Evaluation of Buprenorphine Rotation in Patients Receiving Long-term Opioids for Chronic Pain
A Systematic Review

Victoria D. Powell, MD; Jack M. Rosenberg, MD; Avani Yaganti, BS; Claire Garpestad, MD; Pooja Lagisetty, MD, MSc; Carol Shannon, MPH; Maria J. Silveira, MD, MA, MPH

Abstract

IMPORTANCE Individuals with chronic pain who use long-term opioid therapy (LTOT) are at risk of opioid use disorder and other harmful outcomes. Rotation to buprenorphine may be considered, but the outcomes of such rotation in this population have not been systematically reviewed.

OBJECTIVE To synthesize the evidence on rotation to buprenorphine from full μ-opioid receptor agonists among individuals with chronic pain who were receiving LTOT, including the outcomes of precipitated opioid withdrawal, pain intensity, pain interference, treatment success, adverse events or adverse effects, mental health condition, and health care use.

EVIDENCE REVIEW PubMed, CINAHL, Embase, and PsycInfo were searched from inception through November 3, 2020, for peer-reviewed original English-language research that reported the prespecified outcomes of rotation from prescribed long-term opioids to buprenorphine among individuals with chronic pain. Two independent reviewers extracted data as well as assessed risk of bias and study quality according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines. Quality of evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

FINDINGS A total of 22 studies were analyzed, of which 5 (22.7%) were randomized clinical trials, 7 (31.8%) were case-control or cohort studies, and 10 (45.5%) were uncontrolled pre-post studies, which involved 1616 unique participants (675 female [41.8%] and 941 male [58.2%] individuals). Six of the 22 studies (27.3%) were primary or secondary analyses of a large randomized clinical trial. Participants had diverse pain and opioid use histories. Rationale for buprenorphine rotation included inadequate analgesia, intolerable adverse effects, risky opioid regimens (eg, high dose and/or sedative coprescriptions), and aberrant opioid use. Most protocols were adapted from protocols for initiating treatment in patients with opioid use disorder and used buccal or sublingual buprenorphine. Very low-quality evidence suggested that buprenorphine rotation was associated with maintained or improved analgesia, with a low risk of precipitating opioid withdrawal. Steady-dose buprenorphine was better tolerated than tapered-dose buprenorphine. Adverse effects were manageable, and severe adverse events were rare. Only 2 studies evaluated mental health outcomes, but none evaluated health care use. Limitations included a high risk of bias in most studies.

CONCLUSIONS AND RELEVANCE In this systematic review, buprenorphine was associated with reduced chronic pain intensity without precipitating opioid withdrawal in individuals with chronic pain who were receiving LTOT. Future studies are necessary to ascertain the ideal starting dose, formulation, and administration frequency of buprenorphine as well as the best approach to buprenorphine rotation.


Key Points

Question Is rotation to buprenorphine from full μ-opioid receptor agonists associated with improved pain-related outcomes and acceptable adverse effects in patients with chronic pain and long-term use of opioids?

Findings In this systematic review of 22 studies that addressed prespecified outcomes of rotation to buprenorphine, low-quality evidence suggested that buprenorphine rotation was associated with reduced pain without precipitating opioid withdrawal or other serious adverse effects.

Meaning These findings suggest that buprenorphine rotation may be a viable option for mitigating the harms of long-term opioid therapy in individuals with chronic pain who were receiving unsafe opioid analgesic regimens; further studies are needed to examine the best way to accomplish buprenorphine rotation.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

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Introduction

Some individuals with chronic pain who use long-term opioid therapy (LTOT) have reported modest improvements in pain and functioning\(^1,^2\); however, LTOT confers risks, including opioid misuse, suppression of immune and endocrine function, and accidental overdose.\(^2,^3\) When risks outweigh benefits, tapering or discontinuing LTOT is recommended.\(^4\) In practice, however, tapering is challenging\(^7,^8\) and may result in increased pain and psychological distress.\(^9,^10\) One possible alternative to tapering LTOT is rotation to buprenorphine.\(^8,^11\)

As a partial \(\mu\)-opioid receptor (MOR) agonist, buprenorphine is associated with less respiratory depression, fatal overdose, and overall mortality\(^12-17\) as well as fewer adverse effects than full MOR agonists (ie, morphine sulfate or oxycodone hydrochloride).\(^18-22\) Drug clearance does not change with age, renal impairment, or mild hepatic impairment.\(^23-25\) These properties make buprenorphine an attractive replacement for other opioids. However, rotation to buprenorphine is not without risk.

Buprenorphine has the potential to precipitate severe opioid withdrawal because of its high MOR affinity but partial agonist activity.\(^26\) Older data that showed a ceiling on certain subjective outcomes of buprenorphine\(^13\) have raised concern that rotation to buprenorphine could theoretically worsen pain for individuals who are benefiting from full MOR agonists for analgesia, even though more recent data suggest otherwise.\(^27\) The risks of buprenorphine have been well established in patients with opioid use disorder (OUD) without chronic pain, and the risks primarily include precipitated opioid withdrawal and potential for misuse and diversion.\(^26\) It is hypothesized that these risks would be similar in patients with chronic pain who were prescribed LTOT. However, this hypothesis has not been well characterized.

Moreover, little guidance is currently available on how to conduct such a rotation in this population; protocols developed for individuals with OUD may be inappropriate. Therefore, we conducted a systematic review of the literature to synthesize the evidence on rotation to buprenorphine from full MOR agonists among individuals with chronic pain receiving LTOT, including the outcomes of precipitated opioid withdrawal, pain intensity, pain interference, treatment success, adverse events (AEs) or adverse effects, mental health condition, and health care use.

Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline. One of us (C.S.) searched MEDLINE (PubMed), CINAHL, Embase, and PsycInfo from inception to November 3, 2020, for peer-reviewed, original English-language research that addressed the prespecified outcomes of rotation to buprenorphine from prescribed long-term opioids among individuals with chronic pain. We used the following concepts: chronic pain, opioids, buprenorphine, and pain management (eAppendix in the Supplement). Articles were exported to DistillerSR software (Evidence Partners Incorporated). The systematic review protocol was registered in PROSPERO (CRD42020173272). This study was exempt from institutional review board in accordance with §46.104 (d)(3)(i)(A) of the Basic US Department of Health and Human Services Policy for Protection of Human Research Subjects,\(^28\) because it used deidentified, publicly available data.

Study Eligibility and Selection

Every level of the articles required the input of 2 reviewers (including V.D.P., J.M.R., M.J.S., A.Y., and C.G.), who made the decision on study progression. Inclusion criteria were studies (1) that enrolled participants who had chronic pain, were prescribed full MOR opioids (eg, morphine and oxycodone) for pain on most of the past 90 days, and were initiated on buprenorphine and (2) that reported prespecified outcomes of interest (eFigure in the Supplement). It is challenging to distinguish LTOT-induced physical dependence or tolerance to opioids from OUD that developed from prescription opioid use.\(^29,^30\) Discrimination is further complicated by the removal of dependence and tolerance...
from the OUD diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). For these reasons, the association between LTOT for chronic pain and OUD is complex. Thus, we included studies of individuals with chronic pain who were prescribed any full MOR agonist for the long term, regardless of the presence of OUD diagnosis. We excluded studies whose participants primarily consumed nonprescribed opioids.

Data Extraction, Quality Assessment, and Synthesis
Data extracted included study design, pain characteristics, length of time using opioids, and baseline opioid dose. Outcomes of rotation to buprenorphine included precipitated opioid withdrawal, pain intensity or severity, pain interference, treatment success (eg, completion of protocol, willingness to continue buprenorphine long term, and reduced interest in additional opioids), mental health condition (eg, depression and insomnia), AEs or adverse effects, and health care use (eg, hospitalizations and outpatient visits). We focused on withdrawal symptoms precipitated by initiation of buprenorphine rather than by discontinuation of the original opioid (if that distinction could be made). We also extracted details regarding buprenorphine conversion protocols, including length of time between the most recent baseline opioid dose and the initial buprenorphine administration, dose, formulation, and frequency (eg, twice daily).

Risk of bias and study quality were assessed using the Cochrane Collaboration tool for randomized clinical trials (RCTs) and the Newcastle-Ottawa Scale for cohort and case-control studies. All uncontrolled observational studies (ie, pre-post studies) were considered to have inherently high risk of bias. Data were synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for each outcome. Heterogeneity precluded quantitative meta-analysis.

Results
A total of 2196 unique publications were identified through literature search, of which 128 full-text articles met the initial inclusion criteria. Of the 128 articles, 22 qualified for inclusion in this study (Figure). These articles represented 5 RCTs (22.7%), 7 case-control or cohort studies (31.8%), and 10 uncontrolled pre-post studies (45.5%), which involved a total of 1642

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**Figure. PRISMA Study Flow Diagram**

2248 Records identified through database

52 Duplicates removed

2196 Screened

2068 Excluded

1371 Involved participants who did not have chronic pain

84 Involved participants who were not prescribed LTOT at baseline

613 Did not evaluate rotation to buprenorphine

128 Full-text articles assessed for eligibility

106 Excluded

18 Had an ineligible study type

1 Had no patient-level data

87 Were not an interventional or observational study evaluating rotation to buprenorphine in target population

22 Included

LTOT indicates long-term opioid therapy.
unique participants (Table 1). However, Roux et al.\textsuperscript{36} randomized 51 participants but included only 25 in their analysis, decreasing the total number of participants to 1616 (675 female [41.8%] and 941 male [58.2%] individuals). Six of the 22 key studies (27.3%)\textsuperscript{38,41-45} were primary or secondary analyses of the Prescription Opioid Addiction Treatment Study (POATS).\textsuperscript{56}

Full study details are reported in eTable 1 in the Supplement, details of GRADE scoring are reported in eTable 2 in the Supplement, and details of the risk-of-bias assessment are shown in eTables 3 to 5 in the Supplement. The summary of findings and risk-of-bias assessment is presented in Table 2.

**Study Populations**

Identified studies included participants with mostly chronic musculoskeletal pain but also neuropathic pain and fibromyalgia. In general, participants had diverse pain and opioid use histories. One study exclusively focused on those with chronic cancer pain,\textsuperscript{46} whereas several studies excluded those with cancer.\textsuperscript{35,36,47,48} Participants were rotated to buprenorphine for various indications, including inadequate analgesia with escalating opioid doses, intolerable adverse effects, and risky regimens (eg, high dose and/or coprescription with benzodiazepines).\textsuperscript{39,40,46,47,49-53} Other reasons included aberrant opioid use.\textsuperscript{35-38,48,54,55}

Opioid use disorder was present in some participants in 13 of 22 studies (59.1%),\textsuperscript{35-38,41-45,47,48} whereas in 4 of 22 studies (18.2%)\textsuperscript{27,39,40,46,49-51,53} OUD was an exclusion criterion; however, in 2 of these studies, participants either had some aberrant opioid-related behavior\textsuperscript{56} or were opioid dependent by naloxone challenge.\textsuperscript{27} Although OUD presence was unspecified in 5 of 22 studies (22.7%), problematic behavior or opioid dependence was noted, even when participants used opioids exactly as prescribed.\textsuperscript{55} The baseline daily opioid doses were highly variable (total range, 10-3200 oral morphine milligram equivalents [MMEs]; mean daily dose range, 60-500 MME). A daily dose greater than 1000 MME was prescribed to some individuals in several studies.\textsuperscript{39,40,50,55}

**Rotation Protocols**

Buprenorphine rotation protocols were diverse. Of the 17 unique protocols that were identified, 9 were adaptations of protocols that were originally intended for buprenorphine induction in individuals with OUD without chronic pain. These 9 protocols required the presence of mild opioid withdrawal symptoms before the first buprenorphine dose and/or low starting doses, reassessment of withdrawal symptoms, and additional dose administration if needed.\textsuperscript{35,37,38,40,48-50,52,54} Eight protocols instructed individuals to stop opioids 8 to 24 hours before the first buprenorphine dose,\textsuperscript{27,38,40,48-50,52,53} and 3 protocols required an overnight waiting period.\textsuperscript{35,37,54} Individuals who were switching from methadone hydrochloride or transdermal fentanyl were instructed to wait longer (about 36-72 hours).\textsuperscript{38,47,50,54}

In 2 protocols, participants were randomized to structured buprenorphine tapering conditions\textsuperscript{35,56}; in 1 study, participants were allowed to switch to the steady-dose group if they could not tolerate the tapering.\textsuperscript{35} Another protocol required that patients were unable to taper their previous opioid use before being offered buprenorphine rotation.\textsuperscript{40} In 10 of 14 protocols without a structured tapering condition, rotation to buprenorphine was reported as completely voluntary.\textsuperscript{27,36,39,46,47,49,50,52,54,55} For the 4 remaining protocols, it was not specified whether rotation was voluntary or a contingency of ongoing treatment.\textsuperscript{37,48,51,53}

Buccal or sublingual buprenorphine was used exclusively in 13 protocols, often in combination with naloxone hydrochloride dihydrate.\textsuperscript{27,35,40,48-50,52,54,55} Transdermal buprenorphine was used exclusively in 2 protocols.\textsuperscript{46,51} Two protocols provided multiple buprenorphine formulations.\textsuperscript{47,53} Buprenorphine sublingual or buccal dosing varied widely, from a first-day total dose of 600 μg to a maximum possible dose of 32 mg.\textsuperscript{49,50} Nine protocols divided administration into 2 to 4 doses per day.\textsuperscript{27,35,37,39,46,47,48,52,54} Transdermal buprenorphine dosing also varied widely, from 5 μg/h to 140 μg/h.\textsuperscript{51} The study by Tang et al.\textsuperscript{53} applied a microdose approach to minimize anxiety and withdrawal...
<table>
<thead>
<tr>
<th>Source</th>
<th>Setting and select inclusion criteria</th>
<th>Design</th>
<th>Buprenorphine formulation</th>
<th>Sample size, including control participants (if any)</th>
<th>ROB or quality assessment (instrument used)</th>
<th>Outcomes</th>
<th>Mental health condition</th>
<th>Treatment success</th>
<th>Precipitated opioid withdrawal</th>
<th>Pain interference</th>
<th>Pain intensity or severity</th>
<th>Adverse effects or adverse events</th>
<th>Sample size, including control participants (if any)</th>
</tr>
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<tbody>
<tr>
<td>Aurilio et al,46 2009</td>
<td>Outpatient; participants had chronic cancer pain with inadequate analgesia and intolerable opioid adverse effects; no SUD</td>
<td>Uncontrolled pre-post study</td>
<td>Transdermal patch</td>
<td>32</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>6 of 9 (NOS)</td>
</tr>
<tr>
<td>Baron et al,39 2006</td>
<td>Inpatient setting for detoxification and/or buprenorphine initiation and then outpatient follow-up; participants had inadequate analgesia from current opioid regimen; no concern for overdose, abuse, or addiction</td>
<td>Cohort study</td>
<td>Sublingual without naloxone hydrochloride dihydrate</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>Berland et al,47 2013</td>
<td>Two-center inpatient or outpatient setting for buprenorphine initiation and then outpatient follow-up; participants had worsening pain and function despite increasing long-term opioid doses; 18 participants (24%) had &quot;concern for addiction&quot;</td>
<td>Uncontrolled pre-post study</td>
<td>Combination of formulations</td>
<td>76</td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Blondell et al,35 2010</td>
<td>Inpatient setting for buprenorphine initiation and stabilization and then outpatient follow-up; participants had chronic, nonmalignant pain and met DSM-IV criteria for opioid dependence to prescribed opioids</td>
<td>RCT</td>
<td>Sublingual tab or film with naloxone</td>
<td>12</td>
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<td>Yes</td>
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<tr>
<td>Daitch et al,49 2012</td>
<td>Single-center pain clinic; all participants had inadequately controlled or worsening chronic pain and receiving LTOT</td>
<td>Uncontrolled pre-post study</td>
<td>Sublingual tab or film with naloxone</td>
<td>104</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
<td>Yes</td>
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<tr>
<td>Daitch et al,50 2014</td>
<td>Single-center pain clinic; all participants had high-dose opioids prescription (≥200 MME) for chronic pain</td>
<td>Uncontrolled pre-post study</td>
<td>Sublingual without naloxone</td>
<td>35</td>
<td>Yes</td>
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<td>NA</td>
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<td>Freye et al,33 2007</td>
<td>Mixed setting; all participants were prescribed &gt;120 mg morphine sulfate/d with inadequate analgesia and/or severe adverse effects</td>
<td>Uncontrolled pre-post study</td>
<td>Transdermal patch</td>
<td>42</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
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<td>Malinsoff et al,52 2005</td>
<td>Single-center pain clinic; all participants had worsening chronic pain despite escalating opioid doses; 8.4% of participants met DSM-IV criteria for opioid dependence diagnosis</td>
<td>Uncontrolled pre-post study</td>
<td>Sublingual tab or film with naloxone</td>
<td>95</td>
<td>Yes</td>
<td>NA</td>
<td>NA</td>
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<td>Yes</td>
<td>NA</td>
<td>Inherently high ROB attributed to study design</td>
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<tr>
<td>Neumann et al,14 2020</td>
<td>Primary care-like outpatient; all participants had postsurgical chronic back pain and met DSM-IV criteria for opioid dependence to prescribed opioids</td>
<td>RCT</td>
<td>Sublingual tab or film with naloxone</td>
<td>19</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>High (Cochrane Collaboration tool)</td>
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<td>Pade et al,48 2012</td>
<td>Specialty single-center clinic; participants were veterans who were referred to the clinic for combined chronic pain, high-risk opioid use (ie, high dose or combined with sedating medications), and/or co-occurring SUD</td>
<td>Uncontrolled pre-post study</td>
<td>Sublingual tab or film with naloxone</td>
<td>143</td>
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<td>NA</td>
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<tr>
<td>Rosenblum et al,54 2012</td>
<td>Outpatient single-center pain clinic; participants with chronic pain were prescribed LTOT, all participants had aberrant opioid-related behavior but did not meet current DSM-IV criteria for any SUD diagnosis</td>
<td>Uncontrolled pre-post study</td>
<td>Sublingual tab or film with naloxone</td>
<td>12</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Inherently high ROB attributed to study design</td>
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</table>
| Roux et al,36 2013 | Inpatient research unit; all participants had chronic, nonmalignant pain and met DSM-IV criteria for opioid dependence diagnosis but were not seeking treatment | RCT | Sublingual tab or film with naloxone | 51 | Yes | NA | Yes | Yes | Yes | Yes | NA | High (Cochrane Collaboration tool) | (continued)
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<th>Design</th>
<th>Sample size, including control participants (if any)</th>
<th>Pretreatment</th>
<th>Buprenorphine formulation</th>
<th>ROB or quality assessment (instrument used)</th>
<th>Treatment success</th>
<th>Adverse events or adverse reactions</th>
<th>Mental or ROB or quality assessment (instrument used)</th>
<th>ROB attributed to study design</th>
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<tr>
<td>Streltzer et al,55 2015</td>
<td>Outpatient single-center psychiatry clinics in pain treatment</td>
<td>Case-control study</td>
<td>43</td>
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<td>NA</td>
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<td>Sturgeon et al,56 2015</td>
<td>Outpatient single-center specialty opioid refill clinic for individuals with chronic pain who were prescribed high dose of LTOT and referred by primary care for difficult-to-control chronic pain; all participants met DSM-IV criteria for opioid dependence diagnosis but frequently took opioids as prescribed</td>
<td>Case-control study</td>
<td>39</td>
<td>Yes</td>
<td>No</td>
<td>NA</td>
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<td>Yes</td>
<td>NA</td>
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<td>Tang et al,57 2016</td>
<td>Single-center inpatient setting in which individuals with chronic pain who were initiated on buprenorphine while hospitalized and followed up as outpatients; all participants had either OUD or chronic pain–related opioid dependence</td>
<td>Case-control study</td>
<td>23</td>
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<td>NA</td>
<td>Yes</td>
<td>Yes</td>
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<td>Griffin et al,58 2016</td>
<td>Secondary analysis of POATS; limited to participants with chronic pain who participated in the extended, 12-wk buprenorphine treatment and who met the inclusion criteria</td>
<td>Case-control study</td>
<td>148</td>
<td>Yes</td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
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<td>Webster et al,27 2016</td>
<td>Secondary analysis of POATS; limited to participants with chronic pain who participated in the extended, 12-wk buprenorphine treatment and who met the inclusion criteria</td>
<td>Case-control study</td>
<td>360</td>
<td>NA</td>
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<td>Yes</td>
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<td>Weiss et al,43 2017</td>
<td>Secondary analysis of POATS; limited to participants with chronic pain who participated in the extended, 12-wk buprenorphine treatment and who met the inclusion criteria</td>
<td>Case-control study</td>
<td>125</td>
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<td>7 of 9 (NOS)</td>
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<td>Worley et al,42 2017</td>
<td>Secondary analysis of POATS; limited to participants with chronic pain who participated in the extended, 12-wk buprenorphine treatment and who met the inclusion criteria</td>
<td>Case-control study</td>
<td>149</td>
<td>Yes</td>
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<td>Weiss et al,44 2015</td>
<td>Secondary analysis of POATS; limited to participants with chronic pain who participated in the extended, 12-wk buprenorphine treatment and who met the inclusion criteria</td>
<td>Case-control study</td>
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<td>NA</td>
<td>Yes</td>
<td>Yes</td>
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</tbody>
</table>

Abbreviations: DSM-IV, Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition); LTOT, long-term opioid therapy; OUD, opioid use disorder; POATS, Prescription Opioid Addictio Treatment Study; RCT, randomized controlled trial; ROB, risk of bias; SUD, substance use disorder.

Primary analysis was based on Weiss et al,43 other studies were secondary analyses that met the inclusion criteria.

* Cochrane Collaboration tool assesses the ROB (range: low, unclear, or high) in 6 domains (selection, performance, detection, attrition, reporting, and other). Overall ROB was scored from some concerns to high, with more domains that are scored high-risk indicating higher overall ROB.

** NOS case-control and cohort studies score range 0-9, with higher scores indicating less ROB.
symptoms, whereby a lower-dose transdermal formulation of buprenorphine served as a bridge to higher sublingual doses. Ten protocols allowed additional medication to ease symptoms of withdrawal, although specific medications varied. 27-35-37,39,40,46,47,50,54 eTable 6 in the Supplement describes the buprenorphine rotation protocols.

Precipitated Opioid Withdrawal

Precipitated opioid withdrawal (defined as worsening withdrawal symptoms after receipt of the first dose of buprenorphine) was rare, according to very low- to low-quality evidence. The 7 studies that examined this outcome consisted of 2 small RCTs, 27,36 1 with a case-control design (secondary analysis of a large RCT), 41 and 4 uncontrolled pre-post studies. 47,50,53,54 Withdrawal symptoms were measured in 6 of 7 studies using the Clinical Opiate Withdrawal Scale (score ranges: 13-24, indicating moderate withdrawal; 25-36, indicating moderately severe withdrawal; and >36, indicating severe withdrawal 52) or the Subjective Opiate Withdrawal Scale (score ranges: 1-10, indicating mild withdrawal; 11-20, indicating moderate withdrawal; and 21-30 indicating severe withdrawal 58). Symptoms were typically measured within an hour before or after induction; 1 study took multiple measurements for the 12 hours after buprenorphine was initiated. 27

The incidence of precipitated withdrawal ranged from 3% to 6%. 27,41 Assessed with the Clinical Opiate Withdrawal Scale, the mean severity was in the low to moderate range (mean [SD], 13.6 [2.9]). 41 The risk of withdrawal symptoms was greater when baseline opioid dose was higher. 50,54 The specific full MOR agonist or its formulation (extended release vs immediate release) was not associated with withdrawal symptoms. 41

| Table 2. Summary of Findings and Grading of Recommendations Assessment, Development and Evaluation (GRADE) 

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>Study design (No. of studies)</th>
<th>GRADE score b</th>
<th>Results</th>
</tr>
</thead>
</table>
| Precipitated opioid withdrawal | 7 | RCT (n = 2)27,36 | Low | • Precipitated opioid withdrawal was rare (incidence of 3%-6%) and was generally mild when present
• In a few cases, withdrawal was severe; risk appeared to be higher when participants used high opioid doses before rotation
• Most studies required the presence of mild opioid withdrawal before induction with buprenorphine
• Heterogeneity was observed in assessment of withdrawal and study populations |
| Pain intensity or severity | 17 | RCT (n = 4)27,35-37 | Low | • Improved analgesia was observed after rotation in 12 of 17 studies
• Effect size was attenuated in studies with control groups
• Evidence of dose-response was found (higher buprenorphine doses were associated with better pain control)
• Analgesic effect may be attenuated in those who used high doses before switching
• Heterogeneity of measurement (timing and instruments), study populations, and rationale for rotation were observed |
| Pain interference | 4 | RCT (n = 2)35,37 | Very low | • Improvement in function observed in some individuals after rotation
• Heterogeneity was observed in study populations and instruments measuring function |
| Treatment success: completion of protocol or continuation of treatment | 14 | RCT (n = 5)27,35-38 | Very low | • Protocol completion rates and willingness to continue in treatment were higher when buprenorphine was not tapered off
• Retention rates ranged from 33% to 93%
• Follow-up periods were often nonsystematic outside of RCTs |
| Adverse effects or adverse events | 10 | RCT (n = 4)27,36-38 | Very low | • Adverse effects were common, usually mild, and similar to other opioids
• Occasionally, adverse effects were severe and required drug discontinuation
• No deaths or overdoses were attributed to buprenorphine in any study |
| Mental health condition | 2 | RCT (n = 1)37 | Very low | • One RCT found improvement in depressive symptoms at 6 months; 1 uncontrolled study found improvement in sleep quality |
| Health care use | 0 | NA | NA | No studies examined this outcome |

Abbreviations: NA, not applicable; RCT, randomized clinical trial.

* Controlled observational studies included cohort and case-control study designs.

b GRADE score range: very low to high, with higher scores indicating higher-quality body of evidence.
Pain Severity and Interference

Rotation to buprenorphine was associated with decreased pain severity in 12 of 17 studies (70.6%).35,36,42,43,46-52,54 For example, Roux et al.36 found that higher doses of buprenorphine were associated with better pain control among participants. Under the highest dose condition (16 mg vs 2 mg), the McGill Pain Questionnaire scores significantly decreased (odds ratio, 0.42; 95% CI, 0.20-0.90).36 Under any dose, the median McGill Pain Questionnaire score decreased from 38 to 21 (P < .001).36 In the remaining 5 of 17 studies, no association was found between buprenorphine and pain.27,37,39,40,44 It was suggested that individuals who were rotating from higher doses (>200 MME) of full MOR agonists experienced less analgesia after rotation to buprenorphine; however, the evidence was very low quality.49,54

The evidence supporting an association between buprenorphine and pain intensity was very low to low quality. The 17 studies that examined this outcome included 4 small RCTs,27,35-37 5 controlled observational studies,39,40,42-44 and 8 uncontrolled observational studies.46-52,54 Substantial heterogeneity in timing of pain assessment was found, with some studies assessing pain immediately after buprenorphine was administered27,36 and other studies assessing pain only at the end of the study period37,49,50 or after buprenorphine was discontinued.39 Only 7 studies used detailed, validated instruments, such as the Brief Pain Inventory37,42-44,54 and McGill Pain Questionnaire.36,46 Other studies used unidimensional pain assessments, such as the visual analog scale or numeric rating scale,27,39,40,48,50,52 or unvalidated measures.35,47,51

Pain interference may decrease after rotation to buprenorphine, but only 4 studies examined this outcome and all had high risk of bias.35,37,47,54 Neumann et al.37 found a 21.4% improvement in self-reported function overall but was underpowered to detect a difference that was specific to the buprenorphine group. Studies used varied measures of pain interference. One small RCT used the Roland-Morris Disability Questionnaire,37 1 observational study used the Brief Pain Inventory functional subscale,54 and 2 studies used nonvalidated measures.35,47 Follow-up periods and assessment timing also varied. Overall, the evidence quality was very low.

Treatment Success

The evidence suggested that rotation to buprenorphine can be accomplished successfully in participants with chronic pain who were receiving LTOT.27,35-38,40,42,48,52,53,55 Success rates were higher when buprenorphine was used long term (53%-83%)35,37 rather than tapered off (0%-49%).35,38 Blondell et al.37 found that no participants in the tapering group of a small RCT were able to complete the taper, whereas most participants in the steady-dose group completed the prespecified follow-up period. Similarly, the POATS38 and subsequent secondary analysis42 found that participants with chronic pain were less likely to use additional opioids during the steady-dose phase than after being tapered off of buprenorphine, especially if their pain was controlled with buprenorphine.

Most studies that examined the success of buprenorphine rotation were of very low quality. The RCTs found high rates of protocol completion,27,36,38 willingness to continue using buprenorphine for the long term,35,37 and reduced need for additional opioids while receiving steady doses of buprenorphine.36,38 These studies were all small, with the exception of the POATS.38 Studies had variable and often nonsystematic follow-up periods, which precluded the rigorous assessment of protocol completion or continuation of treatment. Substantial indirectness was found across the body of evidence, with an assortment of primary outcomes, study populations, and length of time that buprenorphine was administered.

Adverse Events or Adverse Effects

Rotation to buprenorphine was associated with little harm to patients, as suggested by the 4 RCTs27,36-38 and 6 uncontrolled observational studies46,47,49,51,52,54 that reported AEs and/or adverse effects. The most common adverse effects included headache, gastrointestinal symptoms (i.e., nausea or vomiting, constipation, and appetite changes), lightheadedness or dizziness, sedation, and
Skin irritation was common in participants who were using transdermal buprenorphine.\textsuperscript{51} The severity of adverse effects was, overall, mild and associated with the opioid class. Rarely were AEs or adverse effects severe enough to require the discontinuation of buprenorphine; for example, the POATS primary analysis reported a 2.5\% discontinuation rate.\textsuperscript{38} When AEs or adverse effects were examined over time, they generally decreased in intensity and, in some cases, resolved completely within a week.\textsuperscript{46,54} Yet, some adverse effects persisted for at least 6 months.\textsuperscript{37} In 1 study, the US Food and Drug Administration placed further recruitment on hold because of severe AEs, such as hospitalization for intense withdrawal symptoms and pain, in 7 of 12 participants.\textsuperscript{54} This small pilot study was focused on developing a buprenorphine transition protocol that underwent multiple iterations during the study course. Its investigators noted that the protocol, which did not take into consideration participants’ baseline opioid formulation or dose, may not have allowed adequate flexibility for those who were using the highest and lowest MME doses.\textsuperscript{34} Heavy sedation was reported by only 1 study in a single patient.\textsuperscript{36} No accidental or intentional overdoses or deaths were attributed to buprenorphine in any studies; a single overdose-related death was reported in 1 participant that occurred months after discontinuing buprenorphine.\textsuperscript{55}

**Mental Health Condition and Health Care Use**

There was insufficient evidence to definitively support an association between outcomes of mental health conditions (eg, depression, anxiety, and insomnia) and buprenorphine rotation. Only 2 studies reported mental health outcomes\textsuperscript{37,51} and both had high risk of bias. Nevertheless, 2 studies suggested that buprenorphine rotation was associated with improved mental health outcomes. Neumann et al\textsuperscript{37} reported a significant decrease in Beck Depression Inventory scores (from 21.2 to 16.2; \( P = .01 \)), which was consistent with a change from moderate to mild depression at 6-month follow-up. Freye et al\textsuperscript{51} reported that, after rotation to buprenorphine from high-dose morphine, 74\% of participants experienced improved quality of sleep vs 14\% of participants before the rotation.

No studies assessed the implication of buprenorphine rotation for health care use, such as outpatient clinic visits, emergency department visits, or hospitalizations.

**Discussion**

We systematically reviewed the literature regarding rotation to buprenorphine in individuals with chronic pain who used LTOT. We found 22 studies that evaluated at least 1 prespecified outcome. Although most studies had a high risk of bias, limiting the strength of the present study’s conclusions, several important findings emerged.

Buprenorphine appeared to be not inferior to full MOR agonists in controlling pain. Continuing buprenorphine rather than tapering it off was associated with higher rates of protocol completion and lower use of additional opioids. Although many approaches to buprenorphine rotation are available, most studies relied on protocols that were adapted from those that are used to induct patients with OUD to buprenorphine, which require that opioid withdrawal symptoms be present before the administration of the first dose of buprenorphine. Previous studies also supported the safety of buprenorphine. Severe AEs were rare, and the adverse effects, although more common, were manageable. The incidence of precipitated opioid withdrawal was low (3\%-6\%).

We believe that this systematic review adds to the growing body of literature that suggests that buprenorphine is safe to use in multiple populations, including those with opioid dependence and chronic pain.\textsuperscript{16,59,60} In contrast, long-term full MOR agonists present significant risks for harmful or fatal overdose, all-cause mortality, and morbidity.\textsuperscript{1,2,6} Thus, this synthesis supports the hypothesis that rotation from full MOR agonists to buprenorphine would reduce harm, although more research is needed into the best way to complete such rotation.

Rotation to buprenorphine was not associated with changes to patients’ pain control. In most studies, buprenorphine was associated with reduced pain severity, although the mechanism for this
finding is not clear. It is possible that opioid rotation in general (through incomplete cross-tolerance to a different opioid), rather than rotation to buprenorphine specifically, was a factor. Alternatively, reduced pain might be associated with buprenorphine's unique role in opioid-induced hyperalgesia. Previous studies have reported the antihyperalgesic outcomes of buprenorphine compared with other full MOR agonists in animal models and in humans.

Participants were much more likely to complete study protocols, remain in treatment, avoid additional opioid use, and achieve analgesia if they continued to receive stable doses of buprenorphine after rotation rather than tapering off of buprenorphine. This outcome was especially apparent in individuals with co-occurring OUD and chronic pain, which is consistent with the literature on OUD without chronic pain that found a greatly increased risk of return to illicit opioid use after buprenorphine taper. Findings from the present study suggest that continuing buprenorphine can be a successful strategy for patients with chronic pain who are unable or unwilling to taper opioids entirely. However, future studies should compare buprenorphine maintenance with tapering directly and should follow up for longer periods.

These findings highlighted not only the many benefits of buprenorphine rotation but also that the state of the science is in its early stages. We did not identify an optimal approach for rotation from full MOR agonists. The most common method of rotation involved a protocol adapted from OUD that used sublingual buprenorphine. This method required cessation of opioids for at least 8 hours and up to 72 hours until mild opioid withdrawal symptoms developed, followed by administration of an initial, low dose of buprenorphine and assessment for precipitated opioid withdrawal. Few harms have been reported with this approach, but it needs to be examined before widespread adoption for several reasons. First, inducing even mild withdrawal symptoms before initiating buprenorphine is likely to exacerbate pain and produce emotional distress. Second, the time, resources, and expertise needed to support and monitor an individual who is going through withdrawal while initiating buprenorphine may exceed the time, resources, and expertise that many outpatient primary care or pain clinics have at their disposal. Thus, a mechanism for switching to buprenorphine with little to no opioid withdrawal symptoms is preferable, and its development should be prioritized in future research. Microdosing (or microinduction) is an alternative approach that involves the overlapping use of low-dose sublingual or transdermal buprenorphine as a bridge to higher doses while full MOR agonists are cross-tapered. Given that this is a relatively new method, more research is needed to assess its superiority over other approaches.

In addition to the various protocols for rotation, there was a wide range of baseline full MOR agonist doses, starting buprenorphine doses, and buprenorphine formulations across studies. A possible explanation for this diversity is the lack of reliable equianalgesic conversions from full MOR agonists to buprenorphine; transdermal buprenorphine equipotency ratios with oral morphine have been reported from 70:1 to 115:1. There is even less consistency regarding the equipotency ratios in sublingual and buccal buprenorphine given that bioavailability varies from 30% to 60% depending on the specific product and individual variation. Future research should address the optimal starting dose, formulation, and administration frequency of buprenorphine that are based on baseline total daily dose, ideally in the form of a standard equipotency ratio. The flexibility in regimen and the ability to frequently adjust doses and timing will be important considerations.

Moreover, the populations studied were highly diverse. Participants demonstrated a wide spectrum of problematic opioid use, reflecting the reality of clinical practice. Although several studies excluded individuals with evidence of any aberrant use, most studies included at least some participants with opioid misuse, opioid dependence, or OUD. Diagnosing OUD in the context of prescription-only opioid use for chronic pain is challenging because no clear consensus exists on how to define and recognize OUD in this setting. Problematic behaviors (e.g., preoccupation with receiving opioids and repeated requests for early refills or dose increases) in this population are common but may not be sufficient to meet the DSM-5 criteria for a diagnosis of OUD. This hypothesis was reflected in several studies included in the present systematic review, which focused on participants with aberrant use but excluded those with OUD.
We believe that the diversity of these participants increases confidence that buprenorphine rotation may be a viable strategy for mitigating the harms of LTOT across a spectrum of individuals with chronic pain who receive it. This diversity also highlights the need for future research into whether buprenorphine might be helpful in certain populations with chronic pain who use LTOT and do not meet the DSM-5 criteria for an OUD diagnosis but show aberrant use or misuse.

Limitations
This study has several limitations. First, most studies in this systematic review were of low quality, primarily because of their design. Of the 22 included studies, only 5 were RCTs, 27,35-38, 7 had a case-control or cohort design, 39-45; and 10 were uncontrolled pre-post assessments of a single clinic's experience. 46-55 These studies had various follow-up periods that were not always prespecified or systematic. Second, there was heterogeneity in outcomes and measures. Many studies used brief, unidimensional measures of pain and some used unvalidated measures. Third, not all outcomes of importance were assessed. For example, pain-related interference, which is considered to be an outcome that is on par with pain intensity, 88 was rarely measured. Similarly, depression and sleep disturbance, which are associated with chronic pain, 89-91 were assessed in only 1 study each. Health care use, which is affected by the initiation of buprenorphine in people with OUD, 92,93 was also not examined.

Conclusions
This systematic literature review found that buprenorphine was associated with reduced chronic pain without precipitating opioid withdrawal or serious adverse effects in patients with chronic pain who used LTOT. The findings, although synthesized from studies that were of low to very low quality, suggested that buprenorphine rotation is a viable strategy for mitigating the harms of LTOT. Future research is warranted to address the optimal starting dose, formulation, and administration frequency of buprenorphine as well as the best approach to buprenorphine rotation.
Drafting of the manuscript: Powell, Rosenberg, Yaganti, Shannon, Silveira.

Critical revision of the manuscript for important intellectual content: Powell, Rosenberg, Yaganti, Garpestad, Lagisetty, Silveira.

Statistical analysis: Yaganti, Silveira.

Administrative, technical, or material support: Rosenberg, Yaganti, Garpestad.

Supervision: Powell, Rosenberg, Lagisetty, Silveira.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was funded by training grant AG062043 from the National Institute on Aging (Dr Powell), a Veterans Affairs (VA) Advanced Fellowship in Geriatrics (Dr Powell), grant 1K23DA047475-01A1 from the National Institute on Drug Abuse (Dr Lagisetty), and grant LIP 19-113 from the Ann Arbor VA Center for Clinical Management Research (Dr Lagisetty).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: The authors thank Joel Gagnier, PhD, and Sandeep Vijan, MD, University of Michigan, Ann Arbor, for their assistance and helpful feedback during manuscript preparation. They were not compensated for their contribution to the work.

REFERENCES


**SUPPLEMENT.**

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