Review Article
Systematic Literature Review and Meta-Analysis of the Efficacy and Safety of Prescription Opioids, Including Abuse-Deterrent Formulations, in Non-Cancer Pain Management

Edward Michna, MD,* Wendy Y. Cheng, MPH, MPhil,† Caroline Korves, ScD,† Howard Birnbaum, PhD,‡ Ryan Andrews, SB,† Zhou Zhou, MS,† Ashish V. Joshi, PhD,‡ David Schaar, MD,‡ Jack Mardekian, PhD,‡ and Mei Sheng, Duh, MPH, ScD†

*Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; †Analysis Group, Inc., Boston, Massachusetts; ‡Pfizer, Inc., New York, New York, USA

Reprint requests to: Mei Sheng Duh, MPH, ScD, Analysis Group, Inc. 111 Huntington Avenue, Tenth Floor, Boston, MA 02199, USA. Tel: +1-617-425-8131; Fax: +1-617-425-8001; E-mail: mduh@analysisgroup.com.

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Abstract

Objective. This study was conducted to compare safety and efficacy outcomes between opioids formulated with technologies designed to deter or resist tampering (i.e., abuse-deterrent formulations [ADFs]) and non-ADFs for commonly prescribed opioids for treatment of non-cancer pain in adults. Methods. PubMed and Cochrane Library databases were searched for opioid publications between September 1, 2001 and August 31, 2011, and pivotal clinical trials from all years; abstracts from key pain conferences (2010–2011) were also reviewed. One hundred and ninety-one publications were identified, 68 of which met eligibility criteria and were systematically reviewed; a subset of 16 involved a placebo group (13 non-ADFs vs placebo, 3 ADFs vs placebo) and reported both efficacy and safety outcomes, and were included for a meta-analysis. Summary estimates of standardized difference in mean change of pain intensity (DMCPI), standardized difference in sum of pain intensity difference (DSPID), and odds ratios (ORs) of each adverse event (AE) were computed through random-effects estimates for ADFs (and non-ADFs) vs placebo. Indirect treatment comparisons were conducted to compare ADFs and non-ADFs.

Results. Summary estimates for standardized DMCPI and for standardized DSPID indicated that ADFs and non-ADFs showed significantly greater efficacy than placebo in reducing pain intensity. Indirect analyses assessing the efficacy outcomes between ADFs and non-ADFs indicated that they were not significantly different (standardized DMCPI [0.39 [95% confidence interval (CI) 0.00–0.76]; standardized DSPID [−0.22 (95% CI −0.74 to 0.30)]). ADFs and non-ADFs both were associated with higher odds of AEs than placebo. Odds ratios from indirect analyses comparing AEs for ADFs vs non-ADFs were not significant (nausea, 0.87 [0.24–3.12]; vomiting, 1.54 [0.40–5.97]; dizziness/vertigo, 0.61 [0.21–1.76]; headache, 1.42 [0.57–3.53]; somnolence/drowsiness, 0.47 [0.09–2.58]; constipation, 0.64 [0.28–1.49]; pruritus 0.41 [0.05–3.51]).

Conclusion. ADFs and non-ADFs had comparable efficacy and safety profiles, while both were more efficacious than placebo in reducing pain intensity.

Key Words. Opioids; Pain Management; Safety
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Introduction

Pain is the most common reason for which patients seek medical care [1]. A recent report by the Institute of Medicine estimated that 100 million people in the US suffer from chronic pain, with an annual cost of chronic pain of up to $635 billion [2]. Undertreatment of chronic non-cancer pain can have significant economic, societal and health impacts, including the inability to work [3].

While prescription opioid medications are often prescribed for the management of pain, potential diversion and abuse of such drugs remain true concerns. According to the 2008–2009 National Survey on Drug Use and Health, nearly 10.4 million people in the US reported having used prescription opioids for nonmedical purposes in the past year. In that study, nonmedical use was defined as use by an individual without a prescription of the individual’s own or simply taking the opioid for the experience or feeling the drug caused [4]. Among individuals who used pain relievers nonmedically, diversion was reported as the main mechanism for obtaining the drug. The majority (55.9%) of individuals received the drug for free from friends and relatives, while others bought drugs or took drugs without asking from friends and relatives (14.3%) [4].

Individuals who use prescription pain medications for nonmedical reasons are a population of particular public health concern as their number quadrupled from 1990 to 2000 [5]. Individuals who use prescription pain medications for nonmedical reasons may do so by tampering with the formulation by chewing, crushing, or dissolving the drug. While tampering varies by drug product, the practice has been reported to be as high as 63% and 72% among individuals using oxycodone extended-release (ER) and morphine ER for nonmedical reasons [6].

Together, evidence suggests that there is a need to balance the risk of abuse against appropriate use of opioid medications for the treatment of pain. In order to mitigate risk of misuse, abuse, and diversion of prescription opioids, opioid formulations that help safeguard appropri- ate use have been developed. Pharmacological strategies and physical barriers help limit one’s ability to obtain quicker and greater euphoric effects for the medications through tampering with them. However, for abuse-deterrent formulations (ADFs) of prescription opioids to be a viable option for pain management, they must be as effective in reducing pain and as safe as currently available non-ADFs.

In the absence of clinical studies that directly compare ADFs with non-ADFs or studies that indirectly compare the two formulations, we carried out a systematic literature review and meta-analysis to compare efficacy and safety outcomes for commonly prescribed short-acting opioids (SAOs) and long-acting opioids (LAOs) in ADFs vs traditional non-ADFs.

Methods

Study Selection Criteria

Types of Studies

Studies were eligible if they were published in English, randomized, single-arm or open-label phase II or III clinical trials, prospective or retrospective observational studies, descriptive studies, meta-analyses, or cross-sectional studies that were published in the past 10 years (September 1, 2001 to August 31, 2011). Other pivotal phase II or III clinical trials published prior to this time period were also included. Studies that assessed the pharmacokinetic and titration properties of the opioids of interest or associated resource utilization with no assessment of efficacy or safety outcomes of interest, studies that assessed only cancer-related pain, studies reporting redundant data from other included studies, and duplicate publications of studies across databases were excluded.

Types of Participants

Participants included in the publications under review were adults aged 18 years and above with chronic non-cancer-related pain (CNCP) treated with either SAOs or LAOs, and adults aged 18 years and above with severe acute pain, or postoperative pain treated with SAOs.

Types of Interventions

Opioids of interest were 12 most commonly prescribed LAOs and SAOs [7], including six LAOs (oxycodone, fentanyl, morphine, tramadol, methadone, and oxymorphone) and six SAOs (hydrocodone, oxycodone, oxycodone combination, tramadol, codeine, and codeine combination). Recently developed ADFs (morphine sulfate and nalbuphine hydrochloride ER, oxycodone hydrochloride controlled-release, and oxycodone hydrochloride ER) were captured in the earlier list as these ADFs contain at least one of the earlier LAO or SAO molecules. In order to focus on more commonly used opioids, other LAOs (e.g., hydromorphone, tapentadol) and SAOs (e.g., hydromorphone, levorphanol) were not included. Nonetheless, given the high prevalence of the opioids studied, results from the current study have considerable applicability.

Types of Outcome Measures

Primary outcomes of interest were efficacy and safety. Efficacy was assessed in terms of the two most commonly reported outcomes—mean change of pain intensity from baseline to end of study, and sum of pain intensity differences over study period. Pain intensity was assessed as a continuous outcome using patient rating scales including the visual analog scale, numerical rating scale, patient rating scale, or brief pain index pain intensity scales (identified, respectively, as VAS 100 mm, NRS 11, PRS 3, or BPI 10 in (Table S1). A positive change of pain...
intensity from baseline to end of study indicated an increase in pain over time, while a negative difference indicated a decrease in pain intensity. The sum of pain intensity difference was computed by first subtracting the pain intensity at specific intervals in the study period from the baseline and then cumulatively adding up these values over the study period. As pain intensity decreased over time, the differences in pain scores over time would be positive, such that a larger sum of pain intensity difference would indicate greater pain improvement.

Safety outcomes included the proportion of patients who experienced the top five most frequently reported adverse events by LAOs and SAOs, and were found to be common in the included studies (defined as an occurrence in at least 15% of patients in any treatment arm in at least one study; a cutoff previously used in other literature reviews on opioid and pain outcomes [8]). A total of seven adverse events were identified as there were ties for the five most frequently reported adverse events, which included nausea, vomiting, dizziness/vertigo, headache, somnolence/drowsiness, constipation, and pruritus. Secondary outcomes of interest were patient satisfaction with medication (i.e., proportion of patients who rated medication as good, very good, or excellent) and quality of life (QoL) (i.e., mean change of overall, physical, and mental QoL from baseline to end of study).

Search Methods

Electronic Searches

Relevant abstracts were identified for review using PubMed and Cochrane Controlled Trials databases, where nonclinical trials published in the 10 years prior to search date and clinical trials published in all years were identified. Two separate searches were conducted for LAO and SAO studies. Key words used included pain, chronic, intractable, refractory, persistent, and the National Library of Medicine Medical Subject Heading term pain. For studies on LAOs, additional key words used included extended release, long acting, and the six LAOs of interest (oxycodone, fentanyl, morphine, tramadol, methadone, and oxymorphone). For studies on SAOs, additional key words were immediate release, short acting, acute, postoperative, post-operative, and the four opioid molecules of the six SAOs of interest (hydrocodone, oxycodone, tramadol, codeine). Limits were also employed in the PubMed searches, such that only studies conducted on adults, humans, and published in English were included. No limits were used in Cochrane Controlled Trials searches.

Additional sources were also queried and included abstracts and presentations from the last 2 years (2010–2011) for three scientific conferences (American Pain Society, American Association of Pain Medicine, and PainWeek), which were accessed via the societies’ websites or through the affiliated journals.
Preserve homogeneity across included studies because was excluded from the main meta-analyses in order to meet the criteria for this review, a study by Katz and colleagues [12]. In addition to studies that did not meet the inclusion criteria for review (despite having a different patient population), a sensitivity analysis was conducted to assess whether the results would differ with its inclusion.

Additionally, other elements of heterogeneity were observed across the studies in the literature review. In particular, treatment duration varied across studies, especially among studies involving SAOs vs LAOs alone. For instance, studies with at least one SAO arm had treatment durations that were as short as 5 hours, whereas LAO studies could be as long as 12 months. In order to account for the variance in treatment length, stratified meta-analyses were conducted for efficacy and safety outcomes to assess the potential effect modification of treatment duration (i.e., <2, 2–3, and >3 months). Furthermore, as effects of SAO and LAO on safety outcomes may differ, safety outcomes were further assessed by LAO/SAO formulations in order to capture potential differential occurrence of various adverse events by LAOs and SAOs.

Assessment of Reporting Biases

Funnel plots with the standard errors of effect estimates (i.e., standardized difference in mean change of pain intensity, standardized difference in sum of pain intensity differences, [log] odds ratios for adverse events) against the effect estimates from all the component studies were developed to assess potential small study effects and publication bias for meta-analyses on non-ADFs studies. Begg’s tests for publication bias were conducted to assess funnel plot asymmetry [13]. Funnel plots and tests for publication bias were not developed for meta-analyses on ADFs vs placebo studies due to the small number of studies available.

Software

All meta-analyses were performed using STATA software [14]. ITCs were conducted using ITCs software [11].

Results

Description of Studies

A total of 191 potentially relevant abstracts were generated from the electronic searches using PubMed and Cochrane Controlled Trials databases. An additional 705 conference abstracts were retrieved from the last 2 years of scientific conferences of interest but were not included in the literature review due to a lack of sufficient information for analysis or duplicate results as those published in full text. Upon review, 123 studies from the electronic searches were not relevant as they did not meet the study inclusion criteria (e.g., opioid was not specified or not of interest, participants were <18 years old or had no pain). Figure 1 illustrates the number of

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Efficacy

Two meta-analyses were conducted for the two efficacy outcomes—mean change of pain intensity from baseline to end of study, and sum of pain intensity differences over study period. Given that both outcomes were continuous and measured using different metrics across studies, standardized mean differences (i.e., standardized difference in mean change of pain intensity, and standardized difference in sum of pain intensity differences) were calculated to compare ADFs vs placebo, and non-ADFs vs placebo. Specifically, standardization was conducted by dividing the difference in mean change of pain intensity (or difference in sum of pain intensity difference) by the pooled standard deviation of the ADF/non-ADF arm and placebo.

Safety

Studies that were included in the efficacy meta-analyses and had reported at least one of the seven adverse events of interest were eligible for the safety meta-analyses. A meta-analysis was conducted for each of the adverse events to assess the summary odds ratios of the adverse event for ADFs vs placebo, and for non-ADFs vs placebo.

Given that no head-to-head comparison studies assessed efficacy or safety outcomes of ADFs vs non-ADFs, indirect treatment comparisons (ITCs) were conducted using the method by Bucher and the software (ITC) developed by the Canadian Agency for Drugs and Technologies in Health [11]. This method employed results from the direct comparisons of ADFs and non-ADFs to a common comparison arm, namely a placebo arm.

Dealing with Studies with Multiple Active Treatment Arms

Some studies eligible for the meta-analyses were multi-arm studies. Given that the inclusion of multiple comparisons from one study would contribute to unit-of-analysis error due to correlation between estimated intervention effects from multiple comparisons, both efficacy and safety outcomes of relevant active treatment arms within a study were combined into a single pairwise comparison against placebo using methods proposed by the Cochrane Collaboration [9]. Specifically, for each of the two efficacy outcomes, a combined mean pain intensity score was computed as the weighted average of pain intensity scores across the relevant active treatment arms. The combined standard deviation was computed as the pooled standard deviation. As for safety outcomes, the combined total number of events was computed as the sum of events across the active treatment arms.

Sensitivity Analyses

In addition to studies that did not meet the inclusion criteria for this review, a study by Katz and colleagues [12] was excluded from the main meta-analyses in order to preserve homogeneity across included studies because its patient population selection criteria were different from those of the other studies. Specifically, patients were all naïve to opioids and had more severe pain intensity at baseline, while other studies included in the literature review did not impose an exclusion criterion for prior opioid exposure. As this study met all the inclusion criteria for review, sensitivity analysis was conducted to assess whether the results would differ with its inclusion.

Additional analyses were conducted for efficacy and safety outcomes to assess the potential effect modification of treatment duration (i.e., <2, 2–3, and >3 months). Furthermore, as effects of SAO and LAO on safety outcomes may differ, safety outcomes were further assessed by LAO/SAO formulations in order to capture potential differential occurrence of various adverse events by LAOs and SAOs.

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Funnel plots with the standard errors of effect estimates (i.e., standardized difference in mean change of pain intensity, standardized difference in sum of pain intensity differences, [log] odds ratios for adverse events) against the effect estimates from all the component studies were developed to assess potential small study effects and publication bias for meta-analyses on non-ADFs studies. Begg’s tests for publication bias were conducted to assess funnel plot asymmetry [13]. Funnel plots and tests for publication bias were not developed for meta-analyses on ADFs vs placebo studies due to the small number of studies available.

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studies from the electronic searches that were excluded and the reasons for exclusion. Of the 68 remaining studies, 52 studies were excluded from the meta-analysis due to the absence of a placebo group (N = 39), or the absence or insufficient data on efficacy outcomes (N = 12). To minimize heterogeneity across studies included in the meta-analysis, one additional study was also excluded due to its participant eligibility criteria being substantially different from those in other studies (i.e., participants were opioid-naïve [vs participants with prior prescription opioid exposure in other studies] and had more severe pain intensity at enrollment [≥50 vs ≥40 mm on a 100 mm VAS]) [12]. A total of 16 studies were included in the meta-analysis, of which 13 assessed non-ADFs vs placebo [15–27] and 3 studies assessed ADFs vs placebo [28–30].

Table S1 illustrates the study designs and patient characteristics of the component studies of this literature review. Of the 68 studies included in the literature review, the majority (k = 65) were clinical trials (i.e., randomized or open-label) [12,15–73]. The remaining three studies were observational [74–76]. Forty-four studies assessed the effects of LAOs (oxycodone [N = 13], fentanyl [N = 2], morphine [N = 19], tramadol [N = 8], methadone [N = 0], oxymorphone [N = 8]) [12,15–23,27,29,30,35,36,46–66,68–79], among which were six studies were with ADFs (morphine sulfate and naltrexone hydrochloride ER [N = 6]; oxycodone hydrochloride ER [N = 2]) [29,30,52,53,61,63,64,73]. Twenty-two studies assessed the effects of SAOs (hydrocodone [N = 1], oxycodone [N = 13], tramadol [N = 7], codeine [N = 0]) [24–26,28,31–34,37–47,67,80,81], of which one study had an ADF as an active treatment (oxycodone hydrochloride controlled-release [N = 1]) [28].

Participants enrolled in the studies in the literature review were mostly middle-aged, with mean age ranging from 31 to 72 years old [45,67]. There were fewer men than women in most of the studies. All participants had non-cancer-related pain at enrollment with the most prevalent pain conditions being osteoarthritis (k = 15 studies) [16,17,19,22,23,29,30,35,49–51,53,55,66,73], low back pain (k = 15) [12,15,18,27,36,37,57–59,69,70,73,77–79], and postoperative pain (k = 14) [24–26,28,33,34,39–42,44,45,47,67].
The majority of studies included in the literature review demonstrated low risk or unclear risk across the seven domains of bias. The greatest risk of bias was found in the domain of binding of participants and personnel, with 44.4% studies at high risk of this bias. This suggests that in a substantial number of studies, participants and investigators had no or incomplete blinding to treatment assignment. The lowest risk of bias was found in selective reporting, where only 6.3% studies were considered at high risk, suggesting that results on prespecified outcomes of interest were sufficiently reported in most studies.

**Risk of Bias in Included Studies**

The sensitivity analysis of the standardized difference in mean change of pain intensity when the study by Katz et al. [12] was included yielded a slightly larger summary effect estimate (−1.16 [95% CI −1.71 to −0.60]).

Indirect analyses assessing the difference in efficacy outcomes between ADFs and non-ADFs found that the standardized difference in mean change of pain intensity (0.39 [95% CI 0.00–0.76]) and the standardized difference in sum of pain intensity difference (−0.22 [95% CI −0.74 to 0.30]) were not significantly different from 0 (P > 0.97).

Stratified analysis by treatment duration was only conducted on one pain intensity outcome—standardized difference in mean change of pain intensity from baseline to end of study and for non-ADFs and placebo, as other studies on ADFs vs placebo and on the other pain intensity outcome—standardized difference in sum of pain intensity differences over the study period—had the same treatment lengths. Results from the stratified analysis indicated that pain intensity outcome did not vary by length of treatment (P = 0.56).

**Adverse Events**

Safety profiles were similar for ADFs and non-ADFs, both of which were associated with higher rates of adverse events than placebo. Of the seven adverse events assessed, the most common adverse event was nausea, occurring at a median rate of 26% (interquartile range 14–34%) among non-ADF treated patients, 21% (13–39%) among ADF-treated patients, and 9% (7–12%) among placebo-treated patients. For other adverse events as well, ADFs and non-ADFs were associated with consistently higher rates than placebo. As shown in Table 1, results from the meta-analyses of the various adverse events demonstrated odds ratios that were greater than 1 and statistically significant in the majority of comparisons between non-ADFs and placebo, and between ADFs and placebo. Heterogeneity was found to be substantial with $\hat{\rho} \geq 56\%$ in the meta-analyses of all adverse events, except headache, where $\hat{\rho}$ was 0%. Summary odds ratios from indirect analyses comparing adverse events for ADFs vs non-ADFs were non-significant [nausea: 0.87 (95% CI 0.24–3.12), vomiting: 1.54 (95% CI 0.40–5.97), dizziness/vertigo: 0.61 (95% CI 0.21–1.76), headache: 1.42 (95% CI 0.57–3.53), somnolence/drowsiness: 0.47 (95% CI 0.09–2.58), constipation: 0.64 (95% CI 0.28–1.49), pruritus: 0.41 (95% CI 0.05–3.51)].

Stratified analyses on all adverse events by treatment duration indicated that the odds of adverse events between non-ADFs and placebo (nausea: $P = 0.20$; vomiting: $P = 0.11$; dizziness/vertigo: $P = 0.48$; headache: $P = 0.99$; somnolence/drowsiness: $P = 0.47$; constipation: $P = 0.28$; pruritus: $P = 0.22$), and between ADFs and placebo did not vary by length of treatment (nausea: $P = 0.14$; vomiting: $P = 0.25$; dizziness/vertigo: $P = 0.30$; headache: $P = 0.39$; somnolence/drowsiness: $P = 0.81$; constipation: $P = 0.73$; pruritus: $P = 0.26$). Likewise,
stratified analysis by LAO/SAO formulation also showed no difference in the odds of adverse events between non-ADFs and placebo (nausea: $P = 0.49$; vomiting: $P = 0.49$; somnolence/drowsiness: $P = 0.71$; constipation: $P = 0.24$; pruritus: $P = 0.48$), and between ADFs and placebo (nausea: $P = 0.14$; vomiting: $P = 0.25$; dizziness/vertigo: $P = 0.30$; headache: $P = 0.39$; somnolence/drowsiness: $P = 0.81$; constipation: $P = 0.73$; pruritus: $P = 0.26$).

**Patient Satisfaction with Medication**

Seven studies on non-ADFs vs placebo assessed patient satisfaction with medication [12,18,24,26,36,44,78]. One study on ADFs vs placebo reported this outcome [30]. In comparing the proportions of patients who reported satisfaction in the non-ADF arms vs placebo, the difference in proportions was always positive, ranging from 6% to 40%. The only study that compared the proportions of patients reporting satisfaction in ADFs vs placebo showed a difference of 13%. The results seem to suggest that patients receiving both non-ADFs and ADFs were consistently more satisfied with their medication than patients receiving placebo.

**QoL**

Three studies reported results on the difference in mean change of overall QoL from baseline to end of study.
**Study, Year [Reference]** | **Standardized difference in sum of pain intensity differences (95% CI)** | **Weight (%)**  
--- | --- | ---  
Aqua, 2007 [24] | 0.46 (0.15 to 0.77) | 25.78  
Daniels, 2009 [25] | 1.28 (1.00 to 1.55) | 26.34  
Gimbel, 2004 [26] | 0.27 (–0.13 to 0.67) | 23.98  
Sunshine, 1996 [45] | 0.89 (0.48 to 1.29) | 23.89  
Overall ($I^2 = 87.1\%, P = 0.000$) | 0.73 (0.26 to 1.20) | 100.00  

**NOTE:** Weights are from random effects analysis.

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**Study, Year [Reference]** | **Standardized difference in sum of pain intensity differences (95% CI)** | **Weight (%)**  
--- | --- | ---  
Daniels, 2011 [28] | 0.51 (0.30 to 0.72) | 100.00  
Overall ($I^2 = 100.00\%, P = .$) | 0.51 (0.30 to 0.72) | 100.00  

**NOTE:** Weights are from random effects analysis.

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**Figure 3** Forest plot of standardized difference in sum of pain intensity differences between non-abuse-deterrent formulation (ADF) vs placebo and ADF vs placebo. CI = confidence interval.

**Table 1** Meta-analysis and indirect comparison results of adverse events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Summary Estimate from Meta-analysis</th>
<th>Indirect Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ADF vs Placebo OR (95% CI)</td>
<td>Non-ADF vs Placebo OR (95% CI)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.52 (1.10–11.32)</td>
<td>4.04 (2.40–6.79)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.18 (2.53–20.40)</td>
<td>4.67 (2.02–10.83)</td>
</tr>
<tr>
<td>Dizziness/vertigo</td>
<td>2.56 (1.04–6.33)</td>
<td>4.20 (2.41–7.34)</td>
</tr>
<tr>
<td>Headache</td>
<td>1.88 (0.78–4.55)</td>
<td>1.32 (1.06–1.64)</td>
</tr>
<tr>
<td>Somnolence/drowsiness</td>
<td>2.31 (0.47–11.25)</td>
<td>4.94 (2.64–9.22)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.24 (1.66–6.31)</td>
<td>5.03 (3.02–8.36)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2.72 (0.36–20.47)</td>
<td>6.72 (3.13–14.43)</td>
</tr>
</tbody>
</table>

ADF = abuse-deterrent formulation; CI = confidence interval; OR = odds ratio.
between non-ADFs and placebo, as assessed using EuroQual 5 Dimension (EQ-5D) \([15,36,49]\). Six studies reported the difference in mean change of physical QoL from baseline to end of study between non-ADFs vs placebo \([15,17,19,21,22,49]\), while five reported the difference in mean change of mental QoL from baseline to end of study between non-ADFs vs placebo \([15,17,21,22,49]\) based on the Short Form (36) Health Survey physical and mental components. There were no studies on ADFs vs placebo that assessed QoL outcomes. All studies that assessed the overall QoL with the exception of one \([49]\) reported greater positive change in the non-ADF arms relative to placebo (median difference in mean change of EQ-5D: 0.21, range -0.01 to 0.36). Greater physical QoL at end of study was also observed in non-ADFs vs placebo. In contrast, among the studies that assessed the difference in mean change of mental QoL, patients receiving non-ADFs experienced worse mental QoL than patients who received placebo.

**Assessment of Reporting Bias**

Funnel plots for the two efficacy outcomes reported in non-ADFs vs placebo studies and their corresponding Begg’s tests for publication bias showed statistically significant asymmetry \((P = 0.02)\), suggesting possible small study effects and publication bias. However, other sources such as true heterogeneity (e.g., true effect estimates may in fact be larger in small studies) and data irregularities could also contribute to such asymmetry. Funnel plots for the adverse events and their corresponding tests for publication bias indicated no substantial asymmetry \((P > 0.05)\).

**Discussion**

The current literature review and meta-analysis showed that among adults with non-cancer-related pain, the use of either ADFs or non-ADFs was associated with significantly greater reduction in pain intensity than placebo. While no head-to-head studies were available in the current review that directly compared the efficacy of ADFs with non-ADFs, the summary effect estimates and corresponding 95% CIs derived from the meta-analyses demonstrated considerable overlap, suggesting that the efficacy of ADFs and non-ADFs are similar. ITCs also indicated that the efficacy of ADFs and non-ADFs were not statistically significant.

Adverse events occurred at higher rates among patients receiving ADFs and non-ADFs compared with placebo. Across the five adverse events that were assessed in this review, the odds ratios for adverse events ranged from 1.88 for headache to 7.18 for vomiting in studies that assessed ADFs vs placebo, and from 1.32 for headache to 6.72 for pruritus in studies that assessed non-ADFs vs placebo. While the CIs were wide and at times included the null, the trends suggested a greater number of adverse events among prescription opioids as compared with placebo. These findings were consistent with existing literature on prescription opioids, which frequently found substantial adverse events in patients using prescription opioids, including somnolence, nausea, vomiting, and dizziness \([82]\). The indirect comparisons of ADFs and non-ADFs showed that the two formulations had similar safety profiles, with both having higher adverse event rates than placebo.

Despite higher adverse event rates among patients receiving non-ADFs compared with those receiving placebo, the few studies that assessed patient satisfaction indicated that patients taking non-ADFs were generally more satisfied with their medications than those taking placebo. Furthermore, they also reported greater overall QoL and physical QoL. This may be largely due to the significantly greater reduction in pain associated with their chronic conditions or surgeries. There was some evidence of the mental QoL among patients receiving non-ADFs being lower than that among patients on placebo. It is unclear why patients on opioids would have a reduction in mental QoL, although similar findings have been reported before in another review \([8]\). One possible reason could be that patients receiving prescription opioids experienced higher rates of adverse events.

A few limitations should be noted in interpreting and generalizing the findings from this review.

While the intent of this review was to compare the efficacy and safety of ADFs and non-ADFs, it was limited by the small number of available studies, particularly on ADFs. As suggested by the wide 95% CIs for efficacy and safety outcome summary effect estimates, the lack of large amount of data contributed to great uncertainty in the summary estimates derived from the meta-analyses of ADFs vs placebo. Furthermore, as suggested by the significant \(I^2\) across the majority of meta-analyses, there was substantial heterogeneity among the studies included, which may have an impact on the generalizability of the effect estimates from the meta-analyses. In particular, the types of opioids included were varied, comprised of both LAOs and SAOs, and administered at different dosages and frequencies. Nonetheless, stratified analyses of adverse events by LAO and SAO did not find statistical differences by formulation. Similarly, studies assessed were of different treatment durations. While stratified analyses by treatment durations of <2, 2–3, and >3 months categories were conducted, and results were not significantly different for both efficacy and safety outcomes across these specified treatment duration strata, within strata differences may still be present. Nonetheless, due to the small number of studies, further stratification into finer gradation of treatment length (e.g., 48 hours, 2–3 weeks, 1–2 months, etc.) was not feasible. In addition, participants had various pain conditions, including both CNCP and acute, postoperative pain, comprising a very heterogeneous study population for the review. It may be worthwhile to assess whether the results from the meta-analyses would vary based on opioid type or across different subpopulations. However, given that the objective of this review was to compare the efficacy and

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safety of ADFs and non-ADFs, the main, unstratified meta-analyses employed in this review were justified. Similarly, the funnel plots and Begg’s tests for publication bias for the meta-analyses for select efficacy and safety outcomes showed significant asymmetry, suggesting possible small study effect and publication bias. Nonetheless, it should be noted that while funnel plot asymmetry may be due to selection biases, other sources could potentially contribute to the asymmetry as well. One source could be the presence of true heterogeneity between large and small studies, which was likely in the current review due to factors described earlier. Lastly, while meta-analysis is a robust analytical technique that allows increased power to study effects of interest and summarize results of multiple studies, results generated from a meta-analysis are only as valid as the results of its component studies. While the exact amount of biases in the component studies is difficult to assess, the assessment of risk of biases indicated that the majority of studies included in the literature review had low to unclear risk of all types.

Despite the noted limitations, this review is the first to assess the efficacy and safety of ADFs and non-ADFs. Previous reviews on efficacy and safety of prescription opioids did not include studies with ADFs that have been developed recently. While previous literature offers support for the efficacy and safety of prescription opioids in pain reduction, it is unclear from these studies whether the efficacy and safety of ADFs and non-ADFs differ. This review addresses this gap in the literature and demonstrates that ADFs and non-ADFs are similar in terms of their efficacy and safety profiles.

Given the potential that ADFs may deter or resist some of the common forms of tampering associated with opioid misuse and abuse, the current findings may offer support for AD’s as an effective treatment option in patients who require opioid for the management of pain. This review serves to provide an overview of the efficacy and safety profiles of ADFs vs non-ADFs for a broad range of therapies and pain types; future research and reviews could further this understanding of the difference between the formulations by investigating efficacy and safety outcomes in different pain types, study populations, and opioids, as well as to include additional studies as the literature evolves.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Characteristics of studies included in the literature review