Treatment of Chronic Pain With Various Buprenorphine Formulations: A Systematic Review of Clinical Studies

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Treatment of Chronic Pain With Various Buprenorphine Formulations: A Systematic Review of Clinical Studies

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Clinical studies demonstrate that buprenorphine is a pharmacologic agent that can be used for the treatment of various types of painful conditions. This study investigated the efficacy of 5 different types of buprenorphine formulations in the chronic pain population. The literature was reviewed on PubMed/MEDLINE, EMBASE, Cochrane Database, clinicaltrials.gov, and PROSPERO that dated from inception until June 30, 2017. Using the population, intervention, comparator, and outcomes method, 25 randomized controlled trials were reviewed involving 5 buprenorphine formulations in patients with chronic pain: intravenous buprenorphine, sublingual buprenorphine, sublingual buprenorphine/naloxone, buccal buprenorphine, and transdermal buprenorphine, with comparators consisting of opioid analgesics or placebo. Of the 25 studies reviewed, a total of 14 studies demonstrated clinically significant benefit with buprenorphine in the management of chronic pain: 1 study out of 6 sublingual and intravenous buprenorphine, the only sublingual buprenorphine/naloxone study, 2 out of 3 studies of buccal buprenorphine, and 10 out of 15 studies for transdermal buprenorphine showed significant reduction in pain against a comparator. No serious adverse effects were reported in any of the studies. We conclude that a transdermal buprenorphine formulation is an effective analgesic in patients with chronic pain, while buccal buprenorphine is also a promising formulation based on the limited number of studies. (Anesth Analg 2017;XXX:00–00)

Buprenorphine, a partial agonist at the μ-opioid receptor and an antagonist at the κ-opioid receptor with high affinity for both receptors, is advantageous in some patients with chronic pain who have an active or history of substance use disorders.4,5 However, opioid-tolerant patients, especially those with opioid-induced hyperalgesia, may also benefit due to “buprenorphine-induced antinociception,” presenting unique opportunities for use in the chronic pain population.1,6-7

The primary objective of this systematic review was to determine the analgesic efficacy of 5 different formulations of buprenorphine when compared with conventional pharmacological management or placebo in the chronic pain patient population. We believe that our systematic review will further contribute to the existing literature about the efficacy and safety of buprenorphine in patients with chronic pain and help guide clinicians to alternative treatments, particularly in the population with a history of substance abuse or opioid-induced hyperalgesia.

METHODS

This systematic review was conducted according to the recommendations of the Cochrane Collaboration,8 and it is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines.

Search Strategy and Study Selection

We conducted comprehensive, serial searches of the literature through June 30, 2017. The following databases were searched for English studies of human subjects: EMBASE, 1947 onward; MEDLINE, 1946 onward; MEDLINE In-Process & Other Non-Indexed Citations (all using the OvidSP Platform); Cochrane Database of Systematic Reviews; PROSPERO; and Cochrane Central Register of Controlled Trials for potential reviews or trials, respectively, that may have been published but missed during the initial search on MEDLINE and EMBASE. We also searched for randomized clinical trials.
controlled trials (RCTs) in the metaregister of controlled trials (www.clinicaltrials.gov). We restricted our search to trials involving human subjects and manuscripts published in English language. For EMBASE and MEDLINE, both controlled vocabulary terms (EMBASE-Emtree; MEDLINE-MeSH) and text-word searching were conducted for each of the following search segments: “Buprenorphine Naloxone and Analgesia,” “Buprenorphine Naloxone and Pain,” “Methadone and Buprenorphine,” “Buprenorphine and Pain,” “Buprenorphine and Analgesia,” “Buprenorphine SL and Analgesia,” “Buprenorphine SL and Pain,” “Buccal Buprenorphine and Pain,” and “Buccal Buprenorphine and Analgesia.” We complemented our search by reviewing the bibliographies of every selected article to look for possible additional articles that had not been retrieved by our electronic search. All 5 authors (R.A., A.G., S.G., A.B., and N.M.) independently evaluated titles, abstracts, and full texts according to the inclusion criteria. All instances of discordance were discussed among the investigators to reach a consensus.

Criteria for Considering Trials for This Review

Only RCTs in English language and involving human subjects were included in this review. Exclusion criteria included reviews, case reports, case series, nonhuman (animal model) studies, RCTs that did not have statistical analysis or were ongoing at the time of review, trials involving use of buprenorphine for nonchronic pain treatment, and if buprenorphine was used as either an adjunct or concurrent therapy. As a result, studies that involved use of buprenorphine as a treatment for both pain and opioid-use disorder were included if change in intensity of pain was a primary outcome in the publication. Only RCTs that involved comparison of buprenorphine against an active analgesic or placebo for treatment of chronic pain were included in this systematic review.

We prespecified eligibility criteria using the population, intervention, comparator, and outcomes approach as follows.

Participants. Only trials with participants above the age of 18 years with chronic pain (duration of at least 3 months) of any etiology but with chronic pain (and not opioid-use disorder) as the primary indication for treatment with buprenorphine were included in this systematic review.

Interventions and Comparators. Intervention was defined as buprenorphine preparation in any dosage administered through any route. Five types of buprenorphine preparations were evaluated: intravenous buprenorphine, sublingual buprenorphine, sublingual buprenorphine/naloxone, buccal buprenorphine, and transdermal delivery system (TDS) buprenorphine. Comparators were any other analgesic or placebo substance.

Outcomes. The primary outcome was analgesic efficacy as assessed by change in pain scores (visual analog or numerical rating scales) from baseline in intervention and comparator groups at least 24 hours after initiation of study treatments. Incidence and types of adverse effects were a secondary outcome of interest for this review.

Risk of Bias Assessment for Individual Trials

Two of the authors (R.A. and N.M.) independently assessed the risk of bias for each included study using the Cochrane Collaboration’s instrument for assessing the risk of bias. The risk of bias instrument assesses the following domains: generation of the allocation sequence, allocation concealment, blinding of investigators and participants, blinding of outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias that have less empirical evidence of bias but together may be considered important (unequal distribution of prognostic factors, industry funding, industry authorship, trial stopped early). Each item was classified as low, unclear, or high risk of bias. A decision to classify “overall bias” as low, unclear, or high was made by the reviewers using the following methods:

- High: Any trial with a high risk of bias listed on 3 or more domains.
- Unclear: Any trial with a high risk of bias listed on >1 but <3 domains.
- Low: Any trial with a high risk of bias on none or 1 domain and with no significant methodologic concerns that may have affected the study results.

Data Collection

The reference data, populations, and outcomes were extracted from the articles into prespecified tables using a standardized data extraction form. The data collection form was piloted tested before its use. We extracted information on studies’ general characteristics (including design, number of arms, and primary outcomes), participants (characteristics of the populations, sample size, duration, and intensity of pain), and experimental intervention (type of buprenorphine preparation, doses, and administration regimes). For continuous data (pain scores), we extracted means and standard deviations from tables or graphs provided in the publications. We also contacted authors of studies included in our systematic review when we needed more information about their analysis or reported results.

RESULTS

A total of 3168 studies were retrieved from the broad search terms used. Identifying and excluding duplicate records resulted in 2834 articles, abstracts of which were then screened and analyzed to exclude irrelevant articles, resulting in 92 studies. We then excluded a further 67 studies for the following reasons: studies were not RCTs, there was an absence of a comparator, absence of pain measurement/outcome, or there was a lack of statistical analysis. This resulted in a final number of 25 articles shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart (Supplemental Digital Content 1, Figure 1, http://links.lww.com/AA/C158). The risk of bias was assessed for each study, and a cumulative risk of bias graph was plotted. The consensus between 2 investigators regarding the study selection and the quality assessment of trials was near unanimous. Overall, the studies with acceptable methodological quality and the low risk of bias were included in this review. The methodological quality and risk of bias of the 25 studies are shown (Figure).
Data on population, intervention, comparator, and outcomes parameters were extracted, and the main features have been summarized in Tables 1–4. The sample sizes for included RCTs ranged from 12 to 749 participants. The earliest publication year was 1996 with many of the studies published in the last 10 years. The pain diagnoses included low back pain, osteoarthritis, neuropathy, and cancer-related pain. Outcomes were recorded between 6 days and 1 year after initiation of trial. Validated tools for reporting outcomes included those for measuring intensity of pain (visual analog scale [VAS], numerical and verbal rating scales, box scale-11, an 11-point Likert scale, and

![Figure.](image)

Methodological quality of the studies included in this systematic review. A, Risk of bias graph for the studies included in this review. B, Bias assessment for each study.
specific domains of the brief pain inventory and the McGill pain questionnaire). Different formulations and a range of doses of buprenorphine were used in studies included in this review. The sole study on oral buprenorphine/naloxone utilized a dose of 14.93 mg/3.73 mg, while the study on sublingual buprenorphine utilized a dose of 0.2 mg every 6–8 hours. For the studies on buccal buprenorphine formulations, the doses were either 150, 300, 450, 600, 750, and 900 µg once every 24 hours or 150, 300, or 450 µg once every 12 hours. Finally, the studies on TDS buprenorphine reported use of a range of doses from patch strengths of 5 to 70 µg/h. Comparators included placebo and or short-acting and sustained-release opioid agonists (methadone, morphine, oxycodone, tramadol, TDS fentanyl).

Of the 25 studies reviewed, 1 study out of 6 on sublingual and intravenous buprenorphine, the only study on sublingual buprenorphine/naloxone, 2 out of 3 studies on buccal buprenorphine, and 10 out of 15 studies for transdermal buprenorphine showed significant reduction in pain against a comparator. Therefore, a total of 14 studies among the 25 trials demonstrated clinically significant benefit in the management of chronic pain by a buprenorphine formulation (Tables 1–3; Supplemental Digital Content 2, Table 1, http://links.lww.com/AA/C159). The 14 studies are summarized and then divided into 2 groups based on the comparator: active analgesics or placebo (Table 4).

Of the 14 studies that showed significant pain relief, only 3 of the trials had active analgesic agents as comparators while the other 11 trials compared buprenorphine to placebo. The greatest amount of data available was for TDS buprenorphine, and only 1 of the 10 trials showed superiority of the TDS buprenorphine when compared to other analgesic agents. When compared to other pharmacotherapies, such as tramadol and immediate-release oxycodone, TDS buprenorphine was not found to be more efficacious and even inferior, respectively. However, TDS buprenorphine may be a viable analgesic option in those patients who cannot tolerate the oral route of administration, as well as in the geriatric population who are more susceptible to the adverse drug reactions related to other opioids.

Adverse effects in the TDS buprenorphine (5–20 µg) trials were consistent. Steiner et al observed during the run-in period that 55% of their total patient population experienced at least 1 adverse effect, consisting of nausea (23%), dizziness (10%), and headache in 10% or more of patients. However, during the double-blind phase, incidence of adverse effects in the randomized TDS treatment group matched placebo (55% vs 52%). In the TDS treatment group, gastrointestinal disorders (21%), administration site problems (17%), and nervous system disorders (14%) were the most commonly reported symptoms. For buccal buprenorphine (75–900 µg), Rauck et al reported that the most common adverse effects were the ones most usually associated with opioids. For the opioid-naive population, nausea was the most common adverse effect during the titration phase. With a population sample size of 749 patients, 15% discontinued medication during the open-label titration phase due to adverse effects. During the double-blind treatment phase, 17% of patients who received either buccal buprenorphine or placebo had treatment-related adverse effects, and 6% vs 3% of patients discontinued buccal buprenorphine versus placebo due to side effects, respectively.

**DISCUSSION**

This systematic review focused on the benefits, efficacy, and adverse effects of buprenorphine in the management of chronic pain, particularly in the opioid-tolerant patient population without a history of substance abuse. While a previous Cochrane database systematic review for buprenorphine for neuropathic pain was comprehensive, our systematic review encompasses the role of buprenorphine in a broader spectrum of chronic pain syndromes (cancer and noncancer). Furthermore, our review includes studies and clinical trials up to 2017; most trials included were conducted in the last 10 years, reflecting increased use and availability of various formulations of buprenorphine in recent years. The current opioid epidemic has heightened the interest in buprenorphine’s role in treating chronic pain as highlighted in the title of a publication, “Buprenorphine: new tricks for an old molecule for pain management.”

Our systematic review demonstrates strong evidence for analgesic efficacy of buprenorphine in patients with chronic pain for TDS buprenorphine (total of 10 trials were positive against placebo). TDS buprenorphine is efficacious in a wide range of chronic pain disorders. However, there was a paucity of evidence for the other formulations of buprenorphine; only 1 study among the sublingual and intravenous buprenorphine formulations showed analgesic benefit, and only 1 study on sublingual buprenorphine/naloxone and 2 studies on buccal buprenorphine reported limited efficacy.

The different formulations of buprenorphine, sublingual and intravenous, should be noted, as we reviewed 6 studies in total of these 2 routes in Table 2. Ling et al were unable to show any significant difference in analgesia between intravenous and sublingual buprenorphine/

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**Table 1. Characteristics of Included Studies That Evaluated Buprenorphine/Naloxone Formulations for Chronic Pain**

<table>
<thead>
<tr>
<th>Reference Year</th>
<th>Patient Population</th>
<th>Study Duration</th>
<th>N</th>
<th>Route and Dose</th>
<th>Comparator</th>
<th>Scale</th>
<th>Mean/Median Pain Score</th>
<th>Outcome and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neumann et al 2013</td>
<td>Chronic nonmalignant pain related to the spine or a large joint</td>
<td>6 mo</td>
<td>54</td>
<td>Average daily sublingual dose of buprenorphine/naloxone was 14.93 mg/3.73 mg</td>
<td>Oral methadone (20–60 mg; divided 3–4 times daily)</td>
<td>NRS</td>
<td>5.5 ± 1.9 after 6 mo compared to initial visit (6.3 ± 1.2)</td>
<td>There was significant difference in pain relief for both buprenorphine and methadone treatment groups (P = .043)</td>
</tr>
</tbody>
</table>

Abbreviation: NRS, numeric rating scale.
Table 2. Characteristics of Included Studies That Evaluated SL and Intravenous Buprenorphine Formulations for Chronic Pain

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Patient Population</th>
<th>Study Duration</th>
<th>N</th>
<th>Route and Dose</th>
<th>Comparator</th>
<th>Scale</th>
<th>Mean/Median Pain Score</th>
<th>Outcome and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ling et al10</td>
<td>2012</td>
<td>Patients had lingering noncancer pain</td>
<td>12 d</td>
<td>12</td>
<td>Intravenous 0.3 mg every 24 h</td>
<td>Buprenorphine (0.3 mg)/naloxone (0.02 mg)</td>
<td>NRS/BPI</td>
<td>6.17 ± 1.57</td>
<td>No significant difference between medications in pre- to postdose pain ratings</td>
</tr>
<tr>
<td>Jain et al11</td>
<td>2011</td>
<td>Forty-five treatment-seeking heroin-dependent males</td>
<td>6 d</td>
<td>45</td>
<td>SL 2 mg</td>
<td>Oral memantine 20 mg/d</td>
<td>VAS</td>
<td>VAS pain scores in the memantine group and the buprenorphine group were (+)10.00 (30–50) and (+)10.00 (−50 to +150), respectively</td>
<td>No significant difference between subjects in VAS (P &gt; .05)</td>
</tr>
<tr>
<td>James et al12</td>
<td>2010</td>
<td>Osteoarthritis pain in the hip(s) and/or knee(s)</td>
<td>28 d</td>
<td>110</td>
<td>SL buprenorphine 200 and 400 μg tablets every 24 h</td>
<td>TDS buprenorphine (5, 10, and 20 μg/h)</td>
<td>BS-11</td>
<td>Mean treatment differences (95% confidence intervals) were 0.00 (−0.68 to 0.69), −0.11 (−0.85 to 0.63), and −0.13 (−0.95 to 0.68) for the morning, midday, and evening scores, respectively.</td>
<td>There was no significant evidence for a difference in the BS-11 pain scores recorded on day 3 and day 7 for either of the treatment groups. Equivalence was shown for the 2 treatments with respect to BS-11 pain scores.</td>
</tr>
<tr>
<td>Goebel et al13</td>
<td>2008</td>
<td>Chronic pain located in the region of lower face to upper thorax, area covered by dermatomes of the maxillary branch of trigeminal nerve (excluding eyes) to T3.</td>
<td>6 d</td>
<td>18</td>
<td>Injection of 27 μg of buprenorphine in 5-mL 0.9% saline to the stellate ganglion, GLOA, and 5-mL normal saline into the buttock (intramuscular)</td>
<td>Reverse saline to the stellate plus intramuscular buprenorphine (SSB)</td>
<td>VAS</td>
<td>All patients had a median preinjection pain intensity of 6.7, before GLOA, and 6.2, before SSB. Five patients had ~50% pain over 6 d (2 patients after GLOA, 2 patients after SSB, and 1 patient after both injections).</td>
<td>Pain reported over a 6-d period (the median of all pain-diary entries within the first 6 d after injection showed no differences between the groups [GLOA: 104%, SSB: 103%])</td>
</tr>
<tr>
<td>Spacek et al14</td>
<td>2002</td>
<td>Refractory trigeminal neuralgia</td>
<td>10 d</td>
<td>19</td>
<td>Stellate ganglion injection (GLOA) consisted of verum 0.045 mg buprenorphine in 1.5-mL 0.9% NaCl</td>
<td>Placebo-GLOA of 1.5-mL 0.9% NaCl</td>
<td>VAS</td>
<td>VAS after GLOA first week Verum-GLOA group: 2.4 ± 2.3 0.9% NaCl group: 2.7 ± 2.0</td>
<td>There was a significant difference in pain relief in both verum-GLOA and placebo-GLOA interventions after the first week (P &lt; .001)</td>
</tr>
<tr>
<td>Brem et al15</td>
<td>1996</td>
<td>Cancer pain</td>
<td>Up to 6 mo</td>
<td>131</td>
<td>Buprenorphine SL 0.2 mg every 6 h to every 8 h</td>
<td>Tramadol 100 mg every 8 h to every 12 h</td>
<td>VAS</td>
<td>Posttreatment scores: tramadol, 6.09 ± 2.78; buprenorphine, 4.74 ± 2.60</td>
<td>Analgesia significantly better in the tramadol group (P &lt; .05)</td>
</tr>
</tbody>
</table>

Abbreviations: BPI, brief pain inventory; BS-11, Box scale-11; GLOA, ganglionide local opioid analgesia; NaCl, sodium chloride; NRS, numeric rating scale; SL, sublingual; SSB, stellate plus intramuscular buprenorphine; TDS, transdermal delivery system; VAS, visual analog scale.
Table 3. Characteristics of Included Studies That Evaluated Buccal Buprenorphine Formulations for Chronic Pain

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Subjects</th>
<th>Route and Dose</th>
<th>Comparator</th>
<th>Scale</th>
<th>Outcome and Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leffler et al</td>
<td>2016</td>
<td>Moderate to severe chronic low back pain</td>
<td>Buccal strengths of 150, 300, 450, 600, 750, and 900 μg, every 24 h</td>
<td>Placebo buccal film NRS</td>
<td>Placebo group 1.92 ± 1.87) and placebo NRS</td>
<td>There was statistical significant difference favoring buccal buprenorphine (P = .0032) in favor of buccal buprenorphine for analgesia.</td>
</tr>
<tr>
<td>Rauck et al</td>
<td>2016</td>
<td>Moderate to severe chronic low back pain</td>
<td>Buccal 300-μg doses, every 12 h; 75 μg twice daily, and then to 150, 300, or 450 μg twice daily</td>
<td>Placebo</td>
<td>NRS</td>
<td>There were no significant differences in pain ratings between treatments.</td>
</tr>
<tr>
<td>Poulain et al</td>
<td>2016</td>
<td>Chronic pain</td>
<td>Morphine sulfate, oxycodone, or placebo</td>
<td>NRS</td>
<td>There was no change from baseline in mean NRS scores through 9 h, followed by slight increases from 9 to 12 h that declined with the second dose.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NRS, numeric rating scale.

Pharmacokinetics and Pharmacodynamics of Buprenorphine Formulations

Transdermal Buprenorphine. The TDS route is optimal for buprenorphine due to its properties that facilitate transdermal absorption such as low molecular weight, high lipophilicity, and high potency. Consequently, among the studies we reviewed, the majority of the positive studies involved use of the TDS formulation. For instance, Poulain et al demonstrated a reduction in pain scores (from 3.5 ± 2.2 to 1.5 ± 1.5) in the group that received buprenorphine, with worsening of pain scores (from 1.5 ± 1.5 to 2.7 ± 1.9) in the placebo group. The trial by Pace et al was the only study that reported analgesic efficacy for TDS buprenorphine when compared to another opioid, 60 mg sustained-release morphine per day. Consequently, further head-to-head trials involving buprenorphine and other opioids are needed to evaluate clinical efficacy relative to the standard opioid regimen.

Buprenorphine TDS is indicated for both moderate to severe cancer pain and severe noncancer pain that is refractory to nonopioid analgesia. The transdermal formulation in the United States is currently available in 5 dosage strengths: 5, 7.5, 10, 15, and 20 μg/h. Doses > 10 μg/h have been shown to be efficacious in patients taking an oral morphine sulfate equivalent dose of < 80 mg/d. In Europe, buprenorphine TDS is available in 3 dosage strengths (35, 52.5, and 70 μg/h), each lasting 72 hours and corresponding to total daily buprenorphine doses of 0.8, 1.2, and 1.6 mg, respectively. It should be noted that for the transdermal formulation available in the United States, the effective dose range is narrow (10–20 μg/h) and the bioavailability decreases to 15% after a 7-day application. This may be advantageous as it can potentially prevent accidental overdose, in case a new patch is placed without removing the existing patch.
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Table 4. Summary of Significant Results: Nonplacebo Versus Placebo

<table>
<thead>
<tr>
<th>Buprenorphine Preparation</th>
<th>No. of Studies With Significant Clinical Benefits (Comparator Is Nonplacebo)</th>
<th>No. of Studies With Significant Clinical Benefits (Comparator Is Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine/naloxone</td>
<td>Neumann et al 9</td>
<td>None</td>
</tr>
<tr>
<td>Sublingual and intravenous injection buprenorphine</td>
<td>Spacek et al 14</td>
<td>None</td>
</tr>
<tr>
<td>Buccal buprenorphine</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Transdermal buprenorphine</td>
<td>Pace et al 19</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total studies</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

**Sublingual Buprenorphine.** Administration of buprenorphine via the sublingual route can quickly reach effective plasma concentrations (onset of effect is 30–60 minutes with a peak effect at about 90–100 minutes), but it may also result in erratic plasma concentrations, and therefore may increase the risk of adverse effects. The oral formulations of buprenorphine have low bioavailability with only 10% of the intravenous route if swallowed, and only between 30% and 50% bioavailability with the sublingual administration. The lower bioavailability of the sublingual formulation is possibly due to incomplete disintegration. Consequently, low bioavailability with oral drug formulations secondary to poor absorption from the gastrointestinal tract and high hepatic first-pass metabolism may have resulted in poor analgesic outcomes in some of the studies with sublingual buprenorphine and sublingual buprenorphine/naloxone. To address these challenges and to account for the analgesic duration of 6–8 hours, Heit and Gourlay have recommended that sublingual buprenorphine for chronic pain management should be administered 3–4 times a day for optimum analgesic effect. Nevertheless, it should be noted that Neumann et al did report statistically significant decrease in pain ($P = .043$) with sublingual buprenorphine/naloxone despite being administered once a day (average daily dose of 14.93/3.73 mg), instead of multiple doses per day. Another benefit of sublingual buprenorphine/naloxone is the reduced risk of adverse effects due to copresence of naloxone. It should be noted that methadone (the comparator analgesic agent) was also found to be effective in providing pain relief with a statistical significance ($P = .043$).

**Buccal Buprenorphine.** Buccal buprenorphine has been introduced and approved by the Food and Drug Administration in 2015 for the management of chronic pain. It is composed of flexible, water-soluble polymeric films that stick to the buccal mucosa and dissolve within a few minutes. The bioavailability of this formulation is 46%–65%, and it is useful in patients who are taking over 80 mg oral morphine sulfate equivalent per day for pain management. This film form was developed to provide rapid absorption, flexible titration, and to expand the range of doses. While only a limited number of studies (3) were reviewed in our study, this formulation is a promising analgesic agent as per the findings of 2 large trials by Gimbel et al (491 patients) and Rauck et al (749 patients). These 2 studies were able to clearly demonstrate statistically significant reduction in pain scores in patients with chronic lower back pain when compared with a placebo.

**Noncancer Pain Comparators**

Several trials in this review included buprenorphine in comparison to a placebo for a variety of noncancer chronic pain conditions, ranging from osteoarthritis to peripheral neuropathy. For chronic lower back pain, buccal buprenorphine performed well when compared to a placebo in both studies by Gimbel et al and Rauck et al, with the dose ranges being approximately similar (150–900 μg). In these 2 studies, statistically significant values of $P < .001$ and $P = .0012$ were reported, respectively, whereas the study by Webster et al did not show any benefit of buccal buprenorphine when compared to an active pharmacological agent (morphine sulfate and oxycodone). For the TDS buprenorphine formulations, a study by Steiner et al showed statistically significant lower pain scores in patients with moderate to severe chronic low back pain ($P = .010$). Similar positive results against a placebo when administering TDS buprenorphine were also shown in the study by Gordon et al for chronic back pain ($P = .022$) and in the study by Munera et al for osteoarthritis ($P = .036$). It should be noted that a result with statistical significance does not always correlate with clinical significance. The study by Steiner et al showed a statistically significant difference in that TDS buprenorphine (20 μg/h) was inferior when compared to oxycodone ($P < .001$). However, the comparison of the pain scores did not appear to reach clinical significance ($3.35$ vs $3.26$, respectively). Finally, Mitra et al showed that TDS buprenorphine was not inferior to TDS fentanyl, and therefore, TDS buprenorphine may be an alternative to TDS fentanyl for the patients in whom the transdermal route is preferred.

**Cancer Pain Comparators**

Throughout our review, many trials included analysis of studies involving patients who had chronic cancer pain. One of the sublingual buprenorphine studies by Brema et al involved a cancer patient population, providing...
evidence for tramadol being superior to buprenorphine for pain management. A few studies showed TDS buprenorphine as a better alternative including the study by Poulain et al, which investigated over 188 patients and showed a statistically significant difference ($P = .0003$) in analgesia when the 70 $\mu$g/h patch was compared with placebo. Robust performance of TDS buprenorphine against placebo was also shown in the study by Sittl et al, with a statistically significant difference of $P = .032$. Stronger evidence for the efficacy of TDS buprenorphine in the cancer population was shown in the study by Pace et al, comparing 35 $\mu$g/h patch with 60 mg/d of sustained-release morphine that showed a statistically significant difference in favor of buprenorphine ($P = .01$). However, the study by Corli et al that compared TDS buprenorphine with oral morphine did not show any statistically significant difference between the two agents for management of chronic cancer pain. While there is strong evidence showing the superiority of TDS buprenorphine when compared to a placebo, the results are more limited and mixed for use of TDS buprenorphine in the cancer patient population when an active analgesic agent is used as a comparator.

Comparison of Buprenorphine and Methadone

Buprenorphine has been shown to effectively reduce illicit opioid use and mortality after overdose. Naloxone is combined with buprenorphine in some preparations to further reduce the risk of opioid abuse, as well as to avoid withdrawal symptoms. The alternative to buprenorphine for this application is methadone, which is a racemic mixture of 2 stereoisomers ($l$- and $d$-methadone) with $l$-methadone being 8–50 times more potent than $d$-methadone. It is a full agonist at the $\mu$-opioid receptor and an antagonist at the $N$-methyl-$d$-aspartate receptor. Although methadone is an effective analgesic for opioid-dependent patients, it has a narrow therapeutic window. On the other hand, buprenorphine demonstrates a ceiling effect which in turn reduces the probability of respiratory depression and deaths related to overdose. Therefore, buprenorphine has a better safety profile as compared to methadone, and thus may make it a safer option for the management of pain in opioid-tolerant patients. Furthermore, buprenorphine was previously thought to have a ceiling on its analgesic effects because of antagonism at the $\kappa$ receptors, but this theory has been invalidated. Our review included a study by Neumann et al who performed a head-to-head trial of buprenorphine/naloxone versus oral methadone for chronic nonmalignant pain, with both pharmacologic agents showing a statistically significant decrease in pain scores ($P = .043$). Consequently, this study suggests the benefits of buprenorphine/naloxone for chronic pain management in the substance abuse population. Finally, one should note that for the management of patients with a history of substance abuse, buprenorphine can be initiated and maintained in an office-based setting, as opposed to methadone that is initiated and maintained through a federally licensed clinic in the United States.

Limitations

There are several limitations of this systematic review. The trials reviewed in this study utilized a variety of pain rating scales and thus potentially provide inconsistent analysis of primary outcomes. Furthermore, there were various types of pain syndromes lasting >3 months that are evaluated for this systematic review; therefore, a significant heterogeneity exists in pain characteristics of the study populations. Both study dosage and clinical dosage with route of administration were delineated in this systematic review; however, the studies were diverse in their dosing strategy and the route of administration. Ultimately, there was difficulty in comparing the findings of the trials to one another, and thereby our analysis becomes descriptive in nature.

Regional differences in buprenorphine formulation availability also influenced our data analysis. For example, it should be noted that in the EU, much higher doses are used with the transdermal system and the patches are replaced every 3 days versus every 7 days in the United States. This difference in clinical practice may also have impacted the results, and this should be strongly considered by physicians prescribing TDS buprenorphine for chronic pain. These reasons also explain our inability to pool results from individual trials into a meta-analysis to obtain summary statistics.

To conclude, this systematic review provides evidence that the transdermal buprenorphine formulation is an effective analgesic in patients with chronic pain when compared to placebo, while buccal buprenorphine is also a promising formulation based on the limited number of studies.

More importantly, for patient populations who struggle with substance dependence and opioid abuse problems, buprenorphine may achieve better analgesic outcomes, while also being helpful to patients and their health care providers in concurrently making determined efforts to deal with addiction and substance use problems.

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REFERENCES


