

# Is Buprenorphine Effective for Chronic Pain? A Systematic Review and Meta-analysis

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## Abstract

**Objective.** The objective was to perform a systematic review and meta-analysis of the literature on the effects of buprenorphine on chronic pain outcomes (i.e., patient-reported pain intensity) in patients with and without opioid use disorder (OUD). **Design.** Ovid/Medline, PubMed, Embase, and the Cochrane Library were searched for studies that explored the effectiveness (in reducing pain) of buprenorphine treatment for chronic pain patients with and without a history of OUD. Randomized controlled trials and observational studies were included in the review. **Methods.** Two separate searches were conducted to identify buprenorphine trials that included chronic pain patients either with or without OUD. Five studies used validated pain report measures and included a chronic pain population with OUD. Nine studies used validated report measures and included chronic pain patients without OUD. **Meta-analysis** was performed using the R, version 3.2.2, Metafor package, version 1.9–7. **Results.** The meta-analysis revealed that buprenorphine has a beneficial effect on pain intensity overall, with a small mean effect size in patients with comorbid chronic pain and OUD and a moderate- to large-sized effect in chronic pain patients without OUD. **Conclusions.** Our results indicate that buprenorphine is modestly beneficial in reducing pain intensity in patients without OUD. Although informative, these findings should be carefully interpreted due to the small amount of data available and the variation in study designs.

**Key Words:** Buprenorphine; Chronic Pain; Opioid Use Disorder

## Introduction

Chronic pain adversely impacts all demographic groups, is one of the most frequent reasons to seek medical care, and represents a major public health problem for both individuals and society [1, 2]. It is estimated that 5–8 million patients with chronic pain are treated with opioids, and chronic low back pain (CLBP) is the top chronic non-cancer condition for which opioids are prescribed [3]. There are very limited data on the long-term efficacy of opioids and much concern about their harms, which are dose-dependent and include worsened mental health, addiction, and overdose death [4, 5]. With the escalating challenge of managing pain in opioid-dependent patients, buprenorphine, a low-efficacy opioid agonist receptor modulator, is increasingly being prescribed for the treatment of chronic pain, especially in patients with

comorbid substance use disorders. To date, however, although buprenorphine is approved for the management of pain and opioid use disorder (OUD), a consensus has yet to be reached with regard to its effectiveness as an analgesic [6–8]. When chronic pain is complicated by a comorbid OUD, the evaluation and treatment of pain may present a complex clinical challenge to physicians and patients [9]. Moreover, some evidence suggests that patients with substance use disorders are less likely to receive effective pain treatment than those without them [10]. Unfortunately, according to a 2015 National Institutes of Health–Agency for Healthcare Research and Quality systematic review of long-term opioid therapy for chronic pain [11], research on risk mitigation strategies for OUD among chronic pain patients is sparse. Buprenorphine is a partial agonist at the  $\mu$ -opioid

receptor and an antagonist at the  $\kappa$ -opioid receptor with high affinity for both receptors. It has shown some promise as an analgesic, though the evidence base remains at a relatively early stage [7, 12, 13]. Unfortunately, patients with chronic pain appear to derive limited analgesic benefit from other OUD treatments including methadone treatment [14]. It is important to illuminate the potential role of buprenorphine in chronic pain management and to identify potential patient-level factors that could impact its effectiveness. One of the challenges is that pain and substance use disorders co-occur frequently, and each can make the other more difficult to treat [9, 15, 16]. Accordingly, the current review and meta-analysis sought to examine the analgesic effect of buprenorphine maintenance treatments, including controlled trials and observational studies (cohort or case-control), for the treatment of patients with chronic pain. Additionally, this review sought to compare the effectiveness of buprenorphine for the treatment of chronic pain in patients with and without a history of OUD.

## Methods

### Systematic Review Methods

#### Data Sources and Search Strategy

This study adheres to the reporting standards outlined by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. A protocol outlining the appropriate methodological design features of this systematic review was discussed and prepared before the onset of the investigation. This protocol is available upon request to the authors. An electronic search was performed in duplicate using CINAHL, PUBMED, Web of Science, Embase, and the Cochrane Library including Cochrane Reviews and the Cochrane Central Register of Controlled Trials databases. No attempt was made to evaluate the gray literature, as this evidence is not subject to the same transparency requirements and scrutiny as studies published in peer-reviewed journals. A comprehensive search strategy was designed a priori and specifically tailored for each database. The search was restricted to 1) completed and 2) human studies. We conducted two independent literature searches. The terms used in the first search included the following: “chronic pain” AND “buprenorphine.” The second search included the following terms: “chronic pain,” “buprenorphine” AND “opioid use disorder,” “opioid substitution treatment,” “opioid analgesic misuse,” “opioid abuse,” “opioid dependen\*,” “opioid-related disorders.” The systematic review was registered in PROSPERO #120812.

#### Selection of Studies

The literature search and data extraction were performed independently in duplicate by two authors (AL, MP). The two authors completed the title search, screened the

articles that were selected based on the title and abstract using predetermined inclusion criteria, and performed a full-text extraction on all eligible articles using pilot-tested data extraction forms. Any disagreements between raters in their title and abstract screening or full-text extraction were resolved by discussion. If discussion between the raters did not lead to a resolution, a third author (RE) was consulted and had the final judgment as to whether the disputed article would be accepted.

The systematic review flow diagram of the article selection process can be seen in [Figure 1](#).

#### Inclusion and Exclusion Criteria

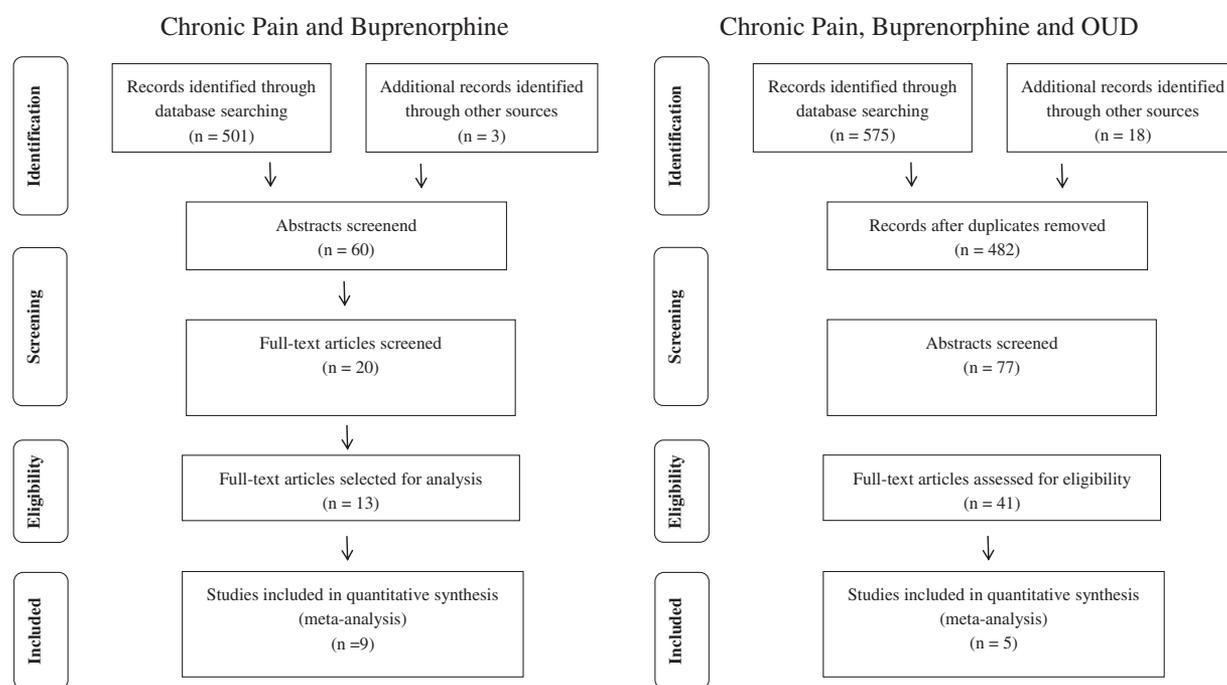
The studies included had to assess pain intensity in chronic noncancer pain patients, either with or without OUD, and patients had to have received buprenorphine via any route of administration, including transdermal. Randomized controlled trials (RCTs), nonrandomized trials (NRTs), and observational studies such as case-control or cohort investigations were included in the review. Qualitative studies or single opinion papers were excluded from the review. No restrictions were placed on the geographic locations or time period of study. However, the study was required to have evaluated patient-reported pain “response” (i.e., change in pain intensity ratings) to buprenorphine or buprenorphine-naloxone maintenance treatment. Any incomplete studies, as well as animal studies, were not eligible for inclusion into this review. Additionally, studies evaluating participants on substitute opioid therapies other than buprenorphine and buprenorphine-naloxone were not eligible for inclusion in the review. Adjunct behavioral interventions to buprenorphine or buprenorphine-naloxone maintenance treatment were also excluded from the review. We only focused on buprenorphine treatments for chronic pain without extensively researching methods for MAT.

#### Data Extraction

The two authors (AL, MP) extracted data from the studies using a pilot-tested data extraction form. Information extracted included author, date of publication, journal of publication, number of study participants, definition of chronic pain, percentage/number of participants with chronic pain, primary outcome of the study, measurement of pain, statistical analysis performed, description of study population (e.g., income), mean buprenorphine or buprenorphine-naloxone dose (mg/d), mean age, overall statistical findings, factors associated with treatment response, and study conclusions ([Tables 1 and 2](#)).

#### Assessment of Methodological Quality

Two authors (AL, MP) assessed the methodological quality of all eligible studies using the Cochrane Risk of Bias Tool for RCTs. Any discrepancies between the independent raters were first resolved by discussion; if discussion



**Figure 1.** Flow of information through the different phases of the systematic review.

did not lead to an adequate solution, a third rater (RE) was brought in to make the final decision.

### Statistical Analysis

We conducted two separate quantitative syntheses to derive meta-estimates of the primary outcome (pain intensity). The quantitative analysis examined the primary outcome at two time points, at baseline and immediately after treatment. Continuous data for the primary outcome were used to analyze the overall estimate of effect size of buprenorphine. Analyses were performed in the R statistical programming language using the “Metafor” package [31].

Because most outcomes were presented as continuous data (mean value or mean changes), we used standardized mean differences (SMDs) as effect measures. SMDs were used because the outcome was often measured using different scales. To calculate SMDs, we used means and change scores and their standard deviations. When only the standard error or the 95% confidence interval was reported, it was converted into standard deviation. For the actual meta-analysis, we used a random-effects model to calculate the pooled effect size, with 95% confidence limits. We assessed heterogeneity using  $I^2$  statistics for quantification and Cochran’s  $Q$  for statistical significance.

The  $I^2$  statistic as a measure of heterogeneity was reported for each meta-analysis. We used an inverse variance method to weigh assessments of outcome, meaning larger studies were given more weight in comparison with smaller studies. Confidence intervals were calculated. Confidence intervals not including zero were

considered statistically significant. Forest plots were used to display pooled estimates.

We used Cohen categories [12] to evaluate the magnitude of the effect size, calculated by SMD, and designated a  $d > 0.2$ – $0.5$  as a small effect size, a  $d > 0.5$ – $0.8$  as a medium effect size, and a  $d > 0.8$  as a large effect size. We used the following descriptors to classify meta-analysis results: “Strong” indicated consistent findings in multiple (at least two) high- or moderate-quality studies; “moderate” indicated consistent findings in multiple low-quality studies or one high- or moderate-quality study.

## Results

### Search Results and Study Characteristics

Our first search using the terms “buprenorphine” and “chronic pain” yielded 501 articles. The second search, including OUD, returned 593 articles. The selection algorithms for both searches are depicted in Figure 1. The administration routes for buprenorphine were buccal, transdermal, and sublingual. No systematic reviews comparing the effectiveness of buprenorphine for chronic pain patients with and without OUD were identified. Articles including cancer-related pain were excluded.

### Results of Search “Chronic Non Malignant Pain (CNMP) Without OUD”

Thirteen articles met all criteria, of which four articles had to be excluded from the analysis because of missing data regarding pain intensity. The remaining nine studies were selected to enter the final analysis [17–25]. These

**Table 1.** Studies' characteristics search 1: Chronic pain and buprenorphine

Reference	Study Design	No.	Mean Age	Type of Pain	Patient Characteristics	BUP Dosage	Results
Yoon et al. 2017 [17]	Prospective, multicenter, open-label, single arm	63	57	CLBP, osteoarthritis, rheumatoid arthritis, or joint/muscle pain	Pain moderate to severe (score of $\geq 4$ on BS-11), requiring an opioid	Initially 5 $\mu\text{g}/\text{h}$ transdermal BUP, titration up to max; 40 $\mu\text{g}/\text{h}$ over 6 wk; after achieving pain control, transition to the treatment period (11 wk)	Pain intensity assessed with an NRS (BS-11); pre-post difference: 3.05
Rauk et al. 2016 [18]	Multicenter, double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study	209	51.2	CLBP for $\geq 6$ mo including CLBP of nonneuropathic origin, neuropathic origin, or after low back pain surgery	$\leq 10$ mg/d MSE; average daily pain intensity score $\geq 5$ to $< 10$ (NRS)	Open-label titration of buccal BUP over 8 wk up to 150, 300, or 450 $\mu\text{g}$ 2 $\times$ /d; then randomization to placebo or the achieved BUP dose for 12 wk	Pain intensity assessed with an NRS; pre-post difference in pain severity: 3.36
Yarlas et al. 2015 [19]	Randomized, placebo-controlled, double-blind clinical trial	122	49.6	Moderate to severe CLBP	Opioid-naïve adult patients with a VAS score $> 5$	Transdermal BUP 10 or 20 $\mu\text{g}/\text{h}$ (run-in period of up to 27 d); then randomization to BUP or placebo for 12 wk	Pain intensity assessed with a 10-point VAS; pre-post difference: 4.5
Gatti et al. 2012 [20]	Open-label, prospective, single-center study	89	71.2	Nononcological, moderate to severe chronic musculoskeletal pain	Opioid-naïve adult patients with a VAS score $> 6$	Titration of transdermal BUP up to 17.5, 23.4, or 35 $\mu\text{g}/\text{h}$ , then treatment for 6 mo	Pain intensity assessed with a 10-point VAS; pre-post difference: 5.31
Gordon et al. 2010 [21]	Randomized, double-blind, placebo-controlled crossover study	26	51.3	Low back pain of at least moderate intensity for $> 3$ mo	Pain intensity $\geq 2$ on a 5-point ordinal scale and currently required $\geq 1$ tablet daily of an opioid analgesic	Titration of transdermal BUP to 20–40 $\mu\text{g}/\text{h}$ or placebo; then double-blind treatment for 8 wk, followed by open-label extension study (6 mo)	Pain intensity assessed with a VAS; pre-post difference: 1.57
James et al. 2010 [22]	Randomized, double-blind, parallel group	102	64.	Moderate to severe pain caused by osteoarthritis of the hip(s) and/or knee(s)	Pain score of $> 4$ on the BS-11	Randomization to a 7-d transdermal BUP patch (5–20 $\mu\text{g}/\text{h}$ ) or sublingual BUP (600–1,200 $\mu\text{g}/\text{d}$ ) or a placebo version of either; then titration over up to 21 d, assessment period up to 28 d	Pain intensity assessed with a VAS; pre-post difference: 3.45
Karlsson & Beggren 2009 [23]	Randomized, open-label, controlled, parallel-group, noninferiority study	69	64.4	Osteoarthritis of the hip and/or knee	Pain score on the BS-11 $> 4$ and inadequate pain relief with paracetamol 4,000 mg/d during the screening wk	Screening phase with paracetamol 4,000 mg/d; treatment phase (12 wk): 1:1 randomization to 7-d BUP patches (titrated up to 40 $\mu\text{g}/\text{h}$ ) or twice-daily oral tramadol (up to 800 mg/d)	Pain intensity assessed with a VAS; pre-post difference: 2.24
Gimbel et al. 2016 [24]	Double-blind, placebo-controlled, enriched-enrollment, randomized-withdrawal study	254	53	Moderate to severe CLBP (non-neuropathic, neuropathic, or symptomatic for $> 6$ mo after low back surgery)	Opioid-tolerant with 30– $\leq 160$ mg/d MSE	Open-label titration of 150–900 $\mu\text{g}/12$ h, buccal BUP (8 wk); then 1:1 randomization to placebo or buccal BUP (12 wk)	Pain intensity assessed with an NRS; pre-post differences in pain severity: 3.89
Hale et al. 2017 [25]	Open-label, single-arm trial	435	52	CLBP, chronic hip pain, foot pain, neuropathic pain, and osteoarthritis	Opioid-tolerant with $\geq 60$ – $\leq 160$ mg/d MSE for $> 4$ wk or with $\geq 300$ $\mu\text{g}$ buccal BUP/12 h	Titration of 150–900 $\mu\text{g}/12$ h buccal; then long-term treatment up to 48 wk	Pain intensity assessed with an NRS; pre-post difference: 1.3; BUP buccal film had a higher percentage of responders than placebo

BUP = buprenorphine; CLBP = chronic low back pain; BS-11 = numerical 11-point box; MSE = morphine sulfate equivalent; NRS = numerical rating scale; VAS = visual analog scale.

**Table 2.** Studies characteristics search 2: Chronic pain, buprenorphine, and OUD

Reference	Study Design	No.	Mean Age, y	Type of Pain	Patient Characteristics	BUP Dosage	Results
Pade et al. 2012 [26]	Retrospective chart review	143	52	CLBP, chronic headaches, fibromyalgia	Diagnosis of opioid dependence (DSM-IV)	BUP/NX 6–28 mg/d, treatment duration 6–18 mo	Pain intensity assessed with an NRS, pre–post difference: 0.79; statistically significant improvement in pain scores with BUP/NLX
Worley et al. 2016 [27]	Multisite, randomized, adaptive trial	119	N/A	CLBP, chronic hip pain, shoulder pain, neck pain	DSM-IV diagnosis of current prescription opioid dependence (in 95% for >1 y)	BUP/NX 8–32 mg/2–8 mg/d for 12 wk	Pain intensity assessed with an NRS, pre–post difference: 1.93; significant decreases in subjective pain during BUP/NLX treatment
Neumann et al. 2013 [28]	Randomized prospective clinical trial	13	38.3	Chronic nonmalignant pain related to the spine or a large joint	Diagnosis of opioid dependence (DSM-IV-TR; DAST score >4)	Open-label randomization in BUP/NX 4–16 mg/1–4 mg/d or methadone 10–60 mg/d for 24 wk	Pain intensity assessed with an NRS, pre–post difference: 0.3 6-mo BUP/NX treatment resulted in a significant analgesia
Nielsen et al. 2014 [29]	Multisite randomized control trial	569	33.4	“Other than everyday kinds of pain”	DSM-IV diagnosis of current prescription opioid dependence	BUP/NX 4–32 mg/1–8 mg/d for 2 wk	Pain intensity assessed with an NRS, pre–post difference: 0.05; difficult BUP-induction experiences did not differ by primary prescription opioid type
Rosenblum et al. 2012 [30]	Longitudinal observational trial	12	50	Moderate to severe chronic pain, not specified	Patients with 1 or more aberrant drug-related behaviors (assessment with COMM)	BUP/NX 8–24 mg for 3 mo	Pain intensity assessed with an NRS, pre–post difference: 4.5; average and worst pain significantly decreased after the switch to BUP/NX

BUP = buprenorphine; BUP/NX = buprenorphine/naloxone; CLBP = chronic low back pain; COMM = Current Opioid Misuse Measure; DAST = Drug Abuse Screening Test; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders–IV; MSE = morphine sulfate equivalent; NRS = numerical rating scale; OUD = opioid use disorder.

studies included 1,369 participants and were conducted in the United States, Canada, UK, Italy, Sweden, Korea, Hong Kong, and the Philippines. The mean age of the participants was 57.2 years. The publication years ranged between 2009 and 2017, and the study design was in all the cases prospective. The administration route of buprenorphine was mostly transdermal; one study was conducted with buccal buprenorphine and another with buccal and transdermal (in this case, the average pain score was used for the analysis). In five out of nine studies, the group receiving buprenorphine was compared with either a placebo group (four studies) or tramadol (one study) (Table 1).

### Results of Search “Chronic Non Malignant Pain (CNMP) with OUD”

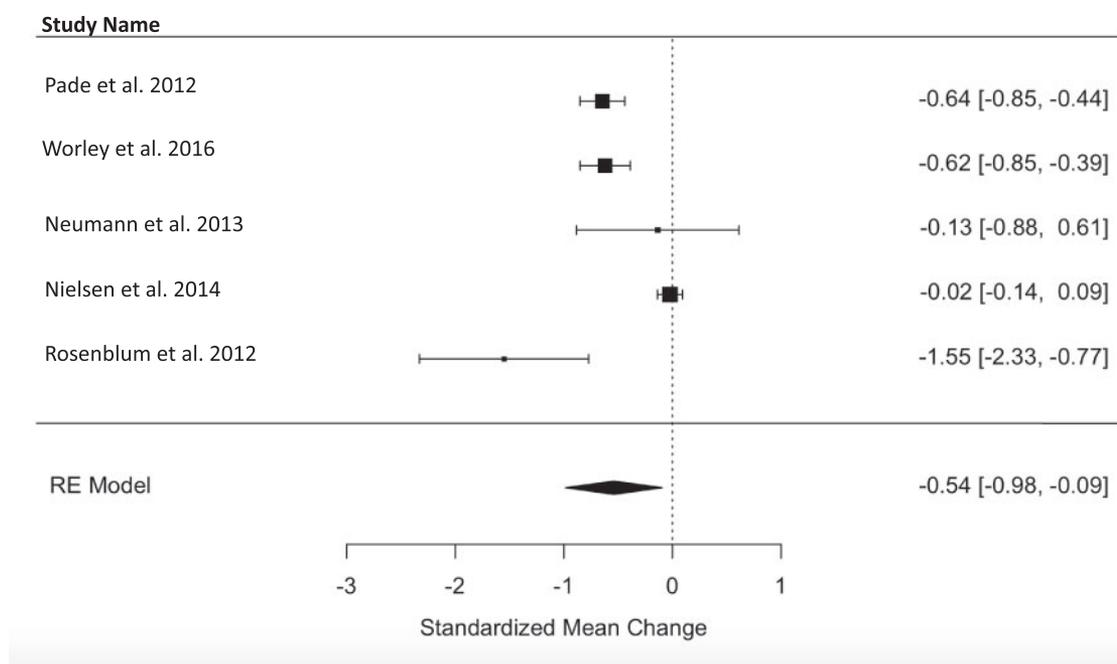
Of all articles, five articles [24–30] were entered into the final analysis according to the inclusion criteria. The selected studies are described in Table 2. The total number of participants was 856 from studies conducted in the United States. Publication dates ranged between 2012 and 2016. Four out of the five studies reported the mean age of the participants; the mean age was equal to 42.8 years old. Buprenorphine was administrated as

sublingual buprenorphine with naloxone in all five studies. One out of the five studies used a comparison group (methadone active comparator group).

Nine other studies presented only OUD data (and not pain intensity data), and others did not measure chronic pain at all. Twelve studies were excluded because they did not assess buprenorphine or buprenorphine-naloxone maintenance treatment outcomes for OUD. Four studies provided incomplete data regarding pain intensity and could therefore not be included. Three studies were excluded because they only assessed opioid dosage patterns without pain intensity measures. Two studies could not be included due to the availability of only a single pain measurement. One study was excluded because the pain assessment involved only pain relief using a verbal rating scale. Among the included studies, the majority were prospective (four studies); one study was retrospective.

### Results of Meta-analysis

Five studies with a total of 856 participants were included in the analysis to investigate whether buprenorphine treatment impacted pain intensity in patients with OUD, and nine studies with 1,369 participants assessed the effectiveness of buprenorphine in patients without



**Figure 2.** Forest plot demonstrating the effect sizes of changes in pain intensity from baseline to post-buprenorphine treatment in patients with chronic pain without opioid misuse.

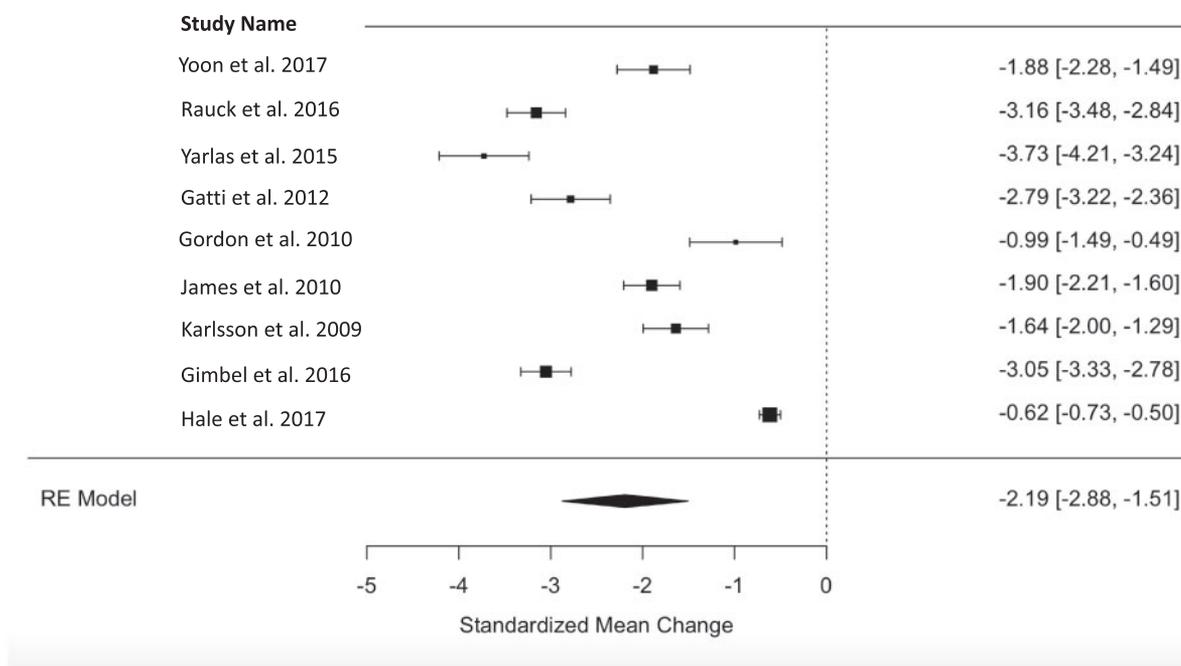
OAD. The pain intensity assessment consisted of the measurement of patient-reported pain intensity using a numerical rating scale at baseline and at the end of buprenorphine or buprenorphine-naloxone treatment, both in the studies that assessed patients with OAD and those that assessed patients without OAD. The duration of treatment varied from two weeks to six months, with only one study reporting data for over six months for patients with OAD. The treatment period of the studies without OAD ranged between four weeks and six months. A meta-analysis for the search “chronic pain, buprenorphine and OAD” produced evidence for a reduction of pain (SMD =  $-0.54$ , 95% confidence interval [CI] =  $-0.98$  to  $-0.09$ ,  $P < 0.5$ ) after buprenorphine administration (Figure 2). Highly significant heterogeneity was observed across comparison effect sizes for pain intensity ( $Q = 49.53$ ,  $P < 0.01$ ,  $I^2 = 92.99\%$ ). Based on Cohen categories, the effect size was small. Meta-analysis for the search “chronic pain and buprenorphine” produced strong evidence for a reduction of pain (SMD =  $-2.19$ , 95% CI =  $-2.88$  to  $-1.51$ ,  $P < 0.5$ ) after buprenorphine administration (Figure 3). There was moderately significant heterogeneity that was observed across comparison effect sizes for pain intensity ( $Q = 582.80$ ,  $P < 0.01$ ,  $I^2 = 97.91\%$ ). Based on Cohen categories, the effect size was moderate to large (Figure 3).

## Discussion

The prevalence of OAD is high in populations treated for chronic pain [32]. Relatedly, chronic pain is quite common in populations seeking treatment for OAD [9]. The

aim of this review was to evaluate the effectiveness of buprenorphine in reducing pain intensity in patients with and without a history of OAD. Buprenorphine’s effectiveness was evaluated in terms of improvement in pain intensity in both populations. Our review provided evidence for pain-reducing treatment effects using RCT and NRT designs for chronic pain patients with and without OAD. Unfortunately, weaknesses in the body of evidence prevent any strong conclusions. Collectively, although significant reductions in pain intensity were observed for patients with chronic noncancer pain treated with buprenorphine, the evidence for substantial analgesic benefits was significantly stronger in the studies of chronic pain patients without OAD. This accords with findings from other treatment modalities (which also suggest that pain patients with OADs derive reduced analgesic benefit from pain treatments [33]) and highlights the complexity of the co-occurrence of chronic pain and OAD. The present review was not designed to identify the mechanisms that reduce the analgesic benefit of buprenorphine in patients with OAD. Possible explanations (for the lower effect size of buprenorphine on pain intensity in patients with OADs) include elevated psychological distress in the OAD group, tolerance to the opioid agonist effects of buprenorphine in the OAD group (as suggested by the much higher daily dosages of buprenorphine in the group with OAD compared with the group without in our study), or altered central nervous system pain-processing circuitry in the OAD group [34].

Findings from this review suggest that relatively few studies have explicitly assessed pain intensity before and after buprenorphine treatment in chronic pain patients.



**Figure 3.** Forest plot demonstrating the effect sizes of changes in pain intensity from baseline to post-buprenorphine treatment in patients with chronic pain with opioid misuse.

We also identified substantial study heterogeneity, and because of this, the results of these analyses should be interpreted with caution. The studies included here varied substantially in design, as well as in the dosing and route of administration of buprenorphine (e.g., sublingual, buccal, transdermal).

Overall, our results might contribute to establishing the basis for a future interest in using buprenorphine as an analgesic, and the growing number of formulations available may facilitate the movement in this direction. Buprenorphine, as a partial  $\mu$ -agonist, has several advantages over full  $\mu$ -agonists, including potential ceiling effects on respiratory depression but not on analgesia [35], a relative lack of immunosuppressive effects [36], drug interactions [37], and cardiac effects [38]. Buprenorphine seems to be well tolerated by patients [18]; in a study included in our report, Gimbel and colleagues reported low opioid-associated gastrointestinal adverse effects (3–8%) and low discontinuation rates (5.1%) due to adverse effects in patients with buccal buprenorphine [24]. Another study included in our report [25] confirmed this finding; adverse events leading to discontinuation of treatment occurred in 2.8% and 3.2% of the patients receiving buccal buprenorphine in the titration phase and long-term treatment phase, respectively [25].

The receptor binding profile of buprenorphine is unique; it binds with high affinity to all three major opioid receptor classes ( $\mu$ -,  $\kappa$ -, and  $\delta$ -) and with lower affinity to the opioid receptor-like 1 (ORL-1) receptor [39, 40]. In contrast to long-term intake of other opioids (that upregulate  $\kappa$ -opioid receptors and dynorphin),

buprenorphine uniquely blocks  $\kappa$ -receptors and thereby reduces craving [41, 42]. In a review including 24 studies that included patients mostly with postoperative pain directly comparing buprenorphine's analgesic effect with analgesics commonly considered full agonists, buprenorphine was shown to have a comparable analgesic effect to morphine, fentanyl, sufentanil, and oxycodone [8]. Although these findings are mostly based on preclinical studies, a randomized trial that was included in our review reports similar reductions in pain from buprenorphine-naloxone and low-dose methadone [28]. Compared with full  $\mu$ -opioid receptor agonists, buprenorphine exhibits a low potential for developing tolerance and addiction. This may be partly explained by the prolonged binding of buprenorphine to  $\mu$ -opioid receptors and the activation of ORL-1 receptors [43]. The favorable safety profile of buprenorphine in terms of side effects, addiction, and overdose makes it a relatively attractive alternative for the comorbid treatment of chronic pain and OUD. Nevertheless, caution is needed when transitioning a patient from a full  $\mu$ -agonist opioid to buprenorphine, as a study included in our review indicated [30, 44–47]. Webster et al. suggest that chronic pain patients receiving around-the-clock full  $\mu$ -opioid agonists can be switched to buccal buprenorphine at  $\sim$ 50% of the full  $\mu$ -opioid agonist dose without an increased risk of opioid withdrawal or decreased pain control (70).

Several limitations should be noted when interpreting the results of the present review. Most of the studies included in part 2 (buprenorphine for chronic pain and OUD) of the current review were nonrandomized studies

that lacked a control group, thereby limiting any causal interpretations regarding buprenorphine's effects. In contrast, in part 1 of the review (buprenorphine for chronic pain without OUD), more than half of the studies (five out of nine) included a control comparison group (placebo or a different opioid). A second limitation is that some studies did not report separate pre-intervention baseline pain intensity scores for the subgroup of patients who completed the study, after excluding the patients who discontinued before the intervention. Recommendations for standardized assessments in future clinical trials can be beneficial in that data can be pooled for future meta-analyses. Finally, the literature is limited by the relatively small sample sizes and the absence of a large study that enrolled chronic pain patients with and without OUD in the same protocol (which would provide a more robust basis for direct comparison of buprenorphine's effects in these two populations).

In summary, buprenorphine appears to show some effectiveness as an analgesic in the context of chronic pain treatment, particularly in those patients with no history of OUD (who showed a moderate to large effect size on pain intensity). The small-sized effect (in a small number of studies) of buprenorphine on chronic pain in patients with a history of OUD suggests that much additional investigation in this area is warranted. We hope that the present review and meta-analysis can serve as a catalyst for further work in this important area.

## Supplementary Data

Supplementary data are available at *Pain Medicine* online.

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