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Patient Outcomes in Dose Reduction or Discontinuation of Long-Term Opioid Therapy

A Systematic Review

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Background: Expert guidelines recommend reducing or discontinuing long-term opioid therapy (LTOT) when risks outweigh benefits, but evidence on the effect of dose reduction on patient outcomes has not been systematically reviewed.

Purpose: To synthesize studies of the effectiveness of strategies to reduce or discontinue LTOT and patient outcomes after dose reduction among adults prescribed LTOT for chronic pain.

Data Sources: MEDLINE, EMBASE, PsycINFO, CINAHL, and the Cochrane Library from inception through April 2017; reference lists; and expert contacts.

Study Selection: Original research published in English that addressed dose reduction or discontinuation of LTOT for chronic pain.

Data Extraction: Two independent reviewers extracted data and assessed study quality using the U.S. Preventive Services Task Force quality rating criteria. All authors assessed evidence quality using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system. Prespecified patient outcomes were pain severity, function, quality of life, opioid withdrawal symptoms, substance use, and adverse events.

Data Synthesis: Sixty-seven studies (11 randomized trials and 56 observational studies) examining 8 intervention categories, including interdisciplinary pain programs, buprenorphine-assisted dose reduction, and behavioral interventions, were found. Study quality was good for 3 studies, fair for 13 studies, and poor for 51 studies. Many studies reported dose reduction, but rates of opioid discontinuation ranged widely across interventions and the overall quality of evidence was very low. Among 40 studies examining patient outcomes after dose reduction (very low overall quality of evidence), improvement was reported in pain severity (8 of 8 fair-quality studies), function (5 of 5 fair-quality studies), and quality of life (3 of 3 fair-quality studies).

Limitation: Heterogeneous interventions and outcome measures; poor-quality studies with uncontrolled designs.

Conclusion: Very low quality evidence suggests that several types of interventions may be effective to reduce or discontinue LTOT and that pain, function, and quality of life may improve with opioid dose reduction.

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Approximately 10 million U.S. adults are prescribed long-term opioid therapy (LTOT) for chronic pain despite inadequate evidence of long-term benefit and growing evidence of harms (1, 2). No published studies have compared LTOT (>1 year) versus placebo, no opioid, or nonopioid therapies (2). In recent decades, a dramatic increase in the prescription of opioid medications has been accompanied by increases in opioid overdose (3); more than 33 000 opioid overdose deaths occurred in 2015 (4). Higher prescribed opioid dose is associated with overdose risk (5–7) as well as incidence of opioid use disorder, depression, fracture, motor vehicle accident, and suicide (8–12). Dose reduction or discontinuation, or opioid tapering, may decrease these risks, and expert guidelines recommend tapering when risks outweigh benefits (13, 14).

Opioid tapering can be challenging for both patients and clinicians. In routine practice, discontinuation of LTOT is uncommon, ranging from 8% to 35% in prior cohort studies (15, 16). In a survey of patients receiving high-dose opioid medications for chronic pain, nearly half reported wanting to cut down or stop, yet 80% were receiving high-dose opioids 1 year later (17). Among patients who had a nonfatal overdose while being prescribed LTOT, 91% continued use of opioid medications after the overdose (18). There is little evidence to guide clinicians in the process of opioid tapering, especially in primary care settings, where most opioid therapy is prescribed (19, 20). In addition, little is known about the risks and benefits of opioid tapering. Potential risks include withdrawal symptoms, increased pain, and loss to follow-up (20). However, some patients report improvements in function and quality of life after tapering (21). The effects of opioid tapering on patient outcomes have not been systematically reviewed.

To address these gaps, we systematically reviewed the evidence on the effectiveness of strategies to reduce or discontinue LTOT prescribed for chronic pain

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and the effect of dose reduction or discontinuation of LTOT on important patient outcomes.

METHODS

A multidisciplinary team of investigators with expertise in pain and opioid management developed 2 key questions to address the study objectives. These key questions assessed 1) the effectiveness of strategies to reduce or discontinue LTOT, and 2) the effect of dose reduction or discontinuation of LTOT on prespecified patient outcomes of pain severity, pain-related function, quality of life, opioid withdrawal symptoms, substance use, or adverse events. We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (22), and the protocol is registered in the PROSPERO database (CRD42015020347).

Data Sources and Searches

We searched MEDLINE, EMBASE, PsycINFO, CINAHL, and the Cochrane Library from inception through 19 April 2017. We consulted with a research librarian to design a search strategy based on our key questions. We developed a MEDLINE search strategy, which was also applied to other databases, using multiple subject headings (where available) and text words for key concepts of "opioids", "tapering", and "pain". No language or year limits were applied. Within this broader search, we identified potentially relevant systematic reviews and meta-analyses published since 2005. The full electronic search strategy for MEDLINE is presented in **Appendix Table 1** (available at Annals.org). We examined reference lists from all included studies and from relevant systematic reviews and published expert guidelines. We also sought input from expert contacts. Records retrieved from each search strategy were organized using the EndNote bibliographic management application (Clarivate Analytics).

Study Selection

Two investigators (J.W.F. and H.R.D.) independently reviewed abstracts identified by the search strategy and, when necessary, the full text to determine inclusion. Discrepancies were resolved by consensus. We included studies that involved adults (aged ≥18 years) who were prescribed LTOT for chronic pain (defined as pain lasting >3 months) and that addressed at least 1 key question. Studies that did not report pain duration were included if the average duration of opioid therapy was more than 3 months. We did not require interventions to involve explicit goals or mandatory conditions of opioid dose reduction. Eligible study designs included randomized trials, cohort studies, case–control studies, and case series. We excluded case reports and cross-sectional studies, as well as studies that did not describe the clinical intervention or report patient-level data. We also excluded studies that were not published in English; involved nonhuman participants; addressed only acute, surgical, postoperative, obstetric, or cancer pain; involved only palliative or hospice care; evaluated only illicit or nonmedical use of opioid medications; or addressed only reduction of interventional pain techniques.

Data Extraction and Quality Assessment

We developed an instrument for data extraction based on prior systematic reviews conducted by the investigators. Three investigators piloted the data extraction instrument using a randomly chosen study, and the results were returned to the pool for formal review. These investigators discussed difficulties with the extraction instrument and reached consensus on minor modifications. Using the finalized instrument, 2 investigators independently extracted data on design, patient sample, setting, interventions, measures, and results from each study. When dose information was not provided by the study, we used a standard algorithm for calculating morphine-equivalent doses (MEDs) of opioid medications (23).

Two reviewers independently assessed study quality (risk of bias in individual studies) using criteria developed by the U.S. Preventive Services Task Force (USPSTF), which facilitate rating of study quality as good, fair, or poor (**Appendix Table 2**, available at Annals.org). The investigators were blinded to each other's ratings, and discrepancies were resolved by consensus or by a third reviewer, if necessary. We did not exclude studies on the basis of quality.

Data Synthesis

We assessed the overall quality of the evidence using a method developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (24). GRADE provides explicit criteria that address study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect to rate the quality of evidence across studies. This method rates the quality of the evidence from high (very confident that the true effect lies close to that of the estimate of effect) to very low (very little confidence in the effect estimate) (**Appendix Table 3**, available at Annals.org). All authors iteratively discussed GRADE assessments to achieve consensus. We present systematic review results organized by key question. We did not attempt meta-analyses because of heterogeneity across studies and methodological limitations of the studies.

Role of the Funding Source

The Veterans Health Administration's Substance Use Disorder Quality Enhancement Research Initiative funded the study through its Locally Initiated Projects program (QLP 59-046). The funding sources had no role in the design and conduct of the study; collection, management, analysis, or interpretation of the data; or preparation, review, or approval of the manuscript.

RESULTS

Database searches identified 3522 abstracts, from which 74 studies met criteria for full-text review. Seventeen additional articles were identified from reference lists and expert contacts. Of these 91 studies, 68 articles representing 67 studies met inclusion criteria

(25–92) (**Appendix Figure**, available at Annals.org). These studies included 11 randomized controlled trials, 8 controlled observational studies, and 48 uncontrolled observational studies. Studies presented data on 12 546 patients (range, 5 to 1457 patients); 10 studies conducted at a single center (32, 33, 36, 44–48, 70, 80) and 2 studies each at 3 centers (37, 49, 50, 52, 63, 64) may have included data on individual participants in more than 1 study. We categorized studies into 8 mutually exclusive intervention types: interdisciplinary pain programs, buprenorphine-assisted dose reduction, behavioral interventions, detoxification, ketamine-assisted dose reduction, acupuncture, other outpatient programs, and other interventional programs (**Table 1**). Interventions occurred in outpatient settings, inpatient settings, or both in 42, 15, and 10 studies, respectively; 5 studies were conducted in primary care settings. Among 48 studies reporting baseline opioid dose for

Table 1. Effectiveness of Strategies to Reduce or Discontinue LTOT (*n* = 67 studies)

Studies, *n*	Participants, *n*	Description	Results*	Quality Ratings
Interdisciplinary pain programs (28, 30, 32, 33, 36, 37, 42, 44–50, 52, 54, 55, 58, 63, 64, 67, 69, 70, 74, 77–81, 86, 88)				
31	9915	Programs delivered interdisciplinary pain care with heterogeneity of program components, personnel, and duration (range, 1–8 wk) 21 outpatient studies, 8 inpatient studies, and 2 studies in both settings Opioid discontinuation mandatory in 22 studies; goal of dose reduction in 5 studies Mean program completion rate, 85% (range, 76%–100%)†; 25 studies	Mean opioid discontinuation rate, 87% (range, 29%–100%); 20 studies	Fair: 11 studies Poor: 20 studies
Buprenorphine-assisted dose reduction (25–27, 34, 35, 59, 71, 72, 75, 83)				
10	470	Studies transitioned patients from LTOT to buprenorphine with heterogeneity of induction protocol, dose, and duration of therapy 5 outpatient studies, 2 inpatient studies, and 3 studies in both settings 4 studies included only patients who had successfully transitioned to buprenorphine	Mean opioid discontinuation rate, 91% (range, 33%–100%); 6 studies	Poor: 10 studies
Behavioral interventions (61, 65, 66, 76, 85, 90, 91)				
6	238	Studies tested heterogeneous behavior-based and cognitive behavior–based therapies, including CBT, meditation, and other CIH methods All studies in outpatient settings; 3 of 6 in primary care settings Goal of opioid discontinuation in 1 study; goal of dose reduction in 1 study	Mean opioid discontinuation rate, 21% (range, 6%–55%); 5 studies	Good: 3 studies Poor: 3 studies
Other outpatient programs (39–41, 73, 84)				
5	1169	2 studies of systemwide interventions in primary care, 2 studies of outpatient specialty care, and 1 study of outpatient medical marijuana treatment Goal of dose reduction in 3 studies	Mean opioid discontinuation rate, 20% (range, 12%–44%); 3 studies	Poor: 5 studies
Other interventional programs (29, 56, 57, 87)				
4	308	2 studies of an implantable device, 1 study of detoxification under anesthesia, and 1 study of lidocaine infusion Goal of opioid discontinuation in 3 studies	Mean opioid discontinuation rate, 70% (range, 33%–79%); 3 studies	Poor: 4 studies
Detoxification (31, 38, 62, 82)				
4	200	Interventions supported opioid dose reduction with symptomatic medications (e.g., clonidine and benzodiazepines) 2 outpatient studies, 1 inpatient study, and 1 study in both settings	Mean opioid discontinuation rate, 91% (range, 91%–100%); 3 studies	Poor: 4 studies
Ketamine-assisted dose reduction (51, 60, 68, 89)				
4	168	Studies examined oral, intravenous, and subcutaneous administration of ketamine 1 outpatient study, 1 inpatient study, and 2 studies in both settings Goal of opioid discontinuation in 1 study; goal of dose reduction in 3 studies	Opioid discontinuation rates of 18% and 27% in 2 studies	Poor: 4 studies
Acupuncture (43, 53, 92)				
3	78	2 studies of electroacupuncture; 1 study of auricular acupuncture 1 outpatient study, 1 inpatient study, and 1 study in both settings Goal of opioid discontinuation in 2 studies	Opioid discontinuation rates of 66% and 86% in 2 studies	Fair: 2 studies Poor: 1 study

CBT = cognitive behavioral therapy; CIH = complementary and integrative health; LTOT = long-term opioid therapy.
* Among studies reporting opioid discontinuation rates.
† Among studies reporting program completion.

participants receiving LTOT, the mean daily dose ranged from 29 to 556 mg MED. Study interventions had an objective of opioid discontinuation or dose reduction in 43 and 12 studies, respectively; 12 studies reported on this outcome in secondary or exploratory analyses.

All included studies assessed the effectiveness of strategies to reduce or discontinue LTOT (key question 1). Study quality as assessed by the USPSTF criteria was good for 3 studies, fair for 13 studies, and poor for 51 studies. The GRADE quality of evidence to address the effectiveness of strategies to reduce or discontinue LTOT was very low (**Table 2**; **Appendix Table 4**, available at Annals.org). In the remainder of this section, we highlight results from good- and fair-quality studies. Descriptions of all included studies are available in **Appendix Table 5** (available at Annals.org).

Thirty-one studies (11 fair-quality and 20 poor-quality) presented data from 19 distinct interdisciplinary pain programs. These programs were described as intensive multimodal treatment with an interdisciplinary team, typically organized around a biopsychosocial model of chronic pain. The 11 fair-quality studies included 2 controlled and 9 uncontrolled observational studies. Ten fair-quality studies described programs that mandated discontinuation as a condition of enrollment; in these programs, 87% of participants discontinued opioid use at program completion (range, 74% to 100%).

Six studies (3 good-quality and 3 poor-quality) with 238 total participants assessed the effectiveness of behavioral interventions. The 3 good-quality studies were small randomized controlled trials; 2 were described as pilot trials, and none were powered to detect clinically meaningful differences in opioid dose reduction. The first good-quality trial compared a 4-month interactive voice response intervention versus usual care among patients with chronic pain (n = 51); a goal of opioid dose reduction was optional. The intervention reduced the mean opioid dose significantly at 4-month (P = 0.04) and 8-month (P = 0.004) follow-up compared with usual care (mean dose change was not reported) (65). The second good-quality trial compared an 8-week group intervention based on mindfulness meditation and cognitive behavioral therapy with usual care among patients receiving LTOT (n = 35); the intervention did not explicitly encourage dose reduction. The mean change in the daily opioid dose from baseline to 26 weeks was −10.1 mg MED in the intervention group compared with −0.2 mg MED in the control group (P = 0.8) (90). The third good-quality trial compared a 22-week opioid taper support intervention (motivational interviewing and pain self-management education delivered by a physician assistant) with usual care (n = 35); opioid dose reduction was the primary outcome. The intervention reduced the mean opioid dose by 43% compared with 19% in the usual care group at 22 weeks (P = 0.07) (76). The remaining 6 intervention types were described in 30 studies (2 fair-quality and 28 poor-quality).

We identified 40 studies that examined the effect of dose reduction or discontinuation of LTOT on patient outcomes (key question 2) (**Table 3**). These studies included 5 randomized controlled trials, 6 controlled observational studies, and 29 uncontrolled observational studies. None of the 40 studies were rated as good-quality. For each of the 6 prespecified patient outcomes, the GRADE quality of evidence was very low (**Table 2** and **Appendix Table 4**).

Thirty-six studies (8 fair-quality and 28 poor-quality) examined the effect of opioid dose reduction on pain severity. The 8 fair-quality studies included 1 controlled and 6 uncontrolled observational studies of interdisciplinary pain programs and 1 uncontrolled observational study of acupuncture; all 8 studies reported improved pain after opioid dose reduction. The effect of dose reduction on pain-related function was assessed in 17 studies (5 fair-quality and 12 poor-quality). The 5 fair-quality studies were observational studies of interdisciplinary pain programs (1 controlled and 4 uncontrolled); all 5 studies reported improved function after opioid dose reduction. The effect of dose reduction on quality of life was assessed in 12 studies (3 fair-quality and 9 poor-quality). The 3 fair-quality studies were uncontrolled observational studies of interdisciplinary pain programs; all reported improved quality of life after opioid dose reduction. Opioid withdrawal symptoms were examined in 18 studies (3 fair-quality and 15 poor-quality); the reported incidence during opioid dose reduction ranged widely. Four poor-quality studies examined new-onset substance use. Eleven poor-quality studies assessed adverse events; 5 assessed mortality outcomes, and 1 reported a single opioid-related overdose death.

DISCUSSION

This systematic review identified 67 studies that examined the effectiveness of strategies to reduce or discontinue LTOT among adults with chronic pain, including 3 small good-quality randomized trials, 1 fair-quality randomized trial, and 12 fair-quality observational studies. Though many studies reported positive dose reduction outcomes, the overall quality of the evidence for effectiveness of all strategies to reduce or discontinue LTOT was very low due to methodological limitations across studies and an absence of adequately powered randomized trials. We identified 40 studies that assessed the effect of dose reduction or discontinuation of LTOT on important patient outcomes, 8 of which were fair-quality observational studies. The fair-quality studies reported improvement in pain severity (8 of 8 studies), function (5 of 5 studies), and quality of life (3 of 3 studies) after opioid dose reduction. However, the overall quality of the evidence was very low for all 6 prespecified patient outcomes.

Common themes across intervention types can provide insight into the program components that may

Table 2. Summary of Findings and Quality-of-Evidence Assessment

Summary of Findings						Quality-of-Evidence Assessment (GRADE)				
Outcome	**Studies, *n***	**Participants, *n***	**Study Design**	**Study Quality**	**Results**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Quality**
Effectiveness of strategies to reduce or discontinue LTOT	67	12 546	RCT: 11 CO: 8 UO: 48	Good: 3 Fair: 13 Poor: 51	Multiple intervention types examined, with heterogeneity of patient populations, study completion, and rates of opioid reduction and discontinuation	Serious	Not serious	Serious	Not serious	Very low
Effect of dose reduction or discontinuation on patient outcomes										
Pain severity	36	7674	RCT: 4 CO: 6 UO: 26	Good: 0 Fair: 8 Poor: 28	8 of 8 fair-quality studies reported improved pain 21 of 28 poor-quality studies reported improved pain, 4 reported no change, and 3 reported worse pain	Serious	Not serious	Not serious	Not serious	Very low
Function	17	4809	RCT: 2 CO: 1 UO: 14	Good: 0 Fair: 5 Poor: 12	5 of 5 fair-quality studies reported improved function 8 of 12 poor-quality studies reported improved function, 2 reported no change, and 2 reported decreased function	Serious	Not serious	Not serious	Not serious	Very low
QOL	12	2880	RCT: 1 CO: 0 UO: 11	Good: 0 Fair: 3 Poor: 9	3 of 3 fair-quality studies reported improved QOL 4 of 9 poor-quality studies reported improved QOL, 4 reported no change, and 1 reported worse QOL	Serious	Not serious	Not serious	Not serious	Very low
Opioid withdrawal symptoms	18	1147	RCT: 4 CO: 0 UO: 14	Good: 0 Fair: 3 Poor: 15	Rates of opioid withdrawal symptoms ranged widely (0%–100%); 4 of 18 studies reported withdrawal symptoms in all patients	Serious	Serious	Not serious	Not serious	Very low
Substance use	4	204	RCT: 1 CO: 0 UO: 3	Good: 0 Fair: 0 Poor: 4	2 studies reported illicit substance use (63% and 64%) (27, 71) 1 study reported nonmedical use of prescription opioids (43%) (77) 1 study reported illicit intravenous opioid administration (<1%) (28)	Serious	Not serious	Not serious	Not serious	Very low
Adverse events	11	519	RCT: 2 CO: 1 UO: 8	Good: 0 Fair: 0 Poor: 11	5 of 11 studies assessed mortality with 1 opioid-related overdose in a single study (75)	Serious	Not serious	Not serious	Not serious	Very low

CO = controlled observational study; GRADE = Grading of Recommendations Assessment, Development and Evaluation; LTOT = long-term opioid therapy; QOL = quality of life; RCT = randomized controlled trial; UO = uncontrolled observational study.

provide effective support for opioid tapering. In the 3 good-quality trials of behavioral interventions and the 11 fair-quality studies of interdisciplinary pain programs, patients received multimodal care that emphasized nonpharmacologic and self-management strategies. Such care is consistent with expert guidelines for management of LTOT and chronic pain (13, 14, 93). In addition to the content of these interventions, the quantity of care provided is likely an important factor. Multidisciplinary care and close follow-up (at least weekly) were common attributes of evaluated programs in good- and fair-quality studies. Such team-

Table 3. Studies of Effect of Dose Reduction or Discontinuation of LTOT on Patient Outcomes (*n* = 40 studies)

Study, Year (Reference)	Study Design	Intervention Type	Sample Size, *n*	Outcomes Assessed						Quality Rating
				Pain	Function	Quality of Life	Opioid Withdrawal	Substance Use	Adverse Events	
Heiwe et al, 2011 (43)	UO	Acupuncture	29	√			√			Fair
Hooten et al, 2009 (46)	UO	IPP	1241	√						Fair
Hooten et al, 2010 (47)	UO	IPP	109	√			√			Fair
Huffman et al, 2017 (50)	CO	IPP	1457	√	√					Fair
Kidner et al, 2009 (52)	UO	IPP	1226	√	√	√				Fair
Krumova et al, 2013 (54)	UO	IPP	102	√	√	√	√			Fair
Murphy et al, 2013 (63)	UO	IPP	705	√	√					Fair
Townsend et al, 2008 (80)	UO	IPP	373	√	√	√				Fair
Baron and McDonald, 2006 (25)	CO	Buprenorphine-assisted	23	√						Poor
Berland et al, 2013 (26)	UO	Buprenorphine-assisted	76	√	√		√		√	Poor
Blondell et al, 2010 (27)	RCT	Buprenorphine-assisted	12	√	√			√		Poor
Buckley et al, 1986 (28)	UO	IPP	173				√	√	√	Poor
Cowan et al, 2003 (30)	UO	IPP	104	√	√		√			Poor
Cowan et al, 2005 (31)	RCT	Detoxification	10	√	√	√	√			Poor
Cunningham et al, 2016 (33)	UO	IPP	131	√	√	√	√			Poor
Daitch et al, 2012 (34)	UO	Buprenorphine-assisted	104	√		√	√			Poor
Daitch et al, 2014 (35)	UO	Buprenorphine-assisted	35	√		√	√			Poor
Drossman et al, 2012 (38)	UO	Detoxification	39	√			√			Poor
Hanson et al, 2009 (39)	CO	Other outpatient program	200	√						Poor
Harden et al, 2015 (40)	UO	Other outpatient program	50	√						Poor
Hassamal et al, 2016 (42)	UO	IPP	5	√	√	√				Poor
Hooten et al, 2015 (48)	RCT	IPP	21	√			√		√	Poor
Kapural et al, 2010 (51)	CO	Ketamine-assisted	36	√					√	Poor
Kroening and Oleson, 1985 (53)	UO	Acupuncture	14	√			√			Poor
Lake et al, 2009 (55)	UO	IPP	267	√						Poor
Maani et al, 2011 (57)	UO	Other interventional program	6						√	Poor
Maclaren et al, 2006 (58)	UO	IPP	127	√	√					Poor
Malinoff et al, 2005 (59)	UO	Buprenorphine-assisted	95	√	√		√		√	Poor
Miller et al, 2006 (62)	UO	Detoxification	53	√						Poor
Nilsen et al, 2010 (66)	UO	Behavioral	11	√	√	√	√			Poor
Quinlan, 2012 (68)	UO	Ketamine-assisted	11	√		√			√	Poor
Rome et al, 2004 (70)	UO	IPP	356	√	√	√				Poor
Rosenblum et al, 2012 (71)	UO	Buprenorphine-assisted	12	√	√		√	√	√	Poor
Roux et al, 2013 (72)	RCT	Buprenorphine-assisted	43	√			√			Poor
Schwarzer et al, 2015 (74)	CO	IPP	32	√						Poor
Streltzer et al, 2015 (75)	UO	Buprenorphine-assisted	43						√	Poor
Taylor et al, 1980 (77)	UO	IPP	7	√	√			√	√	Poor
Tennant and Rawson, 1982 (78)	CO	IPP	42	√						Poor
Webster et al, 2016 (83)	RCT	Buprenorphine-assisted	39				√		√	Poor
Weimer et al, 2016 (84)	UO	Other outpatient program	516	√		√				Poor

CO = controlled observational study; IPP = interdisciplinary pain program; LTOT = long-term opioid therapy; RCT = randomized controlled trial; UO = uncontrolled observational study.

based, intensive support would require additional resources to implement in primary care settings, where most opioid medications are prescribed (19). Given the heterogeneity across interventions and the overall poor quality of studies, data do not currently support assessment of comparative effectiveness of the different models of care or opioid tapering protocols used in included studies.

Although confidence is limited by the very low quality of evidence overall, findings from this systematic review suggest that pain, function, and quality of life may improve during and after opioid dose reduction. Several potential mechanisms may underlie this finding. First, in addition to tapering opioids, most interventions delivered concurrent nonopioid pain management approaches that may have provided more benefit than LTOT. Second, opioid dose reduction may alleviate adverse effects of LTOT that can negatively affect function and quality of life, such as constipation, fatigue, poor sleep, and depressed mood. Third, improvement after opioid dose reduction may result from resolution of opioid-induced hyperalgesia, a paradoxical response in which patients receiving opioids become more sensitive to painful stimuli (94). Finally, given the observational nature of most studies, we cannot exclude reverse causation (that is, patients successfully tapered opioids because pain severity decreased). In the realm of opioid therapy, patient safety and pain relief have often been framed as conflicting and mutually exclusive goals. Evidence about benefits of opioid tapering for pain, function, and quality of life, if confirmed by future high-quality studies, holds the poten-

tial to fundamentally alter the conversation about opioid tapering.

Three prior systematic reviews identified 11 randomized or controlled studies of interventions for dose reduction among patients prescribed opioid medications for chronic pain (2, 95, 96). All 3 reviews determined that the strength of evidence was insufficient to draw conclusions. Our review extends these prior reviews by providing an updated and comprehensive assessment of the literature, adding 2 recent good-quality randomized controlled trials and 11 fair-quality observational studies. Whereas prior reviews assessed outcomes of opioid dose reduction, this is, to our knowledge, the first study to systematically review patient outcomes after dose reduction or discontinuation of LTOT for chronic pain.

The findings of this systematic review should be interpreted in the context of its limitations. First, there was substantial heterogeneity of measures of opioid dose reduction and patient outcomes. Second, we categorized interventions into clinically relevant domains according to the authors' descriptions of key components. There was substantial heterogeneity within domains and overlap across some. Third, most of the included studies examined voluntary participation in a clinical program or research intervention. The findings may therefore not be generalizable to patients for whom LTOT is reduced or discontinued involuntarily. Fourth, publication bias may have limited the evidence that was available for this review. Finally, new data may have emerged since April 2017 in this rapidly evolving area; 39 of the 67 studies included in this review were published since 2010, and 18 were published since 2015.

This systematic review highlights challenges and opportunities for future research (Table 4). First, measurement and reporting of opioid dose reduction were heterogeneous across studies, and consensus on what constitutes meaningful dose reduction is needed, including patients transitioning to buprenorphine. Second, innovative strategies for recruitment and retention will be required for future patient-level randomized trials of opioid tapering because patients' apprehension with regard to tapering may serve as a barrier to participation (21). Such strategies might include randomization of patients to active pain management interventions with optional opioid dose reduction, randomization to different protocols or tapering rates among motivated patients, or randomization at the level of the prescriber or facility. Given that loss to follow-up was common in poor-quality studies in this review, evidence on effective strategies to enhance patient engagement is also needed. Third, future research should examine strategies that are likely to be feasible in busy primary care settings and scalable across health systems. Although 31 studies in this review examined interdisciplinary pain programs, only 5 involved primary care settings. The effectiveness of less resource-intensive team-based models (97, 98) or technology-assisted approaches (99) for supporting opioid tapering warrants further study. Fourth, in the context of ongoing health system and population-level efforts to reduce opioid use and prevent opioid-related harms (100–102), we identified no prospective studies of mandatory, involuntary opioid dose reduction among otherwise stable patients. Finally, this review found insufficient evidence on adverse events related to opioid tapering, such as accidental overdose if patients resume use of high-dose opioids or switch to illicit opioid sources or onset of suicidality or other mental health symptoms. Public health surveillance and large-scale observational studies are needed to assess outcomes of efforts to reduce opioid prescribing at the health system and population levels, especially rare but important adverse events, such as overdose and suicide.

Table 4. Implications for Clinicians and Next Steps for Research

Implications for Clinicians	Next Steps for Research
Discuss with patients receiving LTOT that pain severity, function, and quality of life may improve after opioid tapering.	Researchers should seek consensus on the reporting of opioid dose reduction and definition of clinically meaningful dose reduction.
Consider referring patients to a multidisciplinary, multimodal pain program, when available, to support opioid dose reduction.	Innovative approaches to recruitment and randomization (such as trials with randomization at the provider or facility level) are needed to generate high-quality evidence on outcomes.
Consider team-based strategies with close follow-up to support opioid tapering when multidisciplinary programs are inadequately accessible.	Future studies should examine interventions that are feasible in busy primary care settings and scalable across multiple health systems.
Given inadequate evidence on the risks of opioid tapering, caution and close monitoring are warranted during and after.	Public health surveillance and large-scale observational studies are needed to assess outcomes of efforts to reduce opioid prescribing at health system and population levels.

LTOT = long-term opioid therapy.

In conclusion, this systematic review identified multiple strategies to reduce or discontinue LTOT for chronic pain and found very-low-quality evidence that opioid dose reduction may improve pain, function, and quality of life. In addition to discussing the goals and risks of opioid therapy, clinicians should consider discussing the potential benefits of opioid tapering with patients receiving LTOT. Informed by the multidisciplinary care models among good- and fair-quality studies, clinicians should consider referring patients to multidisciplinary pain programs, when available, or developing team-based approaches to support opioid tapering in outpatient practice. Finally, given inadequate evidence on the risks of opioid tapering, caution and close monitoring are warranted during and after tapering; consideration of overdose prevention strategies, such as naloxone, may be prudent (103). Together, these strategies are well-aligned with the broader goal of patient-centered, evidence-based, effective chronic pain care (104).

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References

1. **Boudreau D, Von Korff M, Rutter CM, Saunders K, Ray GT, Sullivan MD, et al.** Trends in long-term opioid therapy for chronic non-cancer pain. Pharmacoepidemiol Drug Saf. 2009;18:1166-75. [PMID: 19718704] doi:10.1002/pds.1833

2. **Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al.** The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. Ann Intern Med. 2015;162:276-86. [PMID: 25581257] doi:10.7326/M14-2559

3. **Frenk S, Porter K, Paulozzi L.** Prescription Opioid Analgesic Use Among Adults: United States, 1999–2012. NCHS Data Brief no. 189. Hyattsville, MD: National Center for Health Statistics; February 2015.

4. **Rudd RA, Seth P, David F, Scholl L.** Increases in drug and opioid-involved overdose deaths–United States, 2010–2015. MMWR Morb Mortal Wkly Rep. 2016;65:1445-52. [PMID: 28033313] doi:10.15585/mmwr.mm655051e1

5. **Bohnert AS, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al.** Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA. 2011;305:1315-21. [PMID: 21467284] doi:10.1001/jama.2011.370

6. **Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al.** Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Intern Med. 2010;152:85-92. [PMID: 20083827] doi:10.7326/0003-4819-152-2-201001190-00006

7. **Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN.** Opioid dose and drug-related mortality in patients with nonmalignant pain. Arch Intern Med. 2011;171:686-91. [PMID: 21482846] doi:10.1001/archinternmed.2011.117

8. **Scherrer JF, Svrakic DM, Freedland KE, Chrusciel T, Balasubramanian S, Bucholz KK, et al.** Prescription opioid analgesics increase the risk of depression. J Gen Intern Med. 2014;29:491-9. [PMID: 24165926] doi:10.1007/s11606-013-2648-1

9. **Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB, et al.** Relationship of opioid use and dosage levels to fractures in older chronic pain patients. J Gen Intern Med. 2010;25:310-5. [PMID: 20049546] doi:10.1007/s11606-009-1218-z

10. **Gomes T, Redelmeier DA, Juurlink DN, Dhalla IA, Camacho X, Mamdani MM.** Opioid dose and risk of road trauma in Canada: a population-based study. JAMA Intern Med. 2013;173:196-201. [PMID: 23318919] doi:10.1001/2013.jamainternmed.733

11. **Ilgen MA, Bohnert AS, Ganoczy D, Bair MJ, McCarthy JF, Blow FC.** Opioid dose and risk of suicide. Pain. 2016;157:1079-84. [PMID: 26761386] doi:10.1097/j.pain.0000000000000484

12. **Edlund MJ, Martin BC, Russo JE, DeVries A, Braden JB, Sullivan MD.** The role of opioid prescription in incident opioid abuse and dependence among individuals with chronic noncancer pain: the role of opioid prescription. Clin J Pain. 2014;30:557-64. [PMID: 24281273] doi:10.1097/AJP.0000000000000021

13. **Dowell D, Haegerich TM, Chou R.** CDC guideline for prescribing opioids for chronic pain–United States, 2016. JAMA. 2016;315:1624-45. [PMID: 26977696] doi:10.1001/jama.2016.1464

14. **Department of Veterans Affairs; Department of Defense; Opioid Therapy for Chronic Pain Work Group.** VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain. Version 3.0. Washington, DC: U.S. Department of Veterans Affairs; 2017. Accessed at www.healthquality.va.gov/guidelines/Pain/cot on 11 May 2017.

15. **Martin BC, Fan MY, Edlund MJ, Devries A, Braden JB, Sullivan MD.** Long-term chronic opioid therapy discontinuation rates from the TROUP study. J Gen Intern Med. 2011;26:1450-7. [PMID: 21751058] doi:10.1007/s11606-011-1771-0

16. **Vanderlip ER, Sullivan MD, Edlund MJ, Martin BC, Fortney J, Austen M, et al.** National study of discontinuation of long-term opioid therapy among veterans. Pain. 2014;155:2673-9. [PMID: 25277462] doi:10.1016/j.pain.2014.09.034

17. **Thielke SM, Turner JA, Shortreed SM, Saunders K, Leresche L, Campbell CI, et al.** Do patient-perceived pros and cons of opioids predict sustained higher-dose use? Clin J Pain. 2014;30:93-101. [PMID: 23535150] doi:10.1097/AJP.0b013e31828e361b

18. **Larochelle MR, Liebschutz JM, Zhang F, Ross-Degnan D, Wharam JF.** Opioid prescribing after nonfatal overdose and association with repeated overdose: a cohort study. Ann Intern Med. 2016;164:1-9. [PMID: 26720742] doi:10.7326/M15-0038

19. **Chen JH, Humphreys K, Shah NH, Lembke A.** Distribution of opioids by different types of Medicare prescribers. JAMA Intern Med. 2016;176:259-61. [PMID: 26658497] doi:10.1001/jamainternmed.2015.6662

20. **Berna C, Kulich RJ, Rathmell JP.** Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. Mayo Clin Proc. 2015;90:828-42. [PMID: 26046416] doi:10.1016/j.mayocp.2015.04.003
21. **Frank JW, Levy C, Matlock DD, Calcaterra SL, Mueller SR, Koester S, et al.** Patients' perspectives on tapering of chronic opioid therapy: a qualitative study. Pain Med. 2016;17:1838-47. [PMID: 27207301]
22. **Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group.** Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151:264-9. [PMID: 19622511] doi:10.7326/0003-4819-151-4-200908180-00135
23. **Washington State Agency Medical Directors' Group.** Opioid Dose Calculator. Version 2.01. 2015. Accessed at www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm on 11 May 2017.
24. **Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al.** GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64:401-6. [PMID: 21208779] doi:10.1016/j.jclinepi.2010.07.015
25. **Baron MJ, McDonald PW.** Significant pain reduction in chronic pain patients after detoxification from high-dose opioids. J Opioid Manag. 2006;2:277-82. [PMID: 17319259]
26. **Berland DW, Malinoff HL, Weiner MA, Przybylski R.** When opioids fail in chronic pain management: the role for buprenorphine and hospitalization. Am J Ther. 2013;20:316-21. [PMID: 23584313] doi:10.1097/MJT.0b013e31827ab599
27. **Blondell RD, Ashrafioun L, Dambra CM, Foschio EM, Zielinski AL, Salcedo DM.** A clinical trial comparing tapering doses of buprenorphine with steady doses for chronic pain and co-existent opioid addiction. J Addict Med. 2010;4:140-6. [PMID: 20959867] doi:10.1097/ADM.0b013e3181ba895d
28. **Buckley FP, Sizemore WA, Charlton JE.** Medication management in patients with chronic non-malignant pain. A review of the use of a drug withdrawal protocol. Pain. 1986;26:153-65. [PMID: 2876406]
29. **Caraway D, Walker V, Becker L, Hinnenthal J.** Successful discontinuation of systemic opioids after implantation of an intrathecal drug delivery system. Neuromodulation. 2015;18:508-15. [PMID: 26053626] doi:10.1111/ner.12318
30. **Cowan DT, Wilson-Barnett J, Griffiths P, Allan LG.** A survey of chronic noncancer pain patients prescribed opioid analgesics. Pain Med. 2003;4:340-51. [PMID: 14750910]
31. **Cowan DT, Wilson-Barnett J, Griffiths P, Vaughan DJ, Gondhia A, Allan LG.** A randomized, double-blind, placebo-controlled, crossover pilot study to assess the effects of long-term opioid drug consumption and subsequent abstinence in chronic noncancer pain patients receiving controlled-release morphine. Pain Med. 2005;6:113-21. [PMID: 15773875]
32. **Crisostomo RA, Schmidt JE, Hooten WM, Kerkvliet JL, Townsend CO, Bruce BK.** Withdrawal of analgesic medication for chronic low-back pain patients: improvement in outcomes of multidisciplinary rehabilitation regardless of surgical history. Am J Phys Med Rehabil. 2008;87:527-36. [PMID: 18574345] doi:10.1097/PHM.0b013e31817c124f
33. **Cunningham JL, Evans MM, King SM, Gehin JM, Loukianova LL.** Opioid tapering in fibromyalgia patients: experience from an interdisciplinary pain rehabilitation program. Pain Med. 2016;17:1676-85. [PMID: 26755658] doi:10.1093/pm/pnv079
34. **Daitch J, Frey ME, Silver D, Mitnick C, Daitch D, Pergolizzi J Jr.** Conversion of chronic pain patients from full-opioid agonists to sublingual buprenorphine. Pain Physician. 2012;15:ES59-66. [PMID: 22786462]
35. **Daitch D, Daitch J, Novinson D, Frey M, Mitnick C, Pergolizzi J Jr.** Conversion from high-dose full-opioid agonists to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. Pain Med. 2014;15:2087-94. [PMID: 25220043] doi:10.1111/pme.12520
36. **Darchuk KM, Townsend CO, Rome JD, Bruce BK, Hooten WM.** Longitudinal treatment outcomes for geriatric patients with chronic non-cancer pain at an interdisciplinary pain rehabilitation program. Pain Med. 2010;11:1352-64. [PMID: 20735746] doi:10.1111/j.1526-4637.2010.00937.x
37. **Dersh J, Mayer TG, Gatchel RJ, Polatin PB, Theodore BR, Mayer EA.** Prescription opioid dependence is associated with poorer outcomes in disabling spinal disorders. Spine (Phila Pa 1976). 2008;33:2219-27. [PMID: 18725868] doi:10.1097/BRS.0b013e31818096d1
38. **Drossman DA, Morris CB, Edwards H, Wrennall CE, Weinland SR, Aderoju AO, et al.** Diagnosis, characterization, and 3-month outcome after detoxification of 39 patients with narcotic bowel syndrome. Am J Gastroenterol. 2012;107:1426-40. [PMID: 22710577] doi:10.1038/ajg.2012.142
39. **Hanson KA, Loftus EV Jr, Harmsen WS, Diehl NN, Zinsmeister AR, Sandborn WJ.** Clinical features and outcome of patients with inflammatory bowel disease who use narcotics: a case-control study. Inflamm Bowel Dis. 2009;15:772-7. [PMID: 19107782] doi:10.1002/ibd.20847
40. **Harden P, Ahmed S, Ang K, Wiedemer N.** Clinical implications of tapering chronic opioids in a veteran population. Pain Med. 2015;16:1975-81. [PMID: 26119793] doi:10.1111/pme.12812
41. **Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al.** The effect of medicinal cannabis on pain and quality-of-life outcomes in chronic pain: a prospective open-label study. Clin J Pain. 2016;32:1036-43. [PMID: 26889611]
42. **Hassamal S, Haglund M, Wittnebel K, Danovitch I.** A preoperative interdisciplinary biopsychosocial opioid reduction program in patients on chronic opioid analgesia prior to spine surgery: a preliminary report and case series. Scand J Pain. 2016;13:27-31.
43. **Heiwe S, Lönnquist I, Källmén H.** Potential risk factors associated with risk for drop-out and relapse during and following withdrawal of opioid prescription medication. Eur J Pain. 2011;15:966-70. [PMID: 21546290] doi:10.1016/j.ejpain.2011.03.006
44. **Hooten WM, Townsend CO, Sletten CD, Bruce BK, Rome JD.** Treatment outcomes after multidisciplinary pain rehabilitation with analgesic medication withdrawal for patients with fibromyalgia. Pain Med. 2007;8:8-16. [PMID: 17244099]
45. **Hooten WM, Townsend CO, Decker PA.** Gender differences among patients with fibromyalgia undergoing multidisciplinary pain rehabilitation. Pain Med. 2007;8:624-32. [PMID: 18028040]
46. **Hooten WM, Townsend CO, Bruce BK, Warner DO.** The effects of smoking status on opioid tapering among patients with chronic pain. Anesth Analg. 2009;108:308-15. [PMID: 19095867] doi:10.1213/ane.0b013e31818c7b99
47. **Hooten WM, Mantilla CB, Sandroni P, Townsend CO.** Associations between heat pain perception and opioid dose among patients with chronic pain undergoing opioid tapering. Pain Med. 2010;11:1587-98. [PMID: 21029354] doi:10.1111/j.1526-4637.2010.00962.x
48. **Hooten WM, Warner DO.** Varenicline for opioid withdrawal in patients with chronic pain: a randomized, single-blinded, placebo controlled pilot trial. Addict Behav. 2015;42:69-72. [PMID: 25462656] doi:10.1016/j.addbeh.2014.11.007
49. **Huffman KL, Sweis GW, Gase A, Scheman J, Covington EC.** Opioid use 12 months following interdisciplinary pain rehabilitation with weaning. Pain Med. 2013;14:1908-17. [PMID: 23915328] doi:10.1111/pme.12201
50. **Huffman KL, Rush TE, Fan Y, Sweis GW, Vij B, Covington EC, et al.** Sustained improvements in pain, mood, function and opioid use post interdisciplinary pain rehabilitation in patients weaned from high and low dose chronic opioid therapy. Pain. 2017. [PMID: 28328578] doi:10.1097/j.pain.0000000000000907
51. **Kapural L, Kapural M, Bensitel T, Sessler DI.** Opioid-sparing effect of intravenous outpatient ketamine infusions appears short-lived in chronic-pain patients with high opioid requirements. Pain Physician. 2010;13:389-94. [PMID: 20648208]
52. **Kidner CL, Mayer TG, Gatchel RJ.** Higher opioid doses predict poorer functional outcome in patients with chronic disabling occupational musculoskeletal disorders. J Bone Joint Surg Am. 2009;91:919-27. [PMID: 19339577] doi:10.2106/JBJS.H.00286

53. **Kroening RJ, Oleson TD.** Rapid narcotic detoxification in chronic pain patients treated with auricular electroacupuncture and naloxone. Int J Addict. 1985;20:1347-60. [PMID: 2867052]
54. **Krumova EK, Bennemann P, Kindler D, Schwarzer A, Zenz M, Maier C.** Low pain intensity after opioid withdrawal as a first step of a comprehensive pain rehabilitation program predicts long-term non-use of opioids in chronic noncancer pain. Clin J Pain. 2013;29:760-9. [PMID: 23567163] doi:10.1097/AJP.0b013e31827c7cf6
55. **Lake AE 3rd, Saper JR, Hamel RL.** Comprehensive inpatient treatment of refractory chronic daily headache. Headache. 2009;49:555-62. [PMID: 19245391] doi:10.1111/j.1526-4610.2009.01364.x
56. **Levine AB, Steven DA, Parrent AG, MacDougall KW.** Successful long-term nerve root stimulation for chronic neuropathic pain: a real world, single center Canadian experience. Pain Physician. 2017;20:95-106. [PMID: 28158157]
57. **Maani CV, DeSocio PA, Jansen RK, Merrell JD, McGhee LL, Young A, et al.** Use of ultra rapid opioid detoxification in the treatment of US military burn casualties. J Trauma. 2011;71:S114-9. [PMID: 21795869] doi:10.1097/TA.0b013e3182219209
58. **Maclaren JE, Gross RT, Sperry JA, Boggess JT.** Impact of opioid use on outcomes of functional restoration. Clin J Pain. 2006;22:392-8. [PMID: 16691094]
59. **Malinoff HL, Barkin RL, Wilson G.** Sublingual buprenorphine is effective in the treatment of chronic pain syndrome. Am J Ther. 2005;12:379-84. [PMID: 16148422]
60. **Marchetti F, Coutaux A, Bellanger A, Magneux C, Bourgeois P, Mion G.** Efficacy and safety of oral ketamine for the relief of intractable chronic pain: a retrospective 5-year study of 51 patients. Eur J Pain. 2015;19:984-93. [PMID: 25381898] doi:10.1002/ejp.624
61. **Mehl-Madrona L, Mainguy B, Plummer J.** Integration of complementary and alternative medicine therapies into primary-care pain management for opiate reduction in a rural setting. J Altern Complement Med. 2016;22:621-6. [PMID: 27419856] doi:10.1089/acm.2015.0212
62. **Miller NS, Swiney T, Barkin RL.** Effects of opioid prescription medication dependence and detoxification on pain perceptions and self-reports. Am J Ther. 2006;13:436-44. [PMID: 16988540]
63. **Murphy JL, Clark ME, Banou E.** Opioid cessation and multidimensional outcomes after interdisciplinary chronic pain treatment. Clin J Pain. 2013;29:109-17. [PMID: 22751033] doi:10.1097/AJP.0b013e3182579935
64. **Murphy JL, Phillips KM, Rafie S.** Sex differences between veterans participating in interdisciplinary chronic pain rehabilitation. J Rehabil Res Dev. 2016;53:83-94. [PMID: 27005932] doi:10.1682/JRRD.2014.10.0250
65. **Naylor MR, Naud S, Keefe FJ, Helzer JE.** Therapeutic Interactive Voice Response (TIVR) to reduce analgesic medication use for chronic pain management. J Pain. 2010;11:1410-9. [PMID: 20620119] doi:10.1016/j.jpain.2010.03.019
66. **Nilsen HK, Stiles TC, Landrø NI, Fors EA, Kaasa S, Borchgrevink PC.** Patients with problematic opioid use can be weaned from codeine without pain escalation. Acta Anaesthesiol Scand. 2010;54:571-9. [PMID: 19919582] doi:10.1111/j.1399-6576.2009.02164.x
67. **Nissen LM, Tett SE, Cramond T, Williams B, Smith MT.** Opioid analgesic prescribing and use—an audit of analgesic prescribing by general practitioners and The Multidisciplinary Pain Centre at Royal Brisbane Hospital. Br J Clin Pharmacol. 2001;52:693-8. [PMID: 11736881]
68. **Quinlan J.** The use of a subanesthetic infusion of intravenous ketamine to allow withdrawal of medically prescribed opioids in people with chronic pain, opioid tolerance and hyperalgesia: outcome at 6 months [Letter]. Pain Med. 2012;13:1524-5. [PMID: 22978408] doi:10.1111/j.1526-4637.2012.01486.x
69. **Ralphs JA, Williams AC, Richardson PH, Pither CE, Nicholas MK.** Opiate reduction in chronic pain patients: a comparison of patient-controlled reduction and staff controlled cocktail methods. Pain. 1994;56:279-88. [PMID: 8022621]
70. **Rome JD, Townsend CO, Bruce BK, Sletten CD, Luedtke CA, Hodgson JE.** Chronic noncancer pain rehabilitation with opioid withdrawal: comparison of treatment outcomes based on opioid use status at admission. Mayo Clin Proc. 2004;79:759-68. [PMID: 15182090]
71. **Rosenblum A, Cruciani RA, Strain EC, Cleland CM, Joseph H, Magura S, et al.** Sublingual buprenorphine/naloxone for chronic pain in at-risk patients: development and pilot test of a clinical protocol. J Opioid Manag. 2012;8:369-82. [PMID: 23264315] doi:10.5055/jom.2012.0137
72. **Roux P, Sullivan MA, Cohen J, Fugon L, Jones JD, Vosburg SK, et al.** Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone. Pain. 2013;154:1442-8. [PMID: 23707283] doi:10.1016/j.pain.2013.05.004
73. **Schneider JP, Kirsh KL.** Defining clinical issues around tolerance, hyperalgesia, and addiction: a quantitative and qualitative outcome study of long-term opioid dosing in a chronic pain practice. J Opioid Manag. 2010;6:385-95. [PMID: 21268999]
74. **Schwarzer A, Aichinger-Hinterhofer M, Maier C, Vollert J, Walther JW.** Sleep-disordered breathing decreases after opioid withdrawal: results of a prospective controlled trial. Pain. 2015;156:2167-74. [PMID: 26121253] doi:10.1097/j.pain.0000000000000279
75. **Streltzer J, Davidson R, Goebert D.** An observational study of buprenorphine treatment of the prescription opioid dependent pain patient. Am J Addict. 2015;24:357-61. [PMID: 25675861] doi:10.1111/ajad.12198
76. **Sullivan MD, Turner JA, DiLodovico C, D'Appollonio A, Stephens K, Chan YF.** Prescription opioid taper support for outpatients with chronic pain: a randomized controlled trial. J Pain. 2017;18:308-18. [PMID: 27908840] doi:10.1016/j.jpain.2016.11.003
77. **Taylor CB, Zlutnick SI, Corley MJ, Flora J.** The effects of detoxification, relaxation, and brief supportive therapy on chronic pain. Pain. 1980;8:319-29. [PMID: 6105638]
78. **Tennant FS Jr, Rawson RA.** Outpatient treatment of prescription opioid dependence: comparison of two methods. Arch Intern Med. 1982;142:1845-7. [PMID: 6181749]
79. **Thieme K, Gromnica-Ihle E, Flor H.** Operant behavioral treatment of fibromyalgia: a controlled study. Arthritis Rheum. 2003;49:314-20. [PMID: 12794785]
80. **Townsend CO, Kerkvliet JL, Bruce BK, Rome JD, Hooten WM, Luedtke CA, et al.** A longitudinal study of the efficacy of a comprehensive pain rehabilitation program with opioid withdrawal: comparison of treatment outcomes based on opioid use status at admission. Pain. 2008;140:177-89. [PMID: 18804915] doi:10.1016/j.pain.2008.08.005
81. **Vines SW, Cox A, Nicoll L, Garrett S.** Effects of a multimodal pain rehabilitation program: a pilot study. Rehabil Nurs. 1996;21:25-30. [PMID: 8577978]
82. **Wang H, Akbar M, Weinsheimer N, Gantz S, Schiltenwolf M.** Longitudinal observation of changes in pain sensitivity during opioid tapering in patients with chronic low-back pain. Pain Med. 2011;12:1720-6. [PMID: 22082225] doi:10.1111/j.1526-4637.2011.01276.x
83. **Webster L, Gruener D, Kirby T, Xiang Q, Tzanis E, Finn A.** Evaluation of the tolerability of switching patients on chronic full μ-opioid agonist therapy to buccal buprenorphine. Pain Med. 2016. [PMID: 26917621]
84. **Weimer MB, Hartung DM, Ahmed S, Nicolaidis C.** A chronic opioid therapy dose reduction policy in primary care. Subst Abus. 2016;37:141-7. [PMID: 26685018] doi:10.1080/08897077.2015.1129526
85. **Whitten SK, Stanik-Hutt J.** Group cognitive behavioral therapy to improve the quality of care to opioid-treated patients with chronic noncancer pain: a practice improvement project. J Am Assoc Nurse Pract. 2013;25:368-76. [PMID: 24170620] doi:10.1111/j.1745-7599.2012.00800.x
86. **Williams AC, Richardson PH, Nicholas MK, Pither CE, Harding VR, Ridout KL, et al.** Inpatient vs. outpatient pain management: results of a randomised controlled trial. Pain. 1996;66:13-22. [PMID: 8857627]
87. **Williams DR, Stark RJ.** Intravenous lignocaine (lidocaine) infusion for the treatment of chronic daily headache with substantial medication overuse. Cephalalgia. 2003;23:963-71. [PMID: 14984229]

88. **Younger J, Barelka P, Carroll I, Kaplan K, Chu L, Prasad R, et al.** Reduced cold pain tolerance in chronic pain patients following opioid detoxification. Pain Med. 2008;9:1158-63. [PMID: 18564998] doi: 10.1111/j.1526-4637.2008.00475.x
89. **Zekry O, Gibson SB, Aggarwal A.** Subanesthetic, subcutaneous ketamine infusion therapy in the treatment of chronic nonmalignant pain. J Pain Palliat Care Pharmacother. 2016;30:91-8. [PMID: 27092576] doi:10.3109/15360288.2016.1161690
90. **Zgierska AE, Burzinski CA, Cox J, Kloke J, Stegner A, Cook DB, et al.** Mindfulness meditation and cognitive behavioral therapy intervention reduces pain severity and sensitivity in opioid-treated chronic low back pain: pilot findings from a randomized controlled trial. Pain Med. 2016;17:1865-81. [PMID: 26968850]
91. **Zgierska AE, Burzinski CA, Cox J, Kloke J, Singles J, Mirgain S, et al.** Mindfulness meditation-based intervention is feasible, acceptable, and safe for chronic low back pain requiring long-term daily opioid therapy. J Altern Complement Med. 2016;22:610-20. [PMID: 27267151] doi:10.1089/acm.2015.0314
92. **Zheng Z, Guo RJ, Helme RD, Muir A, Da Costa C, Xue CC.** The effect of electroacupuncture on opioid-like medication consumption by chronic pain patients: a pilot randomized controlled clinical trial. Eur J Pain. 2008;12:671-6. [PMID: 18035566]
93. **Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians.** Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2017;166:514-30. [PMID: 28192789] doi:10.7326/M16-2367
94. **Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L.** A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14:145-61. [PMID: 21412369]
95. **Windmill J, Fisher E, Eccleston C, Derry S, Stannard C, Knaggs R, et al.** Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. Cochrane Database Syst Rev. 2013: CD010323. [PMID: 23996347] doi:10.1002/14651858.CD010323.pub2
96. **Peterson K, Anderson J, Ferguson L, Mackey K.** Evidence Brief: The Comparative Effectiveness of Selected Complementary and Integrative Health (CIH) Interventions for Preventing or Reducing Opioid Use in Adults with Chronic Neck, Low Back, and Large Joint Pain. VA ESP Project no. 09-199. Washington, DC: U.S. Department of Veterans Affairs; 2016.
97. **Kroenke K, Krebs EE, Wu J, Yu Z, Chumbler NR, Bair MJ.** Telecare collaborative management of chronic pain in primary care: a randomized clinical trial. JAMA. 2014;312:240-8. [PMID: 25027139] doi:10.1001/jama.2014.7689
98. **Bair MJ, Ang D, Wu J, Outcalt SD, Sargent C, Kempf C, et al.** Evaluation of Stepped Care for Chronic Pain (ESCAPE) in veterans of the Iraq and Afghanistan conflicts: a randomized clinical trial. JAMA Intern Med. 2015;175:682-9. [PMID: 25751701] doi:10.1001/jamainternmed.2015.97
99. **Heapy AA, Higgins DM, LaChappelle KM, Kirlin J, Goulet JL, Czlapinski RA, et al.** Cooperative Pain Education and Self-management (COPES): study design and protocol of a randomized non-inferiority trial of an interactive voice response-based self-management intervention for chronic low back pain. BMC Musculoskelet Disord. 2016;17:85. [PMID: 26879051] doi:10.1186/s12891-016-0924-z
100. **Beaudoin FL, Banerjee GN, Mello MJ.** State-level and system-level opioid prescribing policies: the impact on provider practices and overdose deaths, a systematic review. J Opioid Manag. 2016;12:109-18. [PMID: 27194195] doi:10.5055/jom.2016.0322
101. **Centers for Medicare & Medicaid Services.** Opioid Misuse Strategy 2016. January 2017. Accessed at www.cms.gov/Outreach-and-Education/Outreach/Partnerships/Downloads/CMS-Opioid-Misuse-Strategy-2016.pdf on 11 May 2017.
102. **Smith VK, Gifford K, Ellis E, Edwards B, Rudowitz R, Hinton E, et al.** Implementing Coverage and Payment Initiatives: Results from a 50-State Medicaid Budget Survey for State Fiscal Years 2016 and 2017. The Henry J. Kaiser Family Foundation and the National Association of Medicaid Directors. October 2016. Accessed at http://files.kff.org/attachment/Report-Implementing-Coverage-and-PaymentInitiatives on 11 May 2017.
103. **Coffin PO, Behar E, Rowe C, Santos GM, Coffa D, Bald M, et al.** Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. Ann Intern Med. 2016;165:245-52. [PMID: 27366987] doi:10.7326/M15-2771
104. **Office of the Assistant Secretary for Health; U.S. Department of Health and Human Services.** National Pain Strategy: A Comprehensive Population Health-Level Strategy for Pain. Accessed at https://iprcc.nih.gov/docs/DraftHHSNationalPainStrategy.pdf on 11 May 2017.

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Appendix Table 1. Ovid MEDLINE Search Strategy

Concepts	MeSH Terms	Text Words
Opioid medications	(exp analgesics, opioid/ or codeine/ or hydrocodone/ or morphine/ or oxycodone/) and tu.xs.	(Opioid* or opiate* or codeine or clonidine or morphine or hydrocodone or oxycodone).tw,kf,rn.
Dose reduction or discontinuation	–	(Taper* or wean* or (dose* adj1 reduc*) or detox* or withdraw* or discontinuat* or cessation or tolerance or conversion or substitution).tw,kf,rn.
Chronic pain	(pain/ or exp musculoskeletal pain/ or exp back pain/ or exp chronic pain/ or exp facial pain/ or exp headache/ or metatarsalgia/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or pain, referred/ or exp arthralgia/ or eye pain/ or flank pain/ or glossalgia/ or exp headache/ or exp pelvic pain/ or shoulder pain/) and dt.fs. or "Pain Measurement"/ or Pain Threshold/	(pain).tw,kf,rn.
Systematic reviews and meta-analyses	meta-analysis/	("systematic review" or "systematic reviews").ab,ti,kf. or cochrane.mp. or medline.ab,ti,kf. or pubmed.ab,ti,kf. or cinahl.ab,ti,kf. or embase.ab,ti,kf. or handsearch*.ab,ti,kf. or (hand adj2 search*).ab,ti,kf. or (manual* adj2 search*).ab,ti,kf. or meta-analysis.ab,ti,kf. or meta-analyses.ab,ti,kf. or met analy*.mp. or metanaly*.mp. or meta-analysis/ or (technology adj1 assessment*).ab,ti,kf. or HTA.ab,ti,kf. or HTAs.ab,ti,kf. or (technology adj1 overview*).ab,ti,kf. or (technology adj1 appraisal*).ab,ti,kf.

MeSH = Medical Subject Headings.

Appendix Table 2. USPSTF Quality Rating Criteria for RCTs and Cohort Studies

Criteria
Initial assembly of comparable groups: RCTs—adequate randomization, including concealment and whether potential confounders were distributed equally among groups Cohort studies—consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
Important differential loss to follow-up or overall high loss to follow-up
Measurements: equal, reliable, and valid (includes masking of outcome assessment)
Clear definition of interventions
Important outcomes considered
Analysis: adjustment for potential confounders for cohort studies, or intention-to-treat analysis for RCTs (i.e., analysis in which all participants in a trial are analyzed according to the intervention to which they were allocated, regardless of whether or not they completed the intervention)
Definition of ratings based on above criteria
Good
Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%); reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; important outcomes are considered; and appropriate attention to confounders in analysis.
Fair
Studies will be graded "fair" if any or all of the following problems occur, without the important limitations noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred in follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for.
Poor
Studies will be graded "poor" if any of the following major limitations exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention.

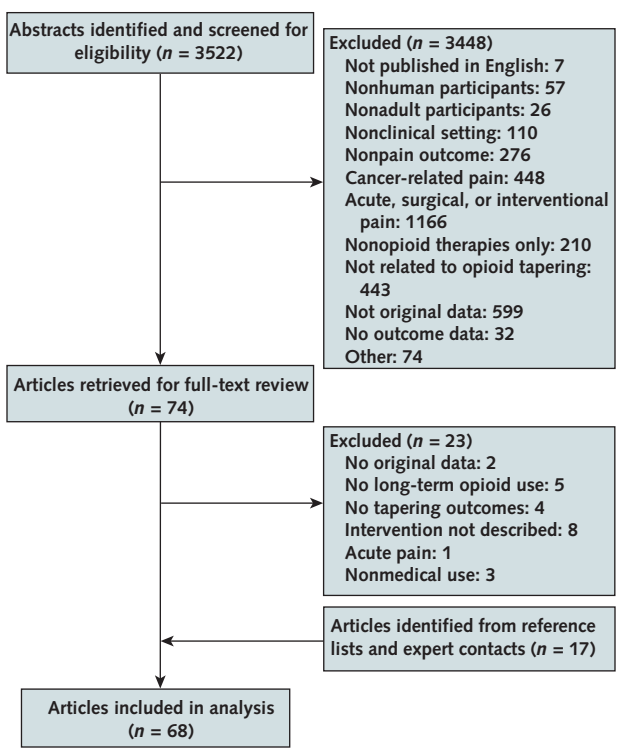
RCT = randomized controlled trial; USPSTF = U.S. Preventive Services Task Force.

Appendix Table 3. GRADE Criteria for Assessing Quality of Evidence*

Initial quality of a body of evidence
Randomized trial = high
Observational study = low
Any other evidence = very low
Decrease GRADE if
Serious (−1) or very serious (−2) risk of bias
Serious (−1) or very serious (−2) inconsistency
Serious (−1) or very serious (−2) indirectness
Serious (−1) or very serious (−2) imprecision
Likely (−1) or very likely (−2) publication bias
Increase GRADE if
Large (+1) or very large (+2) effect
Evidence of a dose response gradient (+1)
All plausible confounders would reduce a demonstrated effect (+1) or would suggest a spurious effect if no effect was observed (+2)
Significance of the 4 levels of evidence
High = We are very confident that the true effect lies close to that of the estimate of the effect
Moderate = We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low = Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low = We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

GRADE = Grading of Recommendations Assessment, Development and Evaluation.
* From reference 24.

Appendix Figure. Study flow diagram.



Appendix Table 4. Derivation of GRADE Score*

Outcome	Initial GRADE Score	Adjustment	Reason for Adjustment	Final GRADE Score
Effectiveness of strategies to reduce or discontinue LTOT	2	−1	Risk of bias; indirectness	Very low
Effect of dose reduction or discontinuation on patient outcomes				
Pain severity	2	−1	Risk of bias	Very low
Function	2	−1	Risk of bias	Very low
Quality of life	2	−1	Risk of bias	Very low
Opioid withdrawal symptoms	2	−1	Risk of bias; inconsistency	Very low
Substance use	2	−1	Risk of bias	Very low
Adverse events	2	−1	Risk of bias	Very low

GRADE = Grading of Recommendations Assessment, Development and Evaluation; LTOT = long-term opioid therapy.
* From reference 24. See **Appendix Table 3** for criteria for assigning GRADE score for quality of evidence.

Appendix Table 5. Characteristics of Studies Evaluating the Effectiveness of Strategies to Reduce or Discontinue LTOT for Chronic Pain

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Baron and McDonald, 2006 (25)	RCS	Inpatient psychiatric facility with outpatient follow-up March 2004-May 2006 United States Funding NR	23 patients referred by PCP for opioid discontinuation Mean age: 50.7 y Female: 30% Pain duration: NR	100% Mean, 556 mg Median, 360 mg	Optional hospitalization Ibuprofen only (n = 7) or ibuprofen plus buprenorphine taper (n = 16)	Yes	Yes	100% (23/23) completed program Range, 14-180 d	Yes	100% discontinued opioid medications 21/23 reported improved pain severity (P < 0.001) Significant pain reduction compared to baseline (mean NRS, 8.0 vs. 3.3; P < 0.001) No significant difference in pain severity reduction between treatment groups	Poor
Berland et al, 2013 (26)	RCS	Two inpatient settings 2009-2010 United States Funding NR	76 consecutive patients with chronic pain Median age: 48 y Female: 58% Pain duration: NR	100% Median, 400 mg	Inpatient opioid discontinuation and buprenorphine initiation with outpatient follow-up	Yes	No	100% (76/76) completed program Range, 0-25 mo 7 (9%) lost to follow-up	Yes	100% discontinued opioid medications At follow-up, 54% on buprenorphine, 26% resumed opioid, and 10% not on opioids 67% reported improved pain, and 60% reported improved function vs. baseline	Poor
Blondell et al, 2010 (27)	RCT	Multidisciplinary outpatient pain management program Dec. 2007-Apr. 2008 United States NIAAA	12 patients prescribed opioids for chronic pain with opioid dependence Mean age: 45 y Female: 50% Pain duration: NR	100% Dose NR	Inpatient opioid discontinuation and buprenorphine initiation with outpatient follow-up with buprenorphine tapering (n = 6) or steady dose (n = 6) protocol	Yes	Yes	42% (5/12) completed program 10/12 (83%) at 6 mo	Yes	100% discontinued opioid medications 0/6 patients in taper group and 5/6 in maintenance group completed intervention At 6 mo, 8/10 patients on buprenorphine, and 2/10 resumed opioid medications At 6 mo, 6/10 reported improved pain, 8/10 reported improved function vs. baseline At 6 mo, 6/10 reported alcohol and/or illicit drug use	Poor
Buckley et al, 1986 (28)	RCS	Inpatient multidisciplinary pain center Jan. 1981-June 1982 United States Funding NR	173 consecutive patients with chronic pain Mean age: 46 y Female: 45% Mean pain duration: 6.8 y	71% (124/173) on opioid or sedative medication Mean, 253 mg	~1 wk inpatient opioid tapering using blinded pain cocktail	Yes	No	94% (116/124) completed program	Yes	116/124 (94%) discontinued opioid medications Effects on pain and function NR 4 patients experienced withdrawal symptoms or adverse event	Poor
Caraway et al, 2015 (29)	RCS	Pain management center Dates NR United States Funding NR	99 patients with implantable drug delivery system for ≥6 mo Mean age: 67 y Female: 68% Mean pain duration: 81% with >5 y	90% (89/99) Dose NR	Implantation of intrathecal drug delivery system and use for ≥6 mo	Yes	No	99% (98/99) at 6 mo 13% (13/99) completed 5 y follow-up	No	68% (67/98) and 74% (73/98) discontinued opioids at 1 and 6 mo postimplantation, respectively For all patients, pain decreased by 2.1 points at 1 mo (P < 0.001) and 1.9 points at 6 mo (P < 0.001) vs. baseline	Poor

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Appendix Table 5—Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Cowan et al, 2003 (30)	RCS	Outpatient pain clinic 1995-1999 United Kingdom Funding NR	104 patients on opioid medications for chronic pain Mean age: 55 y Female: 61% Mean pain duration: 10.5 y	100% 92% with dose ≤60 mg	Multidisciplinary outpatient pain including nonpharmacologic, pharmacologic, and interventional modalities	No	No	Mean treatment duration, 14.1 mo	Yes	57% (59/104) discontinued opioid medications Among patients who stopped opioids, 66% (52/78) reported worsening pain and 50% (39/78) reported a decrease in function; no patients reported improved pain and 3% reported improved function 17% (13/78) reported opioid withdrawal symptoms; 2 patients reported addiction to opioids	Poor
Cowan et al, 2005 (31)	RCT	Outpatient pain clinic Dates NR United Kingdom Janssen-Cilag, Napp Pharmaceuticals	10 patients with chronic pain on long-acting morphine for ≥30 d Mean age: 56 y Female: 40% Mean pain duration: 13.5 y	100% Mean, 40 mg	Double-blind, placebo-controlled, crossover study comparing 60-h periods of cessation vs. morphine continuation	Yes	Yes	100% (10/10) completed trial	Yes	100% discontinued opioids during 60-h abstinence period Patients reported increased pain and increased interference with general activity and enjoyment of life at end of 60-h abstinence period (all $P < 0.05$) 3/10 (30%) reported withdrawal symptoms	Poor
Crisostomo et al, 2008 (32)	RCS	Outpatient multidisciplinary pain rehabilitation center Jan. 2000-April 2006 United States Unfunded	383 consecutive patients with cLBP Mean age: 47 y Female: 62% Mean pain duration: 8.9 y	58% (146/253) Mean, 61 mg	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating opioid discontinuation	Yes	No	84% (322/383) 81% (309/383) at 3 wk	No	Proportion of patients using opioid medications decreased 79% at discharge vs. admission Significant improvements in pain severity and physical function among all patients	Poor
Cunningham et al, 2016 (33)	RCS	Outpatient multidisciplinary pain rehabilitation center Jan. 2006-Dec. 2012 United States Funding NR	131 consecutive patients with fibromyalgia who completed program Mean age: 46 y Female: 81% Mean pain duration: 11.6 y	42% (55/131) Mean, 99 mg; range, 5-600 mg	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating pain medication discontinuation	Yes	No	100% (131/131) completed program	Yes	100% (55/55) discontinued opioid medications Patients taking opioids at baseline had significant improvements in pain (mean NRS, 5.2 vs. 7.2; $P < 0.001$), pain interference (mean MPI, 45.0 vs. 55.2; $P < 0.001$) and QOL (mean SF-36, 42.9 vs. 33.3; $P < 0.001$) at program completion vs. baseline Opioid withdrawal symptoms (peak COWS score) not significantly different based on opioid dose ($P = 0.22$) or duration of use ($P = 0.8$)	Poor

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Appendix Table 5—Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Daitch et al, 2012 (34)	RCS	Interventional pain management practice Dec. 2007-July 2010 United States Unfunded	104 patients with chronic pain, converted to buprenorphine for ≥60 d Mean age: 49 y Female: 42% Pain duration: NR	100% Mean, 180 mg	Outpatient conversion to sublingual buprenorphine	Yes	No	Mean treatment duration, 10.3 mo Range, 2-42 mo	Yes	Study excluded patients who continued to use opioid medications or did not continue buprenorphine ≥60 d Significant reduction in pain severity after conversion to buprenorphine vs. baseline (mean NRS, 2.3-point reduction; $P < 0.01$) Nonsignificant change in QOL	Poor
Daitch et al, 2014 (35)	RCS	Interventional pain management practice July 2010-April 2011 United States Funding NR	35 patients with chronic pain, on high-dose opioid medications converted to buprenorphine for ≥60 d Mean age: 49 y Female: 40% Pain duration: NR	100% Mean, 550 mg	Outpatient conversion to sublingual buprenorphine	Yes	No	Mean treatment duration, 6 mo	Yes	Study excluded patients who continued to use opioid medications or did not continue buprenorphine ≥60 d Significant reduction in pain severity (mean NRS, 7.2 to 3.5; $P < 0.01$) and QOL (mean QOL scale, 6.1 to 7.1; $P < 0.01$) after conversion to buprenorphine vs. baseline	Poor
Darchuk et al, 2010 (36)	RCS	Outpatient multidisciplinary pain rehabilitation center Oct. 2004-April 2006 United States Unfunded	449 patients with chronic pain and functional impairment Mean age: 46 y Female: 79% Mean pain duration: 9.9 y	56% (253/449) Mean, 112 mg	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating opioid discontinuation	Yes	No	92% (411/449) completed program 72% (292/411) completed 6-mo follow-up	No	94% (239/253) discontinued opioid medications at discharge 15% (44/292) reported opioid use at 6-mo follow-up Significant improvements in pain severity and general activity at 6-mo follow-up vs. admission for all patients ($P < 0.001$ for all comparisons)	Fair
Dersh et al, 2008 (37)	RCS	Outpatient interdisciplinary functional restoration program 1994-1999 United States Unfunded	1323 consecutive patients with "chronic, disabling occupational spinal disorders" Mean age: 42 y Female: 38% Mean disability duration: 19 mo	"Most patients" Dose NR	Intensive physical reactivation and pain/disability management with mandatory opioid discontinuation	Yes	No	91% (1200/1323) completed program 100% (1200/1200) completed 1-y follow-up	No	Opioid discontinuation required for program completion but not specifically reported Opioid use at 1-y follow-up NR Among all patients, 80% (955/1200) returned to work and 74% (891/1200) currently employed at 1-y follow-up	Poor
Drossman et al, 2012 (38)	RCS	Inpatient gastroenterology consult service; outpatient gastroenterology clinic Nov. 2008-Nov. 2011 United States Pfizer and Salix Pharmaceuticals	39 patients with severe chronic abdominal pain on opioid medications Mean age: 40 y Female: 92% Mean pain duration: 15 y	100% Mean, 75 mg	Inpatient opioid discontinuation with consult service (n = 34) or outpatient discontinuation (n = 5), both guided by multimodal protocol	Yes	No	97% (38/39) completed program 64% (25/39) completed 3-mo follow-up	Yes	100% decreased opioid dose; 90% (35/39) discontinued opioids at program completion 66% (24/36) resumed opioids at an average of 97 d posttreatment (range, 1-416 d) 51% (20/39) reported ≥30% reduction in pain severity after discontinuation vs. baseline 82% reported opioid withdrawal symptoms	Poor

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Appendix Table 5–Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Hanson et al, 2009 (39)	Case–control	Specialty gastroenterology clinic at a tertiary care referral center Jan. 1999-Dec. 2002 United States Mayo Foundation for Medical Education and Research	100 cases on opioid for IBD-related pain at initial visit; 100 matched controls Median age: 37.4 y Female: 64% Mean disease duration: 6.2 y	50% (50/100) Dose NR	≥1 visit in IBD clinic	No	Yes	76/200 (38%) returned for ≥1 follow-up visit	Yes	Of patients who returned for follow-up, 56% (22/39) discontinued opioid medications Patients who had discontinued opioids were more likely to report none-to-mild pain (73% vs. 18%) vs. those who continued opioids	Poor
Harden et al, 2015 (40)	RCS	Single integrated health care system Jan. 2010-Jan. 2013 United States Funding NR	50 patients with chronic pain on opioid medications Mean age: 54 y Female: 12% Pain duration: NR	100% 64% with dose >200 mg	Routine clinical care with dose reduction implemented by primary care providers, the pain service, or the pharmacist-run pain management clinic	Yes	No	100% (50/50) completed 12-mo follow-up	Yes	94% (47/50) decreased opioid dose at 12 mo; 13% (6/50) discontinued opioid medications Mean opioid dose reduction of 46% at 12 mo 68% of patients either experienced no change or less pain at 12 mo vs. baseline	Poor
Haroutounian et al, 2016 (41)	PCS	Outpatient pain clinic June 2010-Jan. 2013 Israel Unfunded	206 patients with "treatment resistant" chronic pain Mean age: 51.2 y Female: 38% Pain duration: NR	35% (73/206) Median, 60 mg	Cannabis treatment (smoked or edible), supervised by pain management physician with dose titration by protocol	Yes ("encouraged to attempt" dose reduction)	No	85% (176/206) completed 6-mo follow-up	No	44% (32/73) discontinued opioids at 6 mo ($P < 0.01$) Among patients still receiving opioids at follow-up, median dose decreased from 60 mg to 45 mg MED Among all participants, pain severity improved at 6 mo vs. baseline (S-TOPS, 75.0 vs. 83.3; $P < 0.01$)	Poor
Hassamal et al, 2016 (42)	RCS	Outpatient interdisciplinary opioid reduction program Dates NR United States Funding NR	5 patients with cLBP scheduled for spine surgery Mean age: 58 y Female: 80% Mean opioid duration: 10 y	100% Mean, 238 mg	Interdisciplinary, outpatient program involving opioid dose reduction, medication management, and nonpharmacologic therapies (CBT, PT, OT)	Yes	No	100% completed follow-up 1 mo postop	Yes	No patients (0/5) discontinued opioids; mean dose decreased from 238 mg MED at admission to 157 mg MED preop and 139 mg MED postop Improvements in pain (mean NRS, 5.0 vs. 7.6), pain interference (mean, 67.7 vs. 72.4), and satisfaction with participation in social roles (mean, 39.4 vs. 32.8) at 1 mo postop vs. admission	Poor
Heiwe et al, 2011 (43)	RCS	Inpatient and outpatient academic dependency center Feb.-June 2006, Aug. 2006-April 2007 Sweden Funding NR	29 patients with chronic pain on opioid medications Mean age: 44 y Female: 86% Mean pain duration: 11 y	100% 10% (3/29) taking "strong" opioids	Opioid discontinuation with counseling and optional auricular acupuncture and PT	Yes	No	66% (19/29) completed program 97% (28/29) completed data collection at mean follow-up of 2.1 y	Yes	66% (19/29) of patients discontinued opioid medications At follow-up, 32% (6/19) of completers and 78% (7/9) of noncompleters on opioids Among completers, pain severity (median NRS, 4.0 vs. 5.0) and withdrawal symptoms improved at 2-y follow-up vs. baseline	Fair

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Appendix Table 5–Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Hooten, 2007 (44)	PCS	Outpatient multidisciplinary pain rehabilitation center Jan. 2002-Dec. 2003 United States Funding NR	159 consecutive patients with fibromyalgia Mean age: 45 y Female: 86% Mean pain duration: 9.9 y	38% (61/159) Dose NR	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating opioid discontinuation	Yes	No	89% (142/159) completed program	No	93% (57/61) of patients on opioids discontinued at program completion Among all patients, pain severity and physical function improved significantly at program completion vs. admission ($P < 0.01$)	Poor
Hooten et al, 2007 (45)	RCS	Outpatient multidisciplinary pain rehabilitation center Jan. 2002-June 2005 United States Funding NR	33 consecutive male patients with fibromyalgia; 33 matched female patients Mean age: 47 y Female: 50% Mean pain duration: 10.4 y	32% (21/66) Mean, 64 mg for men Mean, 39 mg for women	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating opioid discontinuation	Yes	No	88% (29/33) of male patients completed program	No	95% (20/21) discontinued opioid medications Among all patients, pain severity and physical function improved significantly at program completion vs. admission ($P < 0.01$); these changes did not differ significantly by sex	Fair
Hooten et al, 2009 (46)	RCS	Outpatient multidisciplinary pain rehabilitation center Sept. 2003-Feb. 2007 United States Unfunded	1241 consecutive patients with chronic pain Mean age: 46 y Female: 75% Mean pain duration: 9.9 y	50% (622/1241) Mean, 118 mg	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating opioid discontinuation	Yes	No	85% (1057/1241) completed program	Yes	Proportion of patients using opioid medications decreased from 50% at discharge to 2% at admission Pain severity at program completion was significantly higher among patients who continued to use opioids vs. those who discontinued opioid medications (mean MPI pain subscale, 43.4 vs. 37.0; $P = 0.01$)	Fair
Hooten et al, 2010 (47)	PCS	Outpatient multidisciplinary pain rehabilitation center March 2007-July 2008 United States Foundation for Anesthesia Education and Research	109 patients with chronic pain on opioid medications ≥30 mg MED for >1 mo Mean age: 46.5 y Female: 57% Mean pain duration: 9.9 y	100% Mean, 192 mg	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating opioid discontinuation	Yes	No	93% (101/109) completed program	Yes	98% (99/101) of program completers discontinued opioids For 91 patients completing data collection, pain severity significantly improved at program completion vs. baseline (mean MPI pain subscale, 41 vs. 51; $P = .002$) Mean opioid withdrawal score was 4.5 at program completion	Fair
Hooten and Warner, 2015 (48)	RCT	Outpatient multidisciplinary pain rehabilitation center June 2011-May 2012 United States Mayo Foundation	21 patients with chronic pain on opioid medications ≥60 mg MED Median age: 49.0 y in varenicline group, 46.0 y in placebo group Female: 28% Mean pain duration: 5.8 y	100% Mean, 98 mg	15-d course of varenicline ($n = 10$) vs. placebo ($n = 11$) in context of 3-wk intensive multidisciplinary pain rehabilitation program and opioid discontinuation ($n = 10$)	Yes	Yes	86% (18/21) completed study	Yes	95% (20/21) of study completers discontinued opioids Opioid withdrawal symptoms decreased over time in 5/7 patients in the varenicline group and 4/11 patients in the placebo group Both groups experienced significant improvements in pain severity at program completion vs. baseline (median MPI pain subscale, 10 vs. 31; $P = 0.001$)	Poor

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Appendix Table 5–Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Huffman et al, 2013 (49)	RCS	Outpatient interdisciplinary chronic pain rehabilitation program Jan. 2007-Dec. 2010 United States Funding NR	120 patients who completed program, discontinued opioid medications and returned 12-mo follow-up survey Mean age: 49.5 y Female: 67% Pain duration: NR	100% Mean, 111 mg	3-4 wk interdisciplinary chronic pain rehabilitation program including PT/OT, psychotherapy, education, and medication management including opioid discontinuation	Yes	No	82% (558/682) completed program Among patients who discontinued opioids, 26% (120/459) completed 12-mo follow-up	No	82% (459/558) of program completers discontinued opioid medications by program completion 23% (27/120) resumed an opioid (including buprenorphine and tramadol) at 1 y	Poor
Huffman et al, 2017 (50)	RCS	Outpatient interdisciplinary chronic pain rehabilitation program 2007-2010 United States Funding NR	1457 patients with chronic pain who participated in program Mean age: 46.3 y Female: 62% Pain duration: NR	28% (413/1457) on high-dose (≥100 mg) 36% (528/1457) on low-dose (<100 mg) Mean, 177 mg	3-4 wk interdisciplinary chronic pain rehabilitation program including PT/OT, psychotherapy, education, and medication management including opioid discontinuation	Yes	Yes	82% (1194/1457) completed program Outcome data available for 46% (544/1194) at 6 mo and 39% (461/1194) at 12 mo	Yes	87% (654/754) discontinued opioids, 4% (30/754) discharged on buprenorphine 10% (77/754) continued full-agonist opioids Among patients who discontinued opioids, 31% (128/417) resumed opioid use during 12-mo follow-up Pain and function improved at discharge, 6 mo, and 12 mo vs. admission; these effects did not differ across opioid groups	Fair
Kapural et al, 2010 (51)	RCS	Outpatient pain clinic Dates NR United States Unfunded	18 consecutive patients on LTOT who received ketamine infusions 18 sex-matched controls Mean age: 46 y Female: 44% Mean pain duration: 9 y	100% Mean, 153 mg intervention group Mean, 190 mg control	Intravenous ketamine infusions, ~3 h/treatment, 3-6 weekly infusions	Yes	Yes	61% (11/18) 100% (36/36) completed 8 mo follow-up	Yes	Among 11 patients who completed ≥3 infusions, 18% (2/11) discontinued opioids; opioid dose decreased following last infusion (mean MED, 184 mg to 92 mg; $P = 0.02$) but was not significant at 6 mo (mean, 140 mg MED; $P = 0.3$). 7/11 decreased opioid dose at 6 mo vs. baseline Pain severity improved at 6 mo in 4/7 vs. baseline	Poor
Kidner et al, 2009 (52)	RCS	Outpatient, interdisciplinary functional restoration program Dates NR United States NIMH	1226 consecutive patients with a chronic disabling occupational musculoskeletal disorder Mean age: 43.7 y Female: 51% Mean disability duration: 13.3 y	48.6% (596/1226) 23% ≤30 mg, 10% 31-60 mg, 12% >60 mg	Outpatient, interdisciplinary functional restoration program incorporating opioid discontinuation Program duration NR	Yes	No	78% (954/1226); 74% in "opioids" group vs. 81% in "no opioids" group ($P < 0.01$) 78% (954/1226) completed 12-mo follow-up	Yes	74% (441/596) of patients on opioids at baseline discontinued opioid medications Program completers on opioids at baseline reported improved pain (mean NRS, 4.9 vs. 6.6) and disability (mean ODI, 24 vs. 42) at discharge vs. admission	Fair
Kroening and Oleson, 1985 (53)	RCS	Inpatient pain management service Dates NR United States Funding NR	14 patients with chronic pain on opioid medications Mean age: 45.8 y Female: 36% Mean pain duration: 9.3 y	100% Mean, 73 mg methadone	Inpatient medication management and opioid dose tapering over 2-7 d with electroacupuncture, naloxone administration, and nerve blocks	Yes	No	86% (12/14) completed study	Yes	86% (12/14) discontinued opioid medications; none resumed opioid at follow-up 6-15 mo later while completing a pain management program Per authors, pain "completely, or greatly, alleviated" at follow-up 21% (3/14) experienced opioid withdrawal symptoms	Poor

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Appendix Table 5—Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Krumova et al, 2013 (54)	RCS	Inpatient pain management service Jan. 2001-Dec. 2006 Germany Funding NR	102 consecutive patients with chronic pain on opioid medications Mean age: 51 y Female: 46% Mean opioid duration: 3.6 y	100% Mean, 367 mg	~3 wk inpatient opioid tapering with pharmacologic management of withdrawal symptoms and outpatient multidisciplinary follow-up	Yes	No	100% (102/102) completed program 95% (97/102) completed data collection 6-12 mo after program completion	Yes	76% (78/102) discontinued opioid medications; 24% (24/102) reduced dose by an average of 82%; 42% (31/73) resumed opioid medications at follow-up Pain severity improved at program completion vs. baseline (mean NRS, 5.4 vs. 7.1; $P < 0.001$) At 6-12 mo, pain severity (mean NRS, 5.9 vs. 7.1; $P < 0.001$) and pain-related disability (mean PDI, 30.4 vs. 37.7; $P < 0.001$) were improved vs. baseline	Fair
Lake et al, 2009 (55)	RCS	Inpatient, comprehensive headache treatment center Dates NR United States Funding NR	283 consecutive patients admitted for inpatient headache treatment Mean age: 40 y Female: 79% Pain duration: NR	48% (127/267) Dose NR	Inpatient, comprehensive headache treatment involving medication withdrawal, medication management and nonpharmacologic therapies	Yes	No	94% (267/283) completed program (mean length of stay, 13.0 d)	Yes	All patients discontinued opioid medications. 81% (103/127) achieved "moderate to significant" pain improvement at discharge	Poor
Levine et al, 2017 (56)	PCS	Outpatient academic neurosurgical pain center July 2011-Oct. 2013 Canada No external funding	132 consecutive patients with chronic pain treated with trial of spinal cord stimulation Mean age: 47.3 y Female: 54% Mean pain duration: 6.8 y	NR Mean, 253 mg	3-wk trial of percutaneous stimulation followed by permanent implantation of SCS or DNRS if trial successful	No	No	48% (55/123) with opioid data at 12 mo	No	55% (11/20) DNRS patients decreased dose and 15% (3/20) increased dose; 46% (16/35) SCS patients decreased dose and 31% (11/35) increased dose Among all participants, 47% of DNRS patients and 51% of SCS patients achieved >50% pain reduction	Poor
Maani et al, 2011 (57)	RCS	Inpatient burn center in military medical center Mar. 2008-Feb. 2009 United States Funding NR	6 patients with chronic pain related to burn injury Mean age: 31 y Female: 0% Mean pain duration: 1.8 y	100% Mean, 218 mg	Ultrarapid opioid detoxification under anesthesia	Yes	No	100% (6/6) completed program	Yes	33% (2/6) discontinued opioid medications Mean opioid medication use decreased from 218 mg MED preintervention to 22 mg MED postintervention (range, 0.1–75 mg) There were no adverse events during the detoxification procedure, and 1 patient was readmitted within 1 wk of discharge	Poor
Maclaren et al, 2006 (58)	RCS	Outpatient multidisciplinary rehabilitation program 2001-2003 United States Funding NR	127 consecutive patients with chronic pain related to work injury Mean age: 40.6 y Female: 47% Mean pain duration: 1.9 y	55% (70/127) Mean, 29 mg	4-6 wk outpatient multidisciplinary functional restoration program	No	No	76% (146/193) completed program 88% (127/145) completed 6-mo follow-up	Yes	Of 70 patients on opioids at admission, 14 (20%) decreased dose and 10 (14%) discontinued during treatment. Among patients on opioids at baseline, pain severity (mean MPQ, 18 vs. 23; $P < 0.025$) and pain-related function (mean PDI, 30 vs. 49; $P < 0.025$) improved These effects did not differ significantly between patients decreasing opioid dose vs. patients maintaining opioid dose	Poor

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Appendix Table 5–Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Malinoff et al, 2005 (59)	PCS	Outpatient setting Dec. 2003-Oct. 2004 United States Funding NR	95 consecutive patients referred by pain clinics for detoxification from LTOT Mean age: 51.3 y Female: 48% Mean opioid duration: 8.8 y	100% Dose NR	Outpatient conversion to sublingual buprenorphine	Yes	No	94% (89/95) completed program Mean follow-up, 8.8 mo Range, 2.4-16.6 mo	Yes	94% discontinued LTOT and initiated buprenorphine, and none of these patients returned to opioid medications 86% reported "substantial improvement" in pain severity during follow-up "Most patients" reported improved functional status 6 patients discontinued treatment during detoxification due to side effects; no patients died or were hospitalized	Poor
Marchetti et al, 2015 (60)	RCS	Inpatient and outpatient pain management center 2007-2012 France Funding NR	51 patients who underwent Mean age: 46 y Female: 67% Pain duration: NR	49% (25/51) Dose NR	Intravenous and oral ketamine for up to 3 mo with opioid dose reduction and pharmacologic management of withdrawal symptoms	Yes	No	Median treatment duration, ~3 mo	No	62% of patients on opioid achieved at least a 30% dose reduction Among all patients, 44% (24/55) achieved at least a 50% reduction in pain severity; 51% showed adverse effects	Poor
Mehl-Madrona et al, 2016 (61)	PCS	Rural primary care practice Dates NR United States Coyote Institute, Inc.	42 patients on long-term opioids who completed ≥6 mo of group medical visits 42 matched controls Mean age: 45 y Female: 60% Mean pain duration: 9.1 y	100% Mean, 82 mg	GMVs provided education about nonpharmacologic pain care and taught multiple complementary/alternative medicine techniques. Visits led by family physician, nurse, and behavioral health specialist.	No	Yes	50% (42/84) attended program for >6 mo	No	In GMV group, 19% (8/42) discontinued opioids, and 43% (18/42) reduced opioid dose; mean opioid dose decreased in GMV group (82.1 to 32.4 mg; $P < 0.001$). In treatment-as-usual group, 1/42 decreased opioid dose. Among all GMV participants, pain severity (mean ΔNRS, 0.19; $P < 0.01$) and QOL (mean ΔMYMOP2, −1.42; $P < 0.01$) improved vs. baseline	Poor
Miller et al, 2006 (62)	RCS	Inpatient addiction treatment setting 2001-2003 United States Unfunded	53 patients with chronic pain and prescription opioid dependence who completed program Mean age: 45 y Female: NR Mean opioid duration: 3.7 y	100% Dose NR	Inpatient discontinuation of opioid medications with pharmacologic management of withdrawal symptoms with diazepam and clonidine	Yes	No	Program completion NR	Yes	Study included only patients who discontinued opioid medications Pain severity improved significantly at program completion vs. baseline (mean NRS, 3.4 vs. 5.5; $P = 0.01$)	Poor
Murphy et al, 2013 (63)	RCS	Inpatient chronic pain rehabilitation program July 2006-Mar. 2011 United States VHA	705 patients admitted to pain program Mean age: 50.1 y Female: 20.2% Mean pain duration: 13 y	37% (221/600) of program completers) Mean, 61 mg	3-wk, inpatient interdisciplinary pain program using cognitive behavioral model and incorporating pain medication discontinuation	Yes	No	85% (600/705) completed program	Yes	100% (221/221) discontinued opioid medications at program discharge. Baseline opioid use significantly more common among non-completers (55% vs. 37%) Among patients on opioids at baseline, pain severity (mean NRS, 6.5 vs. 7.0; $P < 0.001$) and function (mean POQ-ADL, 13 vs. 16; $P < 0.001$) improved at program completion vs. baseline	Fair

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Appendix Table 5—Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Murphy et al, 2016 (64)	RCS	Inpatient chronic pain rehabilitation program Aug. 2006-Apr. 2011 United States Unfunded	324 patients with chronic pain who completed program and 3-mo follow-up Mean age: 52 y Female: 21% Mean pain duration: 12.2 y	35% (114/324) Mean, 63 mg	3-wk, inpatient interdisciplinary pain program using cognitive behavioral model and incorporating pain medication discontinuation	Yes	No	100% (324/324) completed study	No	100% discontinued opioid medications at program discharge. At 3-mo follow-up, 17% reported opioid use. There was no difference in follow-up opioid use by sex ($P = 0.83$) Among all patients, both males and females reported improved pain ($P < 0.05$) and pain-related interference ($P < 0.05$) at discharge vs. admission	Fair
Naylor et al, 2010 (65)	RCT	Integrative medicine clinic Feb. 2003-July 2004 United States NIDA, NIAAA, NIAMS	51 patients with chronic pain who had completed 11-wk pain coping skills training Mean age: 46 y Female: 86% Mean pain duration: 11.2 y	63% (32/51) 54% (14/26) in TIVR group 72% (18/25) in control group Mean, ~80 mg	4-mo TIVR to support self-monitoring and skill-building ($n = 26$) vs. standard care ($n = 25$)	No (optional goal reinforced by TIVR)	Yes	100% (51/51) completed study	No	21% (3/14) TIVR patients discontinued opioids at 8 mo; 3 additional control patients initiated opioids at 8 mo At 8 mo, opioid dose decreased in the TIVR group ($P = 0.05$) and increased significantly in the control group ($P = 0.045$)	Good
Nilsen et al, 2010 (66)	PCS	Outpatient, multidisciplinary pain clinic Sept. 2003-May 2005 Norway Funding NR	11 patients with chronic pain and "problematic" opioid medication use Mean age: 43 y Female: 81.8% Mean pain duration: 7.2 y	100% Mean, 36 mg	6 one-hour physician-led CBT sessions during 8-wk period with gradual tapering with goal of discontinuation	Yes	No	100% (11/11) completed program 100% (11/11) completed data collection at 3 mo	Yes	55% (6/11) patients discontinued opioids; 45% (5/11) remained off codeine at 3 mo Mean opioid dose decreased by 81% posttreatment ($P < 0.01$) Pain severity (mean NRS, 5.4 vs. 6.2; $P > 0.05$), function (mean SF-36 physical function subscale, 65 vs. 55; $P = 0.07$), and QOL (mean SF-36 general health subscale 48 vs. 34; $P = 0.15$) did not differ at 3 mo vs. baseline All patients reported withdrawal symptoms	Poor
Nissen et al, 2001 (67)	RCS	Inpatient, multidisciplinary pain center Jan.-Dec. 1998 Australia Funding NR	288 patients with chronic pain Mean age: NR Female: NR Pain duration: NR	83% (239/288) Mean, 89 mg	Inpatient, multidisciplinary pain program	No	No	100% (288/288) completed program	No	Opioid dose decreased at discharge vs. admission (36.9 mg MED vs. 88.7 mg MED; $P < 0.001$); proportion of patients taking an opioid decreased (58% at discharge vs. 83% at admission; $P < 0.05$).	Poor
Quinlan, 2012 (68)	RCS	Inpatient setting Dates NR Australia Funding NR	11 patients with chronic pain on opioid medications Mean age: NR Female: NR Pain duration: NR	100% Dose NR	5-d subanesthetic infusion of ketamine to assist with opioid discontinuation	Yes	No	73% (11/15) completed data collection	Yes	100% discontinued opioids initially; 27% (3/11) remained off opioids at 6 mo 64% (7/11) reported decreased pain severity postprocedure 36% (4/11) reported feeling "much better" at 6 mo 2 patients experienced adverse events	Poor

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Appendix Table 5–Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Ralphs et al, 1994 (69)	PCS	Inpatient pain management program Dates NR United Kingdom Institutional support	108 patients with chronic pain on opioid medications Mean age: 48.6 y Female: 58% Mean pain duration: 10.2 y	100% Mean, 36 mg	4-wk residential multidisciplinary pain program with voluntary opioid dose reduction Nonrandom selection of PCR (n = 63) vs. "cocktail reduction method" (n = 45)	Yes	Yes	100% (108/108) completed program 76% (82/108) completed 6 mo follow-up	No	At discharge, 89% of the "cocktail" group discontinued opioids vs. 68% of the PCR group ($P < 0.05$) At 6 mo, abstinence rates were equivalent with 55% of patients remaining off opioids Among all patients, pain severity and pain-related impairment did not differ between groups at discharge	Fair
Rome et al, 2004 (70)	RCS	Outpatient multidisciplinary pain rehabilitation center Jan. 2002-Dec. 2002 United States Funding NR	356 consecutive patients with chronic pain Mean age: 44.3 y Female: 74.2% Mean pain duration: 7.8 y	38% (135/356) Mean, 78 mg	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating pain medication discontinuation	Yes	No	86% (305/356) completed program 77% (274/356) completed data collection at admission and discharge	Yes	98% (132/135) of patients discontinued opioids by program discharge Patients on opioids at admission reported significant improvement in pain severity (MPI subscale mean difference, 8.4; $P < 0.001$), interference (MPI subscale mean difference, 12.5; $P < 0.001$), and perceived life control (MPI subscale mean difference, −9.1; $P < 0.001$) at program completion vs. admission	Poor
Rosenblum et al, 2012 (71)	PCS	Outpatient pain management center July 2008-Feb. 2010 United States NIDA	12 patients with chronic pain on opioid medications who had exhibited ≥1 aberrant behaviors Mean age: 50 y Female: 42% Mean opioid duration: 8.5 y	100% Mean, 142 mg	Outpatient conversion to sublingual buprenorphine/naloxone	Yes	No	33% (4/12) completed program	Yes	33% (4/12) patients completed transition to buprenorphine Pain severity (mean BPI subscale, 3.4 vs. 6.6; $P < 0.01$) and interference (mean BPI subscale, 2.9 vs. 6.0) decreased vs. baseline 83% (10/12) experienced an adverse effect, including 7 who stopped treatment as a result; 1 patient was hospitalized due to withdrawal symptoms and increased pain	Poor
Roux et al, 2013 (72)	RCT	Inpatient psychiatric setting Dates NR United States NIDA	43 patients prescribed opioids for chronic pain and opioid dependence Mean age: 48 y Female: 36% Median opioid duration: 5 y	100% Median, 60 mg	7-wk inpatient study involving conversion to buprenorphine/naloxone at each of 3 blinded doses in random order	Yes	Yes	72% (31/43) completed program 58% (25/43) completed data collection	Yes	72% (31/43) completed the 7-wk study Pain severity was reduced on buprenorphine/naloxone vs. preadmission ratings (median MPQ, 21 vs. 38; $P < 0.001$) Opioid withdrawal symptoms were reported in 83% of study sessions	Poor
Schneider and Kirsh, 2010 (73)	RCS	Outpatient pain practice Dates NR United States Funding NR	197 patients with chronic pain treated by a single pain specialist for ≥1 y Mean age: 49 y Female: 67% Pain duration: NR	95% prescribed long-acting opioid during follow-up Mean, 180 mg	Treatment for ≥1 y by a single physician trained in internal medicine, addiction medicine, and pain management	No	No	100% (197/197) completed ≥1 y of follow-up Mean follow-up, 4.7 y	No	15% (29/197) decreased opioid dose during follow-up; 2% (3/197) discontinued opioids in setting of aberrant behaviors.	Poor

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Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Schwarzer et al, 2015 (74)	RCS	Inpatient pain management program Nov. 2011-Dec. 2012 Germany Funding NR	18 patients admitted for opioid withdrawal (OG); 14 matched controls with no prior opioid use Mean age: 23 y Female: 50% Pain duration: NR	56% (18/32) Mean, 175 mg	~3 wk inpatient opioid tapering with pharmacologic management of withdrawal symptoms and outpatient multidisciplinary follow-up	Yes	Yes	100% (32/32) completed program	Yes	100% (18/18) patients in OG discontinued opioids; 1/18 resumed low-dose opioids. In the OG, there was a nonsignificant decrease in average pain at discharge vs. baseline (mean NRS, 6.6 vs. 7.2; $P = 0.22$) Central apnea was found in 50% (9/18) OG patients at baseline, and resolved in all patients at discharge.	Poor
Streltzer et al, 2015 (75)	RCS	Outpatient psychiatric pain clinic Jan. 2006-Dec. 2010 United States Funding NR	43 consecutive patients prescribed opioids for chronic pain and transitioned to sublingual buprenorphine Median age: 50 y Female: 30% Pain duration: NR	100% 93% (40/43) on dose ≥120 mg	Outpatient conversion to sublingual buprenorphine	Yes	No	100% (43/43) completed program Treatment duration ranged from 1-85 mo	Yes	100% (43/43) discontinued opioid medications 44% (19/43) maintained buprenorphine treatment; 7% (3/43) discontinued opioids 23% (10/43) resumed opioid medications, dropped out, or were transferred to a licensed opioid treatment program 1 patient died of an overdose several months after discontinuing buprenorphine	Poor
Sullivan et al, 2017 (76)	RCT	Outpatient multidisciplinary pain center May 2013-Sept. 2015 United States NIDA	35 patients with chronic pain on opioid medications Mean age: 54 y Female: 71% Mean pain duration: 13.8 y	100% Mean, 226 mg	22-wk outpatient tapering support including psychiatric consultation and weekly visits with PA for motivational interviewing and pain self-management training ($n = 18$) vs. usual care ($n = 17$)	Yes	Yes	72% (13/18) completed ≥80% of intervention sessions 89% (31/35) completed 22-wk data collection	No	Opioid dose reduction favored intervention but was not significant (adjusted mean difference = −42.9 mg MED; $P = 0.09$) at 22 wk 39% (7/18) in intervention and 12% (2/17) in usual care reduced opioid dose by ≥50% at 22 wk; 1 patient in each group discontinued opioids 22% (4/18) in intervention and 47% (8/17) in usual care did not reduce dose at 22 wk Among all participants, significant differences favoring the intervention were found for pain interference, pain self-efficacy and opioid-related problems	Good

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Appendix Table 5—Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Taylor et al, 1980 (77)	RCS	Inpatient pain management program Dates NR United States Public Health Service Research Grant	7 patients with chronic pain on opioid medications Mean age: 49 y Female: 57% Mean pain duration: 15.6 y	100% Dose NR	Inpatient detoxification from analgesic medications, education on relaxation and supportive therapy	Yes	No	100% (7/7) completed program 86% (6/7) completed 6 mo follow-up	Yes	100% discontinued opioids over an average of 3.7 d (range, 1-6 d); 50% (3/6) patients reported taking an opioid at 6 mo Pain severity reduced at 6-mo follow-up vs. baseline (mean 6-point NRS, 1.44 vs. 2.89; $P < 0.001$) 50% (3/6) reported increased activity at 6 mo 1 patient died in motor vehicle accident during 6 mo follow-up	Poor
Tennant and Rawson, 1982 (78)	RCS	Multidisciplinary outpatient pain program Jan. 1979-Sept. 1981 United States Funding NR	42 patients with chronic pain on opioid medications Mean age: 38.8 y Female: 50% Mean opioid duration: 8.2 y	100% Mean, 123 mg	21-d detoxification with pharmacologic management of withdrawal symptoms followed by nonrandom assignment to psychotherapy (D/C) ($n = 21$) vs. psychotherapy plus optional opioid maintenance (D/M) ($n = 21$)	Yes	Yes	24% (5/21) in D/C group and 95% (20/21) in D/M group completed initial 21-d phase	Yes	24% (5/21) in D/C group discontinued opioid medications; 95% (20/21) in D/M group requested maintenance on opioid medications ($P < 0.001$) At 90 d, 10% (2/21) patients in each group abstinent from opioids; 2 additional patients in D/M group discontinued opioids by 180 d "Significant pain emerged . . . for a majority of patients"	Poor
Thieme et al, 2003 (79)	RCT	Hospital for rheumatic disorders Dates NR Germany Funding NR	61 patients with fibromyalgia Mean age: 47.3 y Female: 100% Mean pain duration: 16.5 y	NR Dose NR	5-wk inpatient, group-based "operant pain treatment" program consisting of medication reduction and education ($n = 40$) vs. 5-wk inpatient, PT program plus antidepressant medication ($n = 21$)	Yes	Yes	97% (61/63) completed study 97% (61/63) with 6- and 15-mo follow-up	No	Intervention patients reported a significant reduction in opioid medication use (effect size not reported; $P < 0.001$) vs. PT Among all intervention patients, there was significant improvement in pain severity (mean MPI subscale, 3.2 vs. 4.4; $P < 0.001$) and interference (mean MPI subscale, 2.8 vs. 4.4; $P < 0.001$) at 15 mo vs. baseline	Poor
Townsend et al, 2008 (80)	RCS	Outpatient multidisciplinary pain rehabilitation center Jan. 2005-Feb. 2006 United States Institutional Small Grant Research Award	373 consecutive patients with chronic pain Mean age: 44.5 y Female: 79.1% Mean pain duration: 9.4 y	57.1% (213/373) Mean, 99 mg	3-wk intensive multidisciplinary pain rehabilitation program using cognitive behavioral model and incorporating pain medication discontinuation	Yes	No	91.2% (340/373) completed program 70% (238/340) completed 6-mo follow-up	Yes	93% (176/190) discontinued opioids by program completion 14% (33/238) of patients were taking opioids at 6-mo follow-up Among patients on opioids at admission, there was improvement in pain severity (mean MPI subscale, 39 vs. 49; $P = 0.002$) and pain interference (mean MPI subscale, 36 vs. 51; $P = 0.002$) at 6-mo follow-up vs. baseline	Fair

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Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Vines et al, 1996 (81)	RCS	Multidisciplinary functional rehabilitation program July 1992-June 1993 United States Funding NR	23 patients with chronic pain on opioid medications Mean age: 46 y Female: 74% Mean pain duration: 9.2 y	100% Dose NR	4-wk intensive outpatient pain rehabilitation program	No	No	52% (12/23) with data collection at program completion 100% (23/23) from 3-11 mo	No	70% (16/23) discontinued opioids by follow-up 3-11 mo after program completion Among all patients, pain severity (mean NRS, 4.3 vs. 8.7) and activity (mean days per week with decreased activity, 2.6 vs. 6.7) improved at follow-up vs. baseline	Poor
Wang et al, 2011 (82)	PCS	Outpatient orthopedic surgery clinic Dates NR Germany Institutional support	1) 35 patients with cLBP on opioids; 2) 35 patients with cLBP not on opioids; 3) 28 healthy controls Mean age: 47.7 y Female: 54% Mean pain duration: 8.8 y	35.7% (35/98) Mean, 107 mg	Outpatient opioid tapering by 50% every 3 d with symptomatic support with doxepin	Yes	No	57% (20/35) in group 1 at 6 mo 54% (19/35) in group 2 at 6 mo 79% (22/28) in group 3	No	91% (32/35) discontinued opioids by day 21 15% (3/20) of patients were taking an opioid medication at 6-mo follow-up	Poor
Webster et al, 2016 (83)	RCT	Inpatient clinical trial setting Dates NR United States Endo Pharmaceuticals	39 patients with chronic pain on opioids (80-220 mg MED) Mean age: 42.3 y Female: 54% Pain duration: NR	85% (33/39) on 80-160 mg MED 15% (6/39) on 161-220 mg MED	Double-blind, placebo-controlled, crossover study comparing 24-h periods of full opioid agonist vs. buccal buprenorphine, both at 50% of baseline opioid dose	Yes	Yes	94% (31/33) in 80-160 mg MED group 83% (5/6) in 161-220 mg MED group	Yes	92% (36/39) completed both 24-h treatment groups In the 80-160 mg MED group, 2 patients experienced opioid withdrawal (COWS ≥13); 1 patient in both groups and 1 patient with full agonist only In the 80-160 mg MED group, 56% and 41% experienced an adverse event during buprenorphine and full agonist, respectively	Poor
Weimer et al, 2016 (84)	RCS	Academic primary care practice May 2011-August 2013 United States Professional society grant	516 patients on long-term opioid medications Mean age: 59 y Female: 63% Pain duration: NR	100% Mean, 263 mg in high-dose (>120 mg) group (n = 116)	Opioid Dosing Limitation Policy (i.e., mandatory dose reduction below 120 mg MED) and provider education intervention	Yes	No	97% (112/116) at 28 mo	Yes	37% (41/112) patients reduced opioid dose below 120 mg MED; 12% (13/112) discontinued opioids. Mean opioid dose decreased from 263 mg to 199 mg (P < 0.001). Among patients who reduced dose, pain (mean NRS, 5.4 vs. 5.6) and QOL (mean NRS, 5.1 vs. 5.7) did not change significantly postintervention vs. preintervention	Poor

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Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Whitten and Stanik-Hutt, 2013 (85)	PCS	Rural primary care practice June-Nov. 2010 United States Funding NR	22 patients with chronic pain on opioid medications Mean age: 61 y Female: 5% Mean pain duration: 20/22 with ≥10 y	100% Mean, 69 mg	6-wk group CBT program located within primary care practice, cofacilitated by psychotherapist and nurse practitioner	No	No	34% (27/80) of eligible patients enrolled 81% (22/27) completed program	No	18% (4/22) discontinued opioids Among all patients, there were nonsignificant improvements in pain (mean BPI subscale, 4.9 vs. 5.6; $P = 0.11$) and physical function (mean SF-36 PC, 32 vs. 29; $P = 0.1$) at 6 wk vs. baseline	Poor
Williams et al, 1996 (86)	RCT	Multidisciplinary pain management program Dates NR United Kingdom Institutional support	121 patients with chronic pain Mean age: 50.0 y Female: 53% Mean pain duration: 8.1 y	63% (27/43) of IP group 67% (30/45) of OP group 50% of WLC Mean, 30 mg for IP group Mean, 22 mg for OP group	Cognitive behavioral programs consisting of exercise, goal setting, education, and opioid discontinuation Random assignment to 4-wk IP vs. 8-wk OP vs. WLC	Yes	Yes	93% (40/43) for IP group 82% (37/45) for OP group 1-y follow-up: 78% (31/40) for IP group 78% (29/37) for OP group	No	50% (21/42) discontinued opioids at 1 mo At 1 y, 80% (24/30) and 55% (17/31) not using opioids in IP and OP groups, respectively ($P < 0.05$). IP but not OP group achieved a significant dose reduction at 1 y. Pain severity did not improve significantly in either treatment group vs. control at 1 mo (not stratified by opioid dose reduction) Multiple measures of function improved significantly in both treatment groups vs. control at 1 mo and 1 y	Poor
Williams and Stark, 2003 (87)	RCS	Inpatient neurology unit Dates NR Australia Funding NR	71 patients with chronic daily headache admitted for inpatient treatment Mean age: 44 y Female: 87% Mean pain duration: 5.5 y	80% (57/71) on codeine; 47% and 31% on other and injectable opioids 23 mg among codeine users	Inpatient medication discontinuation and 7-10 d lidocaine infusion and medication management	Yes	No	93% (66/71) completed protocol 87% (62/71) completed 6 mo follow-up	No	76% (45/57) discontinued opioid at 6 mo follow-up ($P < 0.001$) Of those who were still using codeine-based medications, the mean weekly dose decreased by 22% Pain outcomes not stratified by opioid dose reduction	Poor
Younger et al, 2008 (88)	PCS	Inpatient pain rehabilitation program Dates NR United States Arthritis Foundation, NIGMS, NINDS	12 patients with chronic pain on opioid medications Mean age: 47.9 y Female: 42% Pain duration: NR	100% Mean, 33 mg Median, 194 mg	7-14 d inpatient pain rehabilitation program with opioid detoxification using blinded pain cocktail	Yes	No	100% (12/12) completed program	No	58% (7/12) discontinued opioid therapy; 2 patients greatly reduced high-dose therapy (i.e., ≥400 mg MED) Among all patients, pain severity and opioid withdrawal ratings did not significantly change at discharge vs. admission	Poor
Zekry et al, 2016 (89)	PCS	Inpatient pain management center 2007-2012 Australia Funding NR	70 patients Mean age: 49 y Female: 37% Pain duration: NR	73% (51/70) Mean, 216 mg	Subanesthetic, subcutaneous ketamine infusion with or without subsequent sublingual ketamine, pharmacologic management of withdrawal symptoms	Yes	No	NR 74% (52/70) completed follow-up	No	Mean opioid dose decreased from 216 mg MED to 89 mg MED posttreatment (59% reduction, $P < 0.005$) Among patients continued on ketamine lozenges, 31% discontinued opioids at follow-up (3 mo-2 y) Pain outcomes not stratified by opioid dose reduction	Poor

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Appendix Table 5–Continued

Study, Year (Reference)	Design	Setting, Years, Country, and Funding Source	Sample Characteristics	Baseline Opioid Use and Dose (MED)	Intervention	Program Goal of Dose Reduction	Control Condition	Program Completion and Study Follow-up	Patient Outcomes (KQ2)	Results	Quality Rating*
Zgierska et al, 2016 (90, 91)	RCT	Outpatient primary care Jan. 2013-Oct. 2013 United States NIAAA, institutional support	35 patients with cLBP on ≥30 mg/d MED for >3 mo Mean age: 51.8 y Female: 80% Mean pain duration: 14.2 y	100% Mean, 148 mg	8 weekly, 2-h group sessions (meditation, CBT) and 30 min/day, 6 d/wk of at-home practice plus usual care (n = 21) vs. WLC receiving usual care (n = 14)	No	Yes	100% completed trial	No	Between-group difference in opioid dose change favored intervention but was not significant (9.9 mg/d; P = 0.8). Within-group opioid dose reduction was not significant in either group at 26 wk. Proportion on >200 mg MED decreased in the intervention group (29% to 20%) but not control (21% to 23%) at 26 wk; opioid discontinuation NR The meditation-CBT group reduced pain severity vs. controls at 26 wk (P = 0.045)	Good
Zheng et al, 2008 (92)	RCT	Outpatient pain management center 2005-2006 Australia Institutional support	35 patients with chronic pain on opioid medications Mean age: 49.7 y Female: 49% Mean pain duration: 16.3 y	100% Mean, 376 mg	6-wk intervention of twice-weekly REA (n = 17) vs. SEA (n = 18)	No	Yes	74% (26/35) completed 6-wk treatment period 66% (23/35) completed 20-wk study	No	At week 8, opioid dose significantly decreased in both groups vs. baseline (39% in REA vs. 26% in SEA); the between-group difference was not significant Average pain improved significantly in both groups at week 8 vs. baseline No significant group differences in pain severity or QOL at week 8	Fair

BPI = Brief Pain Inventory; CBT = cognitive behavioral therapy; cLBP = chronic low back pain; COWS = Clinical Opiate Withdrawal Scale; DNRS = dorsal nerve root stimulator; GMV = group medical visit; IBD = inflammatory bowel disease; IP = inpatient program; KQ = key question; LTOT = long-term opioid therapy; MED = morphine-equivalent dose; MPI = Multidimensional Pain Inventory; MPQ = McGill Pain Questionnaire; MYMOP2 = My Medical Outcome Profile, 2nd version; NIAAA = National Institute on Alcohol Abuse and Alcoholism; NIAMS = National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIDA = National Institute on Drug Abuse; NIGMS = National Institute of General Medical Sciences; NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke; NR = not reported; NRS = numerical rating scale; ODI = Oswestry Disability Index; OG = opioid withdrawal group; OP = outpatient program; OT = occupational therapy; PA = physician assistant; PCP = primary care provider; PCR = patient-controlled dose reduction; PCS = prospective cohort study; PDI = Pain Disability Index; POQ-ADL = Pain Outcomes Questionnaire-Activities of Daily Living; PT = physical therapy; QOL = quality of life; RCS = retrospective cohort study; RCT = randomized controlled trial; REA = real electroacupuncture; SCS = spinal cord stimulator; SEA = sham electroacupuncture; SF-36 = 36-Item Short Form Health Survey; S-TOPS = Treatment Outcomes in Pain Survey-Short Form; TIVR = therapeutic interactive voice response; VHA = Veterans Health Administration; WLC = wait-list control.

* See **Appendix Table 2** for U.S. Preventive Services Task Force Quality Rating Criteria.