both continued opioid use and opioid discontinuation.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from VA Health Services Research and Development Service (HSR&D) for an evidence brief on patient outcomes following long-term opioid dose reduction or discontinuation. Findings from this evidence brief will be used to inform prioritization of questions for a State-of-the-Art conference in September 2019.

BACKGROUND

In response to the evolving crisis of opioid-related morbidity, mortality, and misuse fueled initially by prescription opioids,¹ many providers and health systems are reevaluating their approach to opioid therapy for chronic pain. The amount of opioids prescribed in the US peaked in 2010 and has since declined,² reflecting a shift away from routine use of opioids for pain management. Publication of the 2016 Centers for Disease Control & Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain further accelerated this decline by highlighting opioid risks and the lack of strong evidence supporting long-term opioid use for chronic pain (generally excluding cancer-related pain, palliative care, and end-of-life care).^{3,4} Specifically, the 2016 CDC guideline recommends using the lowest effective opioid dose for chronic pain and reevaluating the risks and benefits of opioid doses > 50mg morphine equivalent daily dose (MEDD). The CDC guideline also recommends avoiding or carefully justifying a rationale for prescribing opioid doses > 90mg MEDD and considering dose reductions (also referred to as tapering) for patients already prescribed > 90mg MEDD. Similarly, the Department of Veterans Affairs/Department of Defense (VA/DoD) 2017 Clinical Practice Guideline for Opioid Therapy for Chronic Pain recommends considering opioid tapering when risks of long-term opioids exceed benefits and recommends against prescribing doses > 90mg MEDD.⁵ These recommendations apply broadly to adults with chronic pain who are prescribed LTOT, not just those who show signs of opioid misuse. Patients with chronic pain on LTOT, who are sometimes referred to as “legacy patients,”⁶ and the providers who care for them are thus at the center of a difficult balance between 2 necessary roles of the health care system – reducing suffering due to chronic pain and reducing harms associated with long-term opioid use.⁷

Per VA/DoD guidelines, the goal of opioid tapering is to “improve the balance of risks and clinically meaningful benefits for patients on LTOT.” Potential risks of LTOT include respiratory depression and overdose, opioid-related side effects including constipation and lethargy, drug-drug interactions, and opioid dependence.⁸ Potential benefits of LTOT may include higher quality of life due to lower pain levels and improved function. CDC guidelines suggest using a validated instrument such as the 3-item “Pain average, interference with Enjoyment of life, and interference with General activity” (PEG) Assessment Scale to evaluate pain and function and suggest that a clinically meaningful result would be 30% improvement.

CDC and VA/DoD guidelines emphasize the importance of shared decision-making regarding LTOT tapers and outline patient-centered approaches to tapering with gradual dose reductions and pauses in the tapering process as needed. Specifically, the CDC guidelines recommend using



a taper slow enough to minimize symptoms and signs of opioid withdrawal and suggest that decreasing opioid doses by 10% a week is a reasonable starting point. VA/DoD guidelines recommend individualizing taper speeds and suggest gradual tapers over months to years for patients starting on very high opioid doses by reductions of 5-20% every 4 weeks and faster tapers by 5-20% per week when risks are considered too high to taper gradually. Similar approaches are recommended by the American Academy of Family Physicians and other groups including the Washington State Agency Medical Directors' Group (AMDG) and the Oregon Pain Guidance Clinical Advisory Group.⁸⁻¹⁰ VHA also provides clinicians with a "Pain Management Opioid Taper Decision Tool" to evaluate LTOT risks and benefits and develop a taper plan.¹¹ This tool does not include guidance on how to evaluate the risks and benefits of the tapering process itself, although it does provide specific recommendations on taper speeds, follow-up, and the addition of non-opioid medications and psychosocial supports.

It is likely that with shared decision-making that incorporates patients' preferences and values, some patients will favor tapering LTOT based on risks and benefits, even if it is their clinician who initially suggests a taper. However, despite detailed guidance from the CDC and VA/DoD on approaches to LTOT tapers, challenges may arise with guideline implementation. For example, even with an effort to engage in shared decision-making, patients and providers may experience conflict when they do not have the same views regarding the risks and benefits of continued LTOT prescribing.¹² If patients do not perceive personal risks associated with LTOT or readily identify the potential benefits of tapering, fears about uncontrolled pain and withdrawal symptoms may negatively impact their willingness to taper. A qualitative study by Frank et al found that patients tend to perceive a low risk of overdose when they are thinking about LTOT and themselves personally and are willing to accept opioid-related risks if the trade-off is improved pain.¹³ Lack of access to non-pharmacologic pain treatments such as physical therapy, psychosocial support services, and mental health and substance use disorder treatment may also contribute to patient concerns about stopping opioids without adding more supports. Time constraints, multiple competing demands, and the emotionally demanding nature of discussions related to opioid prescribing may also make it difficult for providers to engage with patients in complex decision-making.^{14,15}

Moreover, concern for opioid misuse may prompt clinicians to initiate tapers without attempts at shared decision-making. Due to increased use of guideline-recommended opioid risk mitigation strategies such as urine drug monitoring and review of state prescription monitoring programs, clinicians are uncovering more signs of opioid misuse than before, such as evidence of illicit drug use and/or opioid prescriptions from multiple providers. In the Transforming Opioid Prescribing in Primary Care (TOPCARE) RCT, patients were more likely to have opioid doses reduced or discontinued if they received care in clinics that were randomized to an intervention to promote guideline-concordant care.¹⁶ Similarly, a retrospective study of 600 VHA patients who discontinued opioids found that 75% of opioid discontinuations initiated by clinicians were because of opioid-related aberrant behaviors including unexpected results of urine drug screens (UDS).¹⁷

Aside from challenges related to shared decision-making when patients and provider disagree on LTOT risks and in cases of suspected opioid misuse, concern also exists that providers, health systems, and payers have misapplied CDC guidelines to impose opioid tapers or dose thresholds on patients. Authors of the CDC guideline recently acknowledged this concern, clarified the intent of the guidelines, and criticized "inflexible application of recommended dosage and

duration thresholds and policies that encourage hard limits and abrupt tapering of drug dosages, resulting in sudden opioid discontinuation or dismissal of patients from a physician's practice."¹⁴ Risks associated with abrupt and involuntary tapers have also been highlighted by the US Food and Drug Administration, which issued a Drug Safety Communication to providers in response to reports of "serious harm, including serious withdrawal symptoms, uncontrolled pain and suicide, in patients who are physically dependent on opioid pain medicines when these medicines are suddenly discontinued or when the dose is reduced too quickly, often without adequate patient communication, follow-up or support."¹⁸ The potential for opioid tapers to result in patient distress and disengagement in care is supported by qualitative data demonstrating that patients experience a sense of loss and betrayal when they are not consulted about tapers and view communication with their providers negatively when they sense that accomplishing a taper is more important than acting in their individual best interest.¹⁹

Tapering may also be more challenging for some patients than for others. Through long-term use of prescribed opioids, many patients on LTOT will develop physiologic dependence on opioids, an "adapted state due to excessive substance stimulation that can cause cognitive, emotional, or physical withdrawal symptoms when substance use is ceased."²⁰ The concept of "complex persistent opioid dependence" has been introduced by experts in the field of pain management and addiction medicine to describe a type of opioid dependence that results from long-term treatment with opioids for pain. For some patients, this dependence is not easily reversible and can manifest as protracted withdrawal symptoms including mood and sleep disturbance, rebound of pain symptoms, irritability and decreased ability to focus, and exacerbation of underlying mental health disorders.^{20,21} While the criteria that define "complex persistent opioid dependence" are still evolving, the concept may help explain the destabilization that can occur for some patients during opioid tapers, which can present as erratic behaviors and new or increased use of illicit opioids and other substances.

Although the association between high-dose opioid prescribing and increased risk of overdose is not in question,²² uncertainty exists regarding the balance of benefits and harms due to LTOT tapers at the population level. As discussed by Pitt et al in a study modeling outcomes of policies to mitigate the opioid crisis, decreasing the prescription opioid supply may reduce deaths associated with prescription opioids, but this benefit may be offset by an increase in heroin-related deaths as some people with opioid use disorder (OUD) who previously used prescription opioids turn to illicit opioids.²³ Rates of opioid overdose among Veterans increased from 14.5 per 100,000 person-years in 2010 to 21.1 per 100,000 person-years in 2016 (adjusted rate ratio = 1.65, 95% CI 1.51 to 1.81), despite a drop in receipt of prescription opioids in the 3 months before death from 54% in 2010 to 26% in 2016.²⁴ Mirroring national trends, opioid overdose rates among Veterans increased primarily due to increased use of heroin and synthetic opioids. The finding that opioid overdose deaths are increasing despite reductions in high-dose prescribing and opioid prescribing overall raises concern that unintended consequences of tapering initiatives are contributing to overdose rates.^{25,26}

Given the urgent need for continued action to reduce opioid overdose deaths and evolving concerns about harms associated with LTOT tapers, improved understanding of patient outcomes following opioid dose reduction and discontinuation is necessary. Anecdotal evidence is accumulating that patients may be exposed to harms when tapering is imposed on patients without adequate communication or support. Uncertainty exists regarding how to identify patients who are at increased risk of adverse events during the tapering process, and how to best

link these high-risk patients to additional resources including treatment for OUD. Additionally, uncertainty exists regarding patient outcomes when tapering is done in a way that reflects best practices according to expert opinion – that is, tapering gradually and with patient input.

To be most applicable to a VHA patient population, the ideal study of patient outcomes following LTOT tapers would include patients who have been prescribed opioids for predominately musculoskeletal pain. Two distinct patient groups with potentially different risks for LTOT tapering harms should be considered, those who voluntarily engage in a tapering plan and those who are tapering due to clinician concerns for LTOT safety and/or opioid misuse. Similarly, patient histories should be well-characterized (*ie*, how many years they have had chronic pain, how many years they have taken opioids, whether they have already tried other pain medications and non-pharmacologic management options, and whether they have previously tried to taper opioids) and the reason for the taper should be clear (*ie*, patient preference, persistent pain despite opioids, opioid side effects, or concern for misuse). This context is necessary for clinicians and other stakeholders to interpret study results and evaluate whether the results apply to a given patient or patient population. An informative study intervention would include a taper aimed at reducing MEDD below a specified threshold and examine a broad range of outcomes including validated measures of pain and function, incidence of rebound pain, and unintended consequences and adverse events such as disengagement from care, increased healthcare utilization, new or increased substance use, overdose, and suicide.

A good-quality 2017 systematic review by Frank et al found inconclusive evidence on the impact of LTOT tapers on pain severity, pain-related function, quality of life, withdrawal symptoms, substance abuse, and adverse effects.²⁷ The aim of the current review is to synthesize the studies of tapering included in Frank et al and those published more recently for a broader range of outcomes, including overdose and suicide and with an emphasis on evidence most relevant and applicable to VHA populations.

SCOPE

This evidence brief will address the following key questions and inclusion criteria:

Key Questions

Key Question 1: Among patients prescribed long-term opioid therapy for chronic pain, what are the benefits and harms of opioid dose reduction or discontinuation?

Key Question 2: Do the benefits and harms of opioid dose reduction or discontinuation vary by:

- Patient co-morbidities (previously diagnosed substance use disorder or mental health diagnoses),
- Indication for dose reduction or discontinuation (factors leading to the consideration of tapering in the first place such as patient preference, side effects, poorly controlled pain on opioids, concern for opioid misuse, change in health system or payer policy, or other reasons),
- Patient engagement in tapering (including whether the taper is patient-initiated, collaboratively/patient-centered, or involuntary/mandated and unilaterally imposed),

- Intent of taper (reduction to target dose vs discontinuation),
- Baseline morphine equivalent daily dose (MEDD),
- Opioid regimen (intermittent use vs daily use; long-acting vs short-acting opioid use), or
- Taper characteristics (fast <1 month or slow >1 month; individualized or per protocol)?

Eligibility Criteria

The ESP included studies that met the following criteria:

- **P**opulation: Adults prescribed long-term opioids (≥ 3 months) for chronic pain (excluding patients receiving palliative care, treatment for cancer-related pain, or undergoing surgery) including patients with co-morbid chronic pain and substance use disorder (excluding patients with substance use disorder only)
- **I**ntervention: Dose reduction or discontinuation (excluding studies of chronic pain interventions not explicitly designed to lower opioid doses)
- **C**omparator: Any
- **O**utcomes (excluding studies that only report MEDD changes without other patient outcomes):
 - Pain severity (Pain Numerical Rating Scale (NRS), Multidimensional Pain Inventory (MPI), Brief Pain Inventory (BPI), *etc*)
 - Pain-related function (Multidimensional Pain Inventory (MPI), Pain Outcomes Questionnaire-VA (POQ-VA), Pain Disability Index, *etc*)
 - Quality of life (Short Form-36 Health Status Questionnaire (SF-36))
 - Opioid withdrawal symptoms (Clinical Opiate Withdrawal Scale (COWS), Short Opiate Withdrawal Scale (SOWS), *etc*)
 - Patient satisfaction
 - Healthcare utilization including retention in primary care (or usual source of care)
 - Change in depression and anxiety symptoms (Patient Health Questionnaire (PHQ-9), Center for Epidemiologic Studies Depression Scale (CES-D), *etc*)
 - New or increased substance use
 - Opioid overdose
 - Suicidal ideation and suicidal self-directed violence
- **T**iming: Any
- **S**etting: Any, but may prioritize to accommodate timeline using a best-evidence approach
- **S**tudy design: Any, but may prioritize to accommodate timeline using a best-evidence approach.

METHODS

SEARCHES AND STUDY SELECTION

To identify articles relevant to the key questions, our research librarian searched MEDLINE, PsycINFO, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Embase from January 1, 2017 (the end search date of the Frank et al review) through March 15, 2019 using terms for opioids, dose reduction, discontinuation, and pain (see supplemental materials for complete search strategies). Additional citations were identified from hand-searching reference lists and consultation with content experts. We limited the search to published and indexed articles involving human subjects available in the English language. Study selection was based on the eligibility criteria described above. Titles and abstracts and full-text articles were reviewed by one investigator and checked by another. All disagreements were resolved by consensus or review from a third investigator.

QUALITY ASSESSMENT

For studies included in previous systematic reviews, we relied on risk of bias ratings within those reviews. For subsequently published studies, we used the Cochrane Risk of Bias Tools to rate the internal validity.^{28,29,30} Risk of bias was not assessed for pre-post or case-control studies. For studies included in previous systematic reviews, we relied on abstracted data for some outcomes from those reviews and abstracted data on additional outcomes of interest as well as data for all new studies. All data abstraction and internal validity ratings were first completed by one reviewer and then checked by another. All disagreements were resolved by consensus or review from a third investigator.

We informally graded the quality of the evidence as a whole using the GRADE framework,³¹ also used by Frank et al, which considers the risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Ratings typically range from high to very low, reflecting our confidence that the evidence reflects the true effect. For this review, we applied the following general algorithm: evidence comprised of multiple mostly uncontrolled studies with consistent findings received a rating of “low”; whereas the same type of evidence with few studies and/or indirectness and inconsistency would be downgraded to “very low.”

SYNTHESIS OF DATA

Due to limited data or heterogeneity, we synthesized the evidence qualitatively. We prioritized the synthesis of studies to those that are the most highly applicable and informative for VHA: 1) studies conducted in VHA settings, 2) studies conducted in non-VHA outpatient settings with sufficiently described patient populations and tapering interventions to make an assessment of VHA applicability, and 3) studies that evaluated serious harms of tapering (*ie*, suicide and overdose).

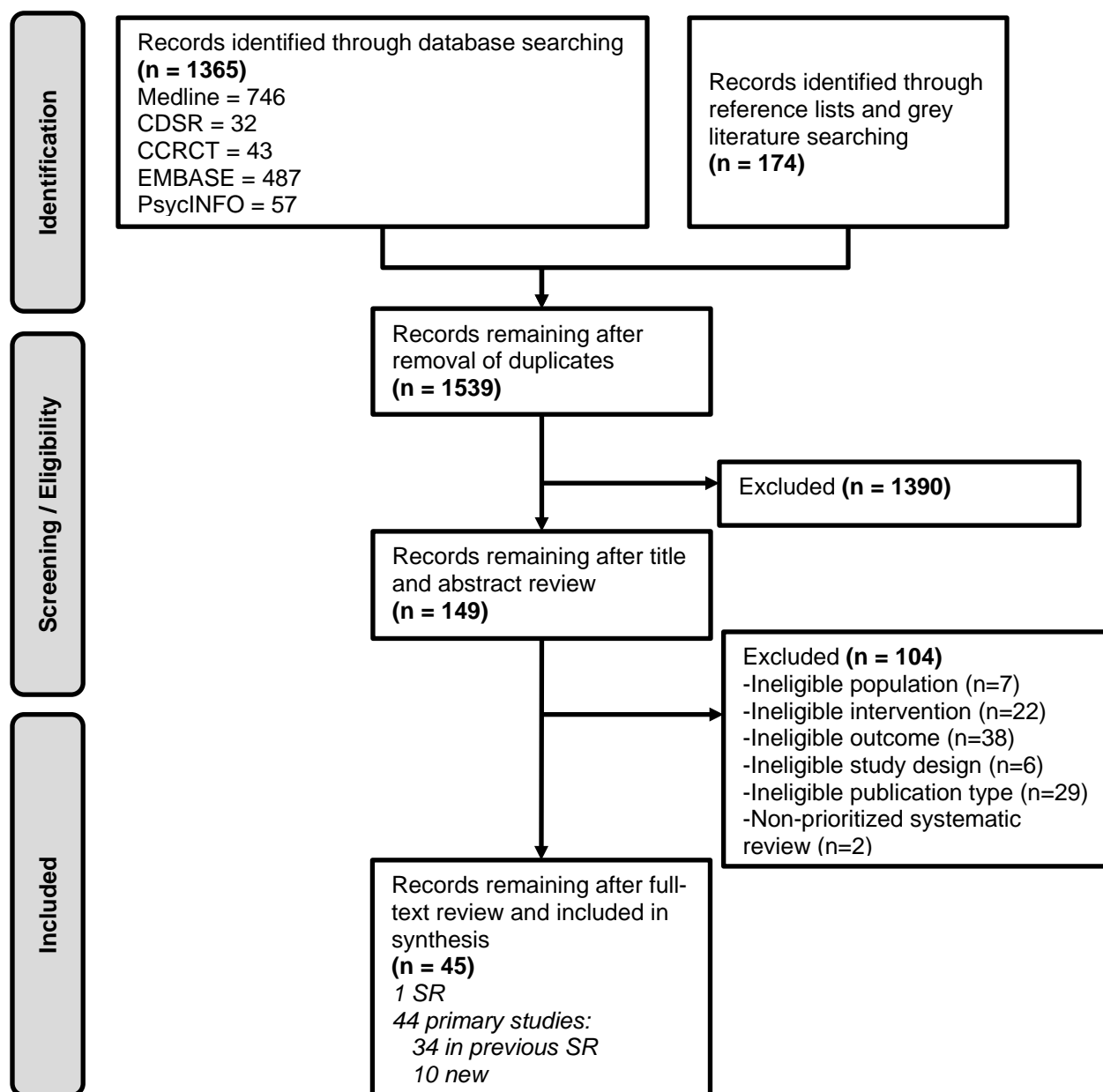
A draft version of this report was reviewed by peer reviewers as well as clinical leadership (see supplemental materials for disposition of peer review comments). The complete description of our methods can be found on the PROSPERO international prospective register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO/>; registration number CRD42019129110).

RESULTS

LITERATURE FLOW

The literature flow diagram (Figure 1) summarizes the results of the search and study selection processes. Among 1,539 potentially relevant citations, we included 45 studies, including 1 systematic review (Frank et al),²⁷ 34 primary studies included in the systematic review,³²⁻⁶⁵ and 10 primary studies published since the search of the systematic review.⁶⁶⁻⁷⁵ See supplemental materials for list of excluded studies and full data tables.

Figure 1. Literature Flowchart



LITERATURE OVERVIEW

The 2017 good-quality systematic review by Frank et al included 40 studies that examined the effect of opioid dose reduction on patient outcomes. Our inclusion criteria were narrower, as we only included studies of interventions explicitly designed to reduce opioid doses, rather than studies of interventions to manage chronic pain or improve another aspect of care that may have also led to opioid dose reduction. We therefore included 34 studies from Frank et al as well as 10 new studies for a total of 44 primary studies – 5 RCTs, 6 controlled observational studies, and 33 uncontrolled observational studies. Characteristics of all included studies can be found in the supplemental materials.

As described above, we prioritized synthesis of evidence that was most likely to be informative and applicable to VHA. Fifteen studies (Table 1) (2 RCTs,^{34,66} 2 controlled observational studies,^{70,72} and 11 uncontrolled observational studies^{43,46,48,49,52,56,71,73-76}) met these criteria, which we refer to as prioritized studies. The remaining studies either had low applicability to VHA patients or care settings or included patients or interventions that were not well-described. Also, we abstracted information from but do not discuss in detail studies included in Frank et al that were deemed poor quality, unless they met our prioritization criteria.

Patient Characteristics

In the studies (14/15)^{34,43,46,48,49,52,56,66,71-76} that reported patient demographic characteristics, mean age ranged from 45 to 61 years, and patients were 21% to 54% male, except in studies conducted in VHA populations, which were 79% to 95% male. All patients were described as having chronic non-cancer pain except in an observational study by Mark et al based on Medicaid insurance claims data in Vermont in which patients without a cancer diagnosis were on > 120mg MEDD for more than 90 days and a diagnosis of chronic pain is implied.⁷⁵ In studies that reported detailed pain characteristics (9/15), patients had back pain or other chronic musculoskeletal pain (24% to 87%).^{43,46,56,66,72,74,76} Other pain conditions included neuropathic pain (6-14%),^{46,66,72,74} fibromyalgia (20%-100%),^{43,49,76} and headaches (2-12%).^{43,46,56,72,74,76} Mean baseline MEDD ranged widely from 61-330mg. The duration of chronic pain in most studies that reported this information was 9 to almost 14 years (the exception is the study by Kurita et al in which pain duration was > 6 months). Mean LTOT duration ranged from 1 to 10 years.

Most studies (12/15) did not report detailed information on the prevalence of baseline mental health co-morbidities. In 2 VHA studies based on the same national sample, patients had co-morbid depression (24-25%), anxiety (25%), post-traumatic stress disorder (31-32%), bipolar disorder (7-8%), or other psychotic disorder (8%).^{72,74} In the Mark et al study of Medicaid beneficiaries in Vermont, 27% had mood disorders and 25% had anxiety disorders.⁷⁵

Taper Characteristics

Most studies (9/15) involved a voluntary and/or patient-initiated taper in the context of specific interventions that ranged from high intensity (6 uncontrolled observational studies of 3-4 week multidisciplinary pain management programs)^{43,48,49,52,74,76} to medium intensity (2 RCTs embedded in multidisciplinary pain clinics, 1 with medication optimization prior to a scheduled taper and 1 with enhanced psychosocial supports),^{34,66} to low intensity (a self-help book paired with individual clinician guidance).⁷¹ The remaining studies (6/15) did not describe specific

tapering interventions. In 5 of these studies, tapers were mostly clinician-initiated or mandated tapers and in 1 study it was not clear whether tapers were voluntary.

Methodologic Limitations

Compared to Frank et al, we have slightly more confidence in the findings for pain severity and pain-related function (low versus very low quality per GRADE). Our higher confidence is explained by the decision to focus our evidence synthesis on a subset of studies with the greatest applicability to VHA. Studies had several limitations including inherent risk of bias associated with observational study designs (due to potential unmeasured confounders), lack of control groups in several studies, unclear fidelity to interventions, and inadequate reporting of missing data and handling of missing data. Despite these limitations, within our subset of studies, findings regarding pain and pain-related function were consistent.

Evidence on the remaining outcomes (quality of life, resolution of opioid-related side effects, withdrawal symptoms, patient satisfaction, healthcare utilization, substance use overdose, and suicide) is inconclusive (very low quality per GRADE). Studies of these outcomes had similar methodological weaknesses but were supported by only a single or few small studies.

Table 1. Characteristics of 15 Highlighted Studies with Most VHA Applicability

Author, Year N, Study Design	Setting Follow-up	Patient Age (mean) % Male % White	Most common pain type	Chronic pain (yrs.)	LTOT (yrs.)	Mean MEDD: Base/ Disch. or % Discont.	Intervention	Taper schedule	Taper speed
<i>RCTs</i>									
Kurita, 2018 ^{*66} 35 RCT	Multidisciplinary Pain Centre University Hospital, Denmark 6 mos.	53 yrs. 40% male Race NR	Neuropathic and nociceptive somatic pain (49.3%)	>6 mos.	>3 mos.	280mg/ 227mg	Voluntary or patient- initiated; opioid dose stabilization followed by taper vs usual care	Dose reduction 10% every 1-2 weeks	Slow
Sullivan, 2017 35 RCT	UW Medicine Center for Pain Relief 22 weeks	54 yrs. 29% male 85.7% white	NR	13.8 yrs.	10.2 yrs.	226mg 37% decreased dose	Voluntary; CBT and self- management skills building vs usual care	10% reduction per week	Slow
<i>Controlled Studies</i>									
Demidenko, 2017^{*72} 509 Case-control	VHA national sample 12 mos.	55 yrs. 94.3% male 70.7% white	MSK (85.1%)	NR	NR	76mg 100% discont.	85% clinician-initiated; no specific intervention	NR	NR
Von Korff, 2019 ^{*70} 31,142 Retrospective cohort	Group Health system, Washington 8 yrs.	Age NR Sex NR Race NR	NR	NR	NR	76mg/ 40mg	Clinician-initiated; no specific intervention	NR	NR
<i>Uncontrolled Studies</i>									
Darchuk, 2010 ²⁷ 292 Pre-post	Mayo Clinic Pain Rehabilitation Center 6 mos.	45.8 yrs. 21.4% male 95.3% white	Low back pain (24.5%)	10.7 yrs.	NR	112mg 94% discont.	Voluntary; 3-week intensive outpatient program	Individualized	Fast

Author, Year N, Study Design	Setting Follow-up	Patient Age (mean) % Male % White	Most common pain type	Chronic pain (yrs.)	LTOT (yrs.)	Mean MEDD: Base/ Disch. or % Discont.	Intervention	Taper schedule	Taper speed
Darnall, 2018* ⁷¹ 82 Pre-post	Community pain clinics, California 4 mos.	51 yrs. 40% male Race NR	NR	NR	6 yrs.	288mg/ 150mg	Voluntary; use of self- help book	Individualized; up to 5% in month 1, up to 10% per week in mos. 2-4	Slow
Harden, 2015 50 Pre-post	Philadelphia VA Medical Center 12 mos.	54 yrs. 88% male 60% white	Back (35%)	NR	12 mos.	>200mg (64%) 94% decreased dose	Clinician-initiated with patient consent; no specific intervention	Individualized	Slow
Hooten, 2007b 66 Pre-post	Mayo Clinic Pain Rehabilitation Center 3 weeks	46.8 yrs. 50% male 90.6% white	Fibromyalgia (100%)	Men: 11.3 yrs.; Women 9.5 yrs.	NR	Men: 64mg, Women: 39 mg 95% discont.	Voluntary; 3-week intensive outpatient program	Individualized	Fast
Hooten, 2009 1241 Pre-post	Mayo Clinic Pain Rehabilitation Center 3 weeks	46.5 yrs. 25.2% male 94.9% white	Low back (27%)	9.9 yrs.	NR	118mg 96% discont.	Voluntary; 3-week intensive outpatient program	Individualized	Fast
Huffman, 2017 1457 Pre-post	Cleveland Clinic Pain Rehabilitation Outpatient Program 12 mos.	46.3 yrs. 35.6% male Race: NR	NR	NR	>3 mos.	117mg 87% discont.	Voluntary or patient- initiated; 3-4 week intensive outpatient program	Individualized	Fast
Hundley, 2018*⁷³ 43 Pre-post	North Florida/South Georgia Veterans Health System 5 yrs.	61 yrs. 95.3% male 83.7% White	NR	NR	7.8 yrs.	330mg 65% discont.	Mandated; no specific intervention	Individualized	Slow

Author, Year N, Study Design	Setting Follow-up	Patient Age (mean) % Male % White	Most common pain type	Chronic pain (yrs.)	LTOT (yrs.)	Mean MEDD: Base/ Disch. or % Discont.	Intervention	Taper schedule	Taper speed
Mark, 2019 ^{*75} 494 Uncontrolled cohort	Medicaid beneficiaries in Vermont 90 days	47 yrs. 51% male Race NR	NR	NR	Mean 613 days	≥120 mg 100% discont.	NR	86% < 21 days 9% 21 to < 90 days 5% ≥ 90 days	Varied
McPherson, 2018^{*74} 551 Pre-post	VHA national sample 24 mos.	54.6 yrs. 95% male 71% white	MSK (87%)	NR	NR	76mg 100% discont.	85% clinician-initiated; no specific intervention	NR	NR
Murphy, 2013 705 Pre-post	VHA Chronic Pain Rehabilitation Program, Florida 3 weeks	49.08 yrs. 82.4% male 66.1 white	Back (60.2%)	12.69 yrs.	NR	61mg 100% discont.	Voluntary; 3-week inpatient intensive multidisciplinary program	Individualized	Fast
Townsend, 2008 373 Pre-post	Mayo Clinic Pain Rehabilitation Center 6 mos.	44.5 yrs. 20.9% male 95.7% white	Low back (24.4%)	9.4 yrs.	3.9 yrs.	99mg 93% discont.	Voluntary; 3-week intensive outpatient program	Individualized	Fast

*New since Frank 2017; Bold = VHA study

Abbreviations and definitions: MEDD = morphine equivalent daily dose; Discont. = discontinued; Disch = discharge; LTOT = long-term opioid therapy; Fast taper <1 month; Slow taper >1 month; NR = not reported; yrs. = years; mos. = months; MSK = musculoskeletal; NCM = nurse care management; CBT = cognitive behavioral therapy

FINDINGS FOR KQ1

Table 2 provides a summary of findings for KQ1. Specific outcomes are discussed below.

Pain Severity

Although fears about uncontrolled pain are thought to play a role in patients' willingness to taper, no studies reported the proportions of patients who experienced a clinically significant worsening in pain severity following LTOT tapers. One retrospective study of 50 patients at the Philadelphia VA Medical Center who had an average 46% reduction in MEDD at 12 months compared with baseline reported that pain improved for 40% of patients, was unchanged for 28%, and worsened for 33% at 6 to 12 months.⁴⁶ However, magnitudes of change are not reported for patients who had less or more pain, so it is not known whether these changes were clinically significant. Seven of the 8 studies from Frank et al reported mean pain scores at baseline and endpoint;^{34,43,46,48,49,52,56,76} among these, mean pain severity scores improved by a range of 7.8% to 47% after opioid tapers. While findings of improvement or nonsignificant changes in mean pain scores are encouraging, these types of outcome assessments are of lower utility as they do not provide enough information to determine how clinically meaningful the changes were to the individual patients.

Studies differed in the intensity of co-interventions, and average pain severity scores improved in LTOT patients participating in the most intensive pain management interventions that incorporated opioid tapers. In the majority of the studies^{43,48,49,52,56,76} from Frank et al, including a study of patients who participated in the VHA Chronic Pain Rehabilitation Program,⁵⁶ the interventions were 3-4 week intensive multimodal programs that included additional supports such as cognitive behavioral therapy. Among these studies, the greatest pain reduction (47%) was observed when 1457 patients with an unspecified type of pain on LTOT (mean MEDD 117mg) participated in the intensive Cleveland Clinic outpatient Interdisciplinary Chronic Pain Rehabilitation Program (ICPRP) (pain score of 6.61 at baseline, decreased to 3.50 on 11-point Likert scale) without any use of adjuvant medication.⁵² Although pain intensity started increasing after discharge, it was still 33% lower than admission at 6 months and 30% lower at 12 months. This ICPRP involved participation from "7:30 AM to 5:00 PM Monday to Friday, and includes daily medical management, individual psychotherapy (2-3 per week), group psychotherapy (7 hours per week), and cognitive behavioral group interventions and psychoeducation, physical and occupational therapy, substance use education, weaning from habituating medications, and optional monthly aftercare."⁵² Most patients (82%) completed the intervention, although single patients and those with more pain were less likely to complete the intervention. Results of this study have limited applicability as many VHA patients would not be able to complete such an intensive intervention.

In an RCT included in the Frank review, patients with chronic pain on LTOT who were interested in tapering were randomized to usual care versus a tapering support intervention that included psychiatric consultation and 18 weekly meetings with a physician assistant to improve self-management skills. In both groups, patients had lower pain severity ratings at 22 weeks and patients in the intervention group also had improvements in pain interference and pain self-efficacy.³⁴ While not as intense as the functional rehabilitation programs described above, the intervention in this study offered more intensive pain management support than is typically available in routine primary care.

In patients who tapered opioids voluntarily in less intensive pain management programs, average pain scores did not change significantly between baseline and endpoint. Three new studies that evaluated pain outcomes had less intensive or undefined co-interventions, and in these studies pain severity did not significantly change after opioid dose reduction or discontinuation (mean reduction, 3.1% to 10%).^{66,71,74} In an uncontrolled observational study of a national sample of 551 VHA patients with mean baseline MEDD of 76mg in which 85% of patients underwent clinician-initiated tapers, average pain intensity after opioid discontinuation did not worsen. This study did not specify details of tapering approaches or co-interventions. The other 2 new studies were conducted within pain clinics; in 1 an individualized taper approach was only accompanied by a self-help book,⁷¹ and in the other – a RCT comparing protocolized tapers to usual care – patients did not receive specific additional supports.⁷⁴

Pain-related Function

LTOT tapering paired with more intensive interventions is also associated with greater improvements in pain-related function. The most improvement was observed in the group of 1457 patients with an unspecified type of pain on LTOT (mean MEDD 117mg) who participated in the intensive Cleveland Clinic ICPRP described above.⁵² In this study, mean scores on the Pain Disability Index (PDI) decreased from 42.95 at baseline to 18.29 at discharge (-57.4%) and was 23.7 after 6 to 12 months of follow-up (-44.8%).⁵² The only VHA study that evaluated pain-related function was also an intensive intervention in which 705 Veterans on a mean baseline MEDD of 61mg for primarily low back pain voluntarily participated in a 3-week interdisciplinary pain program incorporating opioid cessation. In this study, the score on an interference in activities of daily living scale decreased from 16 at baseline to 13 at 3-week discharge (-18.8%) when measured using the VA Pain Outcomes Questionnaire-interference in Activities of Daily Living (POQ-ADL).⁵⁶ Other types of reductions in pain interference included a 28.4 to 29.4% reduction on the Multidimensional Pain Inventory (MPI)^{43,76} and a 28.6% reduction on the Brief Pain Inventory.⁷⁶

The smallest (and statistically nonsignificant) change came following the least intense intervention, in which an individualized taper was accompanied only by a self-help book.⁷¹ In that study, pain interference did not change between baseline and endpoint when measured using the PROMIS (63 versus 63).

Quality of Life

The impact of LTOT tapers on quality of life is unclear, as evidence is sparse and inconsistent. No studies examining quality of life were conducted in VHA settings. In 2 uncontrolled observational studies of patients participating in intensive multimodal rehabilitation programs, quality of life improved on SF-36 subscales. The primary aim of one of these studies was to compare treatment responses among patients on LTOT to patients who were not on LTOT⁷⁶ at the beginning of the study. Patients on LTOT at baseline had improved post-treatment (SF-36) emotional factors (36.5 vs 46.2), physical factors (29.6 vs 41.3), and social functioning (29.8 vs 43.4) (all $P < 0.001$) and these results were similar to patients not on opioids. In another study of the same pain rehabilitation program comparing treatment effects between men and women with fibromyalgia, mean differences in all pre- and post-treatment outcome measures demonstrated a significant treatment response, but men had lower post-treatment scores on the SF-36 health perception ($P = 0.023$), role limitations-physical ($P = 0.021$), and social functioning ($P = 0.033$) subscales.⁴⁹

Only 1 new study included quality of life measures. In a RCT comparing scheduled opioid tapers to usual care (in which patients did not taper opioids) at a pain center in Denmark, patients in the taper group reported feeling significantly more rested at follow-up (80% intervention vs 35% control, $P = .0082$).⁶⁶ The intervention did not result in other differences in quality of life as measured by SF-36, and no variations in quality of life outcomes were reported due to baseline patient characteristics.

Resolution of Opioid-related Side Effects

The impact of LTOT tapers on resolution of opioid-related side effects is unclear, as none of the 15 prioritized studies reported this outcome.

Patient Satisfaction

The impact of LTOT tapers on patient satisfaction is unclear because most studies did not evaluate this outcome. In a retrospective study of 705 patients who participated in an intensive 3-week VHA Chronic Pain Rehabilitation Program in Florida, patients on LTOT who tapered during the program had similarly favorable treatment satisfaction scores as patients who were not taking opioids (8.30 vs 8.22 on a 0-10 scale with 10 = “completely satisfied”).⁵⁶ We did not identify other studies of patient satisfaction that described patient characteristics or tapering interventions in sufficient detail to determine applicability to VHA.

Healthcare Utilization

The impact of LTOT tapers on healthcare utilization rates is unclear because few studies evaluated this outcome and those that did had inconsistent results. In a retrospective study of tapering outcomes among 43 VA patients, no significant differences were identified in primary care visits, emergency department visits, hospitalizations, or psychiatric hospitalizations in the year before and after tapering among 28 patients who completely discontinued opioids.⁷³ Conversely, in a 2019 study by Mark et al based on Medicaid claims data in Vermont, almost half (49%) of 494 patients who discontinued opioids had an ED visit or hospitalization due to an opioid-related adverse event, specifically opioid poisoning (2%) or substance use disorder diagnosis (98%).⁷⁵

Change in Depression and Anxiety Symptoms

The impact of LTOT tapers on depression and anxiety symptoms is unclear, as few studies evaluated these outcomes and those that did had inconsistent results. Among 3 studies that we prioritized from Frank et al of patients who tapered opioids in the context of an intensive outpatient programs with the Mayo Clinic Pain Rehabilitation Center, depression scores as measured by Center for Epidemiologic Studies-Depression (CES-D) scale improved in all studies by the end of the 3-week program, and in 1 study treatment gains were sustained at 6 months.⁴³ However, improvements were not sustained at 6-month follow-up in 1 study⁷⁶ and not evaluated at 6 months in another study.⁴⁹ Similarly, in an observational study of an intensive intervention at the Cleveland Clinic ICPRP, patients with moderate levels of depression and anxiety at baseline as measured by the Depression, Anxiety, and Stress Scale (DASS) had improved anxiety and depression scores by the end of the 3-week program. However, these improvements were not sustained at 12-month follow-up.⁵² In a new RCT conducted at a pain center in Denmark comparing a protocolized taper to usual care, depression and anxiety

symptoms were not different between the control and intervention groups several weeks into the trial.⁶⁶

Withdrawal Symptoms

The frequency and severity of withdrawal symptoms during LTOT tapers is unclear because only 1 prioritized study included this outcome. In a 2-phase RCT at a pain center in Denmark, in which patients were first stabilized on sustained release opioids and then randomized to a protocolized slow opioid taper (dose reduction 10% every 1-2 weeks), the taper group did not develop severe withdrawal symptoms as measured by Subjective Opiate Withdrawal Scale (SOWS) and Objective Opiate Withdrawal Scale (OOWS) compared to the control group (which did not taper opioids).⁶⁶ No VHA studies evaluated withdrawal symptoms.

Tapers were accomplished quickly (within 3 weeks) in studies of intensive multimodal rehabilitation programs, where patients would have been in close contact with clinicians to manage withdrawal symptoms. In the remainder of studies that described tapering speed, the tapers were gradual, with 5-10% dose reductions every 1-2 weeks. It is likely that patients would not have experienced severe withdrawal symptoms with gradual dose reductions, but because studies did not report this information we cannot say one way or the other.

Substance Use

The impact of LTOT tapers on new or increased substance use is unclear, as studies have not directly examined this outcome. The best evidence comes from the 2019 study by Mark et al of Medicaid claims data in Vermont among patients who discontinued opioids.⁷⁵ Retrospectively, the investigators assembled a cohort of 694 Medicaid recipients who were on ≥ 120 mg MEDD. Between 2013 and 2017 opioids were discontinued in 494 of these patients. Prior to discontinuation, 60% of patients had a diagnosis of substance use disorder and almost half (49%) of patients had an ED visit or hospitalization due to opioid poisoning or substance use disorder, but a minority of patients (<1%) were prescribed medication to treat substance use disorders. This study does not describe the circumstances regarding opioid discontinuation or exclude the potential for reverse causality (*ie*, a diagnosis of substance use disorder was the reason prescription opioids were discontinued). This limitation highlights why understanding the indications for LTOT discontinuation is important to interpret the impact of tapering on new or increased substance use.

Opioid Overdose

Evidence of the impact of LTOT on opioid overdose is unclear, as few studies have examined this outcome. Only 1 study of VHA patients reported overdose rates; in a retrospective study of 43 VA patients tapered due to opioid agreement violations, no patients overdosed.⁷³ An important limitation of this and other observational studies based on chart review is likely underreporting of total opioid overdoses due to inability to account for patients who disengage in medical care or who seek care elsewhere.

A large retrospective cohort study of opioid overdose rates following different phases of an opioid risk reduction initiative found that although overdose rates decreased by 17% per year within the intervention group (patients in Washington's Group Health practice) after a dose reduction effort (relative annual change 0.83; 95% CI 0.70 to 0.99), the reduction was not

significantly different when compared to the control group (patients followed at Group Health's contracted community clinics).⁷⁰ Intervention and control group patients were both subject to a change in Washington State's opioid prescribing guidelines recommending against doses \geq 120mg MEDD, but providers in the intervention group with patients on high opioid doses also received "feedback and supervisory guidance by medical directors." The within-group analysis demonstrated a significant decrease, but the between-groups analysis did not. Overall, the results of this study provide inconsistent support that reducing opioid doses leads to lower overdose rates. Importantly, the study does not capture the potential for reverse causation (that opioid dose reductions were a factor in overdoses among some patients) and therefore does not address a central question of this review regarding tapering harms.

Suicidal Ideation and Suicidal Self-directed Violence

Evidence of the impact of LTOT tapers on suicidal ideation and suicidal self-directed violence is unclear, as few studies have evaluated this outcome. The best evidence from an retrospective study by Demidenko et al of VHA patients with substance use disorder compared to match controls supports anecdotal observations that LTOT tapers can lead to suicidal ideation for some patients. In this retrospective study of 509 VA patients who underwent clinician-initiated tapers due mostly (75%) to aberrant behaviors, 47 (9.2%) had new-onset suicidal ideation and 12 patients (2.4%) had suicidal self-directed violence in the year following opioid discontinuation.⁷² Baseline PTSD (OR = 2.56, 95% CI 1.23 to 5.32) and psychotic disorders (OR = 3.19, 95% CI 1.14 to 8.89) were associated with suicidal ideation and suicidal self-direction violence, while other co-morbidities including substance use disorder and baseline MEDD were not. This study also found that self-identified Hispanic ethnicity was associated with increased risk for suicidal ideation and suicidal self-direction violence, but authors note that this finding contradicts prior evidence and should be further explored. This study has important limitations, including likely underestimates of the actual proportion of patients who experienced suicidal ideation and suicidal self-directed violence, as this information was obtained by chart review only and patients who died in the year after opioid discontinuation were excluded from analysis. The study also excluded patients who had no VHA contact in the year following discontinuation, which also could have led to an underestimate of suicidal ideation and suicidal self-directed violence.

FINDINGS FOR KQ2

Very limited evidence is available to address the question of whether benefits and harms of opioid dose reduction or discontinuation vary by different patient characteristics or taper approaches. Regarding taper approaches, the most informative evidence on the role of patient and tapering intervention characteristics on outcomes comes from the Mark et al study based on Medicaid claims data in Vermont finding that rapid tapers (<3 weeks) are associated with increased ED visits and hospitalizations due to opioid-related adverse events than slower tapers.⁷⁵ For patient characteristics, the most informative information comes from the VHA study by Demidenko et al (discussed above) that found higher rates of suicidal ideation and suicidal self-directed violence following LTOT tapers among patients with baseline PTSD and psychotic disorders.⁷²

Because most studies did not perform subgroup analysis, we attempted to supplement this gap by indirectly comparing outcomes of different subgroups *between* studies. However, we were not able to draw any conclusions based on this approach because potential confounders such as the

specific tapering intervention, medications use, and percentage of MEDD reduction may have contributed to variations in outcomes. Lack of information about tapering effects in patient subgroups is an important evidence gap.

Table 2. Outcomes Reported in 15 Highlighted Studies with Most VHA Applicability

Author, Year	Patient Outcomes						Adverse Events		
	Pain Severity	Pain-related Function	Quality of Life	Patient Satisfaction	Healthcare Utilization	Depression or Anxiety	Withdrawal Symptoms	SUD or Opioid Overdose	Suicidal Ideation or SSV
<i>High Intensity Interventions</i>									
Darchuk, 2010 ⁴³	P	P				P			
Hooten, 2007b ⁴⁹	P	P	P			P			
Hooten, 2009 ⁴⁸	P								
Huffman, 2017 ⁵²	P	P				P			
McPherson, 2018^{*74}	=								
Townsend, 2008 ⁶²	P	P	P			P			
<i>Moderate/Low/Unknown Intensity Interventions</i>									
Darnall, 2018 ^{*71}	=	=							
Demidenko, 2017^{*72}									0
Harden, 2015	P								
Hundley, 2018^{*73}					=			0	0
Kurita, 2018 ^{*66}	=		P			=	0		
Mark, 2019 ⁷⁵					0			0	
Murphy, 2013	P	P	P	P					
Sullivan, 2017 ³⁴	P	P							
Von Korff, 2019 ^{*70}								0	
Overall Evidence Quality	Low	Low	Very low	Very low	Very Low	Very Low			

*New since Frank 2017; Bold = VHA study; Abbreviations: SUD = substance use disorder, SSV=suicidal self-directed violence
 Blank cells no data reported; No studies reported on opioid-related side effect outcomes

P Symptoms improved; **=** No change in symptoms; **0** Unclear effect on symptoms/no comparator

DISCUSSION

Shared decision-making between patients and providers regarding LTOT tapers, as recommended by CDC and VA/DoD guidelines, is a complex process that requires weighing the benefits and risks of continued opioid use with the benefits and risks of opioid discontinuation, and should take into account patients' preferences and values. Despite our inclusion of new studies published since the 2017 review by Frank et al and our prioritization of studies with the most relevance and applicability to VHA, we found that evidence regarding patient outcomes following tapers remains inadequate to fully assess benefits and risks of continuing LTOT versus tapering. The biggest evidence gap is related to tapering harms. We agree with Frank et al that more evidence is needed to guide shared decision-making regarding LTOT tapers and that caution and close monitoring are warranted during opioid tapers given insufficient information about risks.

Despite concerns about rebound pain following opioid dose reduction and discontinuation, no studies reported the proportions of patients who experienced a clinically significant worsening in pain severity. It is encouraging that patients with chronic pain on LTOT participating in intensive pain management interventions that incorporate opioid tapering may experience improvements in average pain severity and pain-related function scores and that patients who taper opioids with less intensive co-interventions may have unchanged pain severity and pain-related function scores. However, these types of assessments of mean change are of limited utility because they do not provide information regarding whether a change in score was clinically meaningful for patients and/or necessitated a change in pain management.

Compared to Frank et al, we have slightly more confidence in the findings for pain severity and pain-related function (low versus very low). However, the distinction between low and very low quality of evidence has little clinical importance as the bottom line is the same: despite findings that pain severity and pain-related function may improve or remain unchanged with LTOT tapers, limitations of the evidence do not allow strong conclusions to be made based on these results and future studies may have different findings.

Evidence on the remaining outcomes (quality of life, resolution of opioid-related side effects, withdrawal symptoms, patient satisfaction, healthcare utilization, substance use overdose, and suicide) is also inconclusive. Moreover, we were not able to evaluate which patient or tapering characteristics are associated with greater benefits and harms, aside from subgroup analyses from 2 observational studies – the study by Mark et al finding that gradual reductions in LTOT (>3 weeks) are associated with lower rates of ED visits and hospitalizations due to opioid-related adverse events compared with abrupt opioid discontinuation and rapid tapers < 3 weeks and the study by Demidenko et al suggesting that VHA patients with PTSD and psychotic disorders may be at higher risk of suicidal ideation following LTOT tapers.^{72,75}

It is notable that all studies included patients who reduced their opioid doses, regardless of whether tapers were voluntary or mandated or whether the interventions were high or low intensity. Thus, the question is not *whether* opioid doses can be lowered, but *how* to taper opioids effectively and safely to achieve the VHA's stated goal to "improve the balance of risks and clinically meaningful benefits for patients on LTOT."⁵

Studies with the most detailed information regarding patient baseline characteristics and tapering interventions are studies of voluntary and/or patient-initiated tapers. Patients who we know the least about are in studies of clinician-initiated and/or mandated tapers, who may have tapered due to aberrant findings with UDS and state prescription drug monitoring programs. It is likely that some of these patients have undiagnosed OUD or “complex persistent opioid dependence,” the definition of which is still evolving. Speculation about the associations of LTOT tapering, illicit substance use, and overdose raise concerns that patients with OUD or complex persistent opioid dependence may also be the patients who are most likely to experience serious harms with LTOT tapering. Further study of these at-risk populations is therefore urgently needed to inform ongoing efforts to reduce opioid-related morbidity, mortality, and misuse.

SUMMARY OF CLINICAL IMPLICATIONS

Clinicians who are discussing LTOT tapers with patients should consider the following:

- Close monitoring of patients during and after LTOT tapers is warranted given the potential for harms including overdose and suicide, which have not been sufficiently studied. Particular caution is needed for VHA patients with PTSD and psychotic disorders, who may be at higher risk of suicidal ideation and suicidal self-directed violence following LTOT tapers.
- Gradual LTOT tapers (>3 weeks) may be associated with lower rates of ED visits and hospitalizations due to opioid-related adverse events than abrupt LTOT discontinuation and rapid tapers (<3 weeks).
- Pain severity and pain-related function may improve with intensive tapering co-interventions and remain unchanged with less intensive interventions. However, additional evidence is needed to have more confidence in these findings.

POLICY IMPLICATIONS

Findings of this review also have implications for providers, health systems, and payers considering changes to opioid prescribing policies and/or mandated tapers. Although evidence suggests that many patients will tolerate a taper in terms of pain and pain-related function, the impact of LTOT tapers on serious harms including overdose and suicide is unclear, as few studies have evaluated these outcomes. Specifically, it is known that a subset of patients with chronic pain on LTOT have underlying OUD, but it is not known how often tapering interventions that “unmask OUD” lead to substance use or overdose or how to mitigate these risks. Similarly, evidence suggests that VHA patients with PTSD and psychotic disorder are at increased risk of suicidal ideation and suicidal self-directed violence following LTOT tapers, but additional specific risk factors for suicide following LTOT tapers have not been identified. Therefore, we cannot say with confidence that broadly implemented health system- or clinician-initiated tapers do not expose some patients to serious harms.

Publication of the 2016 CDC guidelines⁴ and changes in opioid prescribing policies at the level of health systems and payers have generated controversy regarding the ethics of mandated tapers. Although the CDC and VA/DoD⁵ guidelines do not recommend involuntary opioid dose reduction or discontinuation among patients on LTOT for chronic pain unless there are acute safety risks, providers and patient advocates have expressed concern about providers going a step

further than these guidelines recommend to mandate tapers in otherwise stable patients.⁶ This review serves to highlight some gaps in the evidence regarding risk recognition and mitigation during LTOT tapers that warrant further study.

LIMITATIONS

The evidence base included in this review has several important limitations. The majority of studies were uncontrolled, and therefore generally subject to bias due to unmeasured confounders. Most studies were small and conducted in a single center, limiting their power and generalizability to other practice settings. Similarly, several studies including those in VHA settings were of patients with very high baseline MEDD (> 200mg). At this stage of the opioid crisis, fewer patients may be prescribed high-dose opioids overall, and therefore results from studies of patients on higher doses may have limited applicability. Other changes in opioid prescribing practices (eg short-acting vs long-acting or specific opioids such as methadone vs other opioids) may also limit the applicability of studies to current practice. Length of follow-up was also too short (<1 year in most studies) to evaluate the durability of treatment outcomes. Improved understanding of the impact of taper interventions over time, including longer-term impacts on function, depression and anxiety symptoms, and the percentage of patients who restart or increase opioids, would help inform risks/benefit assessments.

In terms of our review methods, limitations include our literature search start date of January 1, 2017 (the end search date of the Frank et al review) and the possibility that we did not identify relevant studies published before that date, our use of 2nd reviewer checking in lieu of dual independent review, and our scope that focused on studies directly evaluating opioid tapers and not other chronic pain interventions that also may have led to reduced opioid doses. However, considering that our findings are similar to those in the review by Frank et al, it is unlikely that changes in our review processes would have led to important changes in our conclusions.

GAPS AND FUTURE RESEARCH

The findings of this review highlight important evidence gaps in the following areas:

- Rates of serious adverse events associated with LTOT tapers including opioid overdose, suicidal ideation, and suicidal self-directed violence; patient and intervention characteristics associated with these risks.
- Rates of newly diagnosed OUD during LTOT tapers, prevalence of “complex persistent opioid dependence” and criteria distinguishing this diagnosis from OUD, and the percentage of patients who are referred to substance use treatment.
- Association of baseline substance use disorders and mental health diagnoses with LTOT outcomes.
- Specific patient and intervention characteristics associated with improved pain and function following opioid tapers, including how outcomes differ between voluntary/patient-initiated tapers and mandated tapers and by opioid regimen.

Characterizing the potential harms associated with opioid tapers should be a priority of future research, as this is the largest gap in the evidence and the most critical to support patients and

providers with shared decision-making and inform future health system policy changes. In the same way that tools are being developed to help clinicians evaluate the risks of opioid prescribing for acute and chronic pain,⁷⁷ clinicians would benefit from a risk assessment tool to evaluate the impact of opioid tapers in patients already on LTOT. The concept of using risk assessment tools to weigh the balance of 2 undesirable outcomes is familiar to clinicians. The best example is the use of the CHADS2 score to evaluate the risk of stroke in patients with atrial fibrillation and the HAS-BLED tool to evaluate the risk of bleeding with anticoagulation.⁷⁸ This same kind of approach could be used to weigh the potential benefits and harms of continued opioid use in patients on LTOT against the potential benefits and harms of tapering.

We did not identify a single high-quality controlled study that evaluated a broad range of patient outcomes following opioid dose reduction or discontinuation. Rather, studies of patient outcomes following opioid tapers have to date focused more on change in MEDD and a small number of additional outcomes, thereby limiting conclusions that can be drawn about the full scope of patient experiences given a specific tapering intervention. A controlled study within the VHA setting be the most applicable to the unique VHA patient population and care setting. Given that multiple studies to date have been conducted in pain clinics or other specialized settings such as functional rehabilitation programs, further research in primary care settings is needed to evaluate outcomes with moderate- and low-intensity interventions. Future VHA studies would ideally report patient baseline characteristics including co-morbid substance use and mental health conditions, baseline MEDD, use of non-opioid and non-pharmacologic pain treatments, indication for tapering (patient preference or clinician-initiated), and engagement with the tapering process (*ie*, whether the taper is voluntary), as well as intervention characteristic such as taper schedules and speeds. Due to the potential of previously unrecognized OUD to be diagnosed during a LTOT taper, future research regarding tapering interventions should also evaluate the success of linking patients with OUD to appropriate treatment.

Several VHA studies related to opioid tapering are ongoing, including a prospective cohort study of patient outcomes including pain, quality of life and substance use following opioid discontinuation¹⁷ and an RCT of a brief, tailored motivational enhancement intervention to reduce overdose risk behaviors following tapering.⁷⁹ VHA researchers are also conducting a feasibility study of a multicomponent tapering intervention in a VA primary care setting⁸⁰ and a study evaluating use of a mobile website program to support patients during the taper process.⁸¹ Results from these studies will hopefully contribute to our understanding of the patient experience with LTOT tapering and how to achieve tapering benefits while minimizing risks.

CONCLUSIONS

This review found that evidence is inadequate to fully weigh the balance of the benefits and harms of LTOT against the benefits and harms of tapering, primarily due to limited information on tapering harms. For patients with chronic pain on LTOT who are concerned about worsening pain with tapers, evidence suggests that patients participating in intensive pain management interventions that incorporate opioid tapering may experience improvements in pain severity and pain-related function and that patients who taper opioids with less intensive co-interventions may have unchanged pain severity and pain-related function. However, given that these results are based on average changes in pain severity and function scores, we still lack clarity regarding how often LTOT tapers lead to rebound pain necessitating a change in management. Our confidence in these findings is low and additional evidence is needed before drawing stronger conclusions.

Findings regarding other patient outcomes following LTOT tapers, including serious harms, are inconclusive and should be a priority of future research. Caution and close monitoring are warranted during and after opioid tapers given the potential for adverse events including overdose and suicide, which have not been sufficiently studied.

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The ESP Coordinating Center (ESP CC) is responding to a request from Department of Veterans Affairs (VA) Health Services Research and Development Service (HSR&D) for an evidence brief on patient outcomes following long-term opioid dose reduction or discontinuation. Findings from this evidence brief will be used to inform prioritization of questions for a State-of-the-Art conference in September 2019. The scope was further developed with input from the SOTA workgroup members.

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

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Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

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Peer Reviewers

The Coordinating Center sought input from external peer reviewers to review the draft report and provide feedback on the objectives, scope, methods used, perception of bias, and omitted evidence. Peer reviewers must disclose any relevant financial or non-financial conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The Coordinating Center and the ESP Center work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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