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REVIEW

Oxycodone/Naloxone: Role in Chronic Pain Management, Opioid-Induced Constipation, and Abuse Deterrence

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ABSTRACT

The use of opioids in the treatment of chronic pain is widespread; the prevalence of specific opioids varies from country to country and depends on product availability, national formulary systems, and provider preferences. Patients often receive opioids for legitimate treatment of pain conditions, but on the opposite side of the spectrum, nonmedical use of opioids is a significant public health concern. Opioids are associated with several side effects, and constipation is the most commonly reported and persistent symptom. Unlike some adverse effects associated with opioid use, tolerance does not develop to constipation. Opioid-induced constipation (OIC) is the most prevalent patient complaint associated with opioid use and has been associated with declines in various quality of life measures. OIC can be extremely difficult for patients to tolerate and may prompt patients to decrease or discontinue opioid treatment. Current management strategies for OIC are often insufficient. A prolonged-release formulation of oxycodone/naloxone (OXN) has been investigated for the treatment of nonmalignant and cancer pain and mitigation of OIC, and evidence is largely favorable. Studies have demonstrated the capability of OXN to alleviate OIC while maintaining pain control comparable to oxycodone-only regimens. There is insufficient evidence for OXN efficacy for patients with mild OIC or patients maintained on high doses of opioids, and use in these populations is controversial. The reduction of costs associated with OIC may provide overall cost effectiveness with OXN. Additionally, the presence of naloxone may deter abuse/misuse by those seeking to misuse the formulation by modes of administration other than oral ingestion. Most studies to date have occurred in European countries, and phase 3 trials continue in the United States. This review will include current therapeutic options for pain and constipation, unique characteristics of OXN, evidence related to use of OXN and its place in

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therapy, discussion of opioid abuse/misuse, and various abuse-deterrent mechanisms, and areas of continuing research.

Keywords: Abuse-deterrent formulations; Chronic pain treatment; Opioid-induced constipation; Opioids; Oxycodone/naloxone

INTRODUCTION

Chronic nonmalignant pain is experienced by 20–40% of adults, and cancer pain by up to 70% of oncology patients [1, 2]. Opioids are routinely employed in pain treatment for both etiologies, despite a lack of data to characterize potential implications of long-term use for nonmalignant pain [1, 3]. The United States (US) ranks 3rd for opioid consumption per capita, with hydrocodone and oxycodone most commonly prescribed [4]. Despite increasing use of opioid analgesics, pain is still frequently undertreated in the US and around the world [4, 5].

Oxycodone/naloxone (OXN) prolonged-release (PR) is indicated for treatment of severe pain requiring treatment with opioids; a low dose of naloxone added to the fixed-dose combination (FDC) antagonizes opioid receptors in the gastrointestinal tract, providing relief of opioid-induced constipation (OIC) [6]. OXN is the first product with a dual mechanism for achieving opioid analgesia while targeting the underlying cause of OIC, thus proactively addressing constipation symptoms. OXN was initially approved in Germany in 2006 and is now approved for use in 36 countries. Currently, it is under review by the Food and Drug Administration for approval in the US [7]. This review will explore the utility of OXN for use in pain management while providing relief of OIC, and implications of potential abuse deterrence.

METHODS

A literature search was conducted in the MEDLINE database using term "oxycodone and naloxone" through December 2013. All clinical and pharmacokinetic studies and reviews of OXN (as the FDC or separate formulations) were included. The MEDLINE search generated 177 results, with 59 containing relevant information for OXN. A search on clinicaltrials.gov for "oxycodone and naloxone" was performed in December 2013, and additional references were identified in published bibliographies. This review does not contain any new studies with human or animal subjects performed by any of the authors.

OPIOID-INDUCED CONSTIPATION

Opioids are well known for causing gastrointestinal disturbances, including nausea, vomiting, and constipation [8]. OIC is primarily caused by stimulation of opioid receptors in the gastrointestinal tract, resulting in relaxation of the colon and small intestine due to anticholinergic mechanisms, decreased motility, reduced secretions, and extended transit time of gastrointestinal contents [9, 10]. These factors contribute to symptoms such as constipation, gastroesophageal reflux, bloating, and abdominal cramping, a constellation of symptoms referred to as opioid-induced bowel dysfunction (OIBD) [10]. Constipation is the most commonly reported adverse effect of opioids, affecting an estimated 40% of patients with nonmalignant pain and 70–95% of patients with cancer pain [10–12]. Unlike other side effects associated with

opioids, constipation does not typically resolve with continued use [8, 13–24]. Although the interaction of opioids with the enteric nervous system is primarily responsible for OIC, there is evidence of a centrally mediated component as well [11, 25, 26]. Intraspinal administration of opioids has been shown to delay gastric emptying and prolong intestinal transit time, and research indicates possible differences in receptor mechanisms and sites (peripheral versus central) within the opioid class [26–30]. At this time, the full impact of centrally medicated OIC is unclear, as gastrointestinal function correlates more closely with opioid concentrations in the enteric nervous system than in the central nervous system (CNS) [11, 18].

OIC has been linked to higher healthcare costs ranging from $4,880 to $36,152 per patient, lower work productivity, and declines in quality of life measures [10–15, 31, 32]. The negative impact and incidence of opioid-related side effects may be underestimated by practitioners. More than half of chronic pain patients rate constipation as at least moderately bothersome compared to side effects unrelated to gastrointestinal function [33]. Due to the intolerability of OIC, patients may unsuccessfully adjust or discontinue their regimen in attempt to improve bowel symptoms [31–33]. Because OIC occurs at lower doses than those needed for pain control, tapering the dose may not resolve OIC or allow for sufficient analgesia [16]. Some practitioners have suggested opioid rotation to transdermal routes, but this does not reliably lessen the burden of OIC [17]. Overall, the impact of OIBD and OIC may be underappreciated [18]; appropriate steps must be taken to address these symptoms to maximize opportunity for patient adherence and pain management.

TREATMENT OF OIC

Prevention of OIC is considered more effective for patients on chronic opioid treatment, yet OIC is often managed in a reactive fashion [1, 19]. Nonpharmacological interventions (e.g., fluid and fiber intake), laxatives, and stool softeners used for prevention or treatment of OIC do not adequately address the underlying mechanisms and are unsuccessful for many patients [19–21]. Up to half of patients with OIC treated with laxatives will fail to reach treatment goals [21, 22]. Treatment guidelines for both cancer and nonmalignant pain have recommended prophylactic laxatives for patients treated with opioids, but to date there is a lack of quality evidence regarding efficacy or safety [23, 24, 34]. Prolonged use of laxatives can contribute to tissue or nerve damage in the gastrointestinal tract, loss of vitamins or minerals, kidney stones, or renal failure [35]. Medications approved for the treatment of chronic idiopathic constipation, such as prucalopride and lubiprostone, have insufficient data supporting efficacy for OIC, and more research is needed [36].

The peripheral μ-opioid receptor antagonists alvimopan and methylnaltrexone are used to ameliorate the gastrointestinal effects of opioids. Both medications antagonize opioid receptors in the gastrointestinal tract but not the CNS; the net effect is a reduction in OIBD symptoms while sparing opioid analgesia [11]. Despite their effectiveness, both are restricted to very specific indications that limit broad application. Methylnaltrexone is approved in Canada, US, and the European Union for the treatment of OIC in patients with advanced illness receiving palliative care that have not responded to treatment with laxatives [37]. Methylnaltrexone is administered subcutaneously and, according to the manufacturer, has not been studied for use

exceeding 4 months duration [38]. Oral formulations with enteric coating are currently under development [39, 40]. Alvimopan is indicated for short-term use in hospitalized patients following bowel resection surgery to reduce postoperative ileus. Adverse effects such as cardiovascular events, neoplasms, and fractures have been observed during treatment with alvimopan; it also does not hold an indication for OIC and studies for this condition have been limited [35, 37]. Due to safety considerations, use of alvimopan in the US is restricted to registered hospitals in the Entereg Access Support and Education (E.A.S.E.^{TM}) program [37, 41]. While the use of peripheral opioid antagonists can be an effective strategy for managing opioid-induced gastrointestinal effects, some experts have proposed that response rates may be incomplete due to the central mechanism of action of OIC [42, 43].

OXYCODONE/NALOXONE SUSTAINED RELEASE FORMULATIONS

OXN is supplied in the following combinations of oxycodone/naloxone: 5/2.5 mg, 10/5 mg, 20/10 mg, 40/20 mg. The usual starting dose is 10/5 mg every 12 h and the maximum daily dose is 80/40 mg. Naloxone undergoes significant first-pass intestinal and hepatic metabolism to inactive metabolites, primarily by glucuronidation by uridine 5′-diphospho-glucuronosyltransferases (UGT) 1A8 and 2B7, with a lesser role for N-dealkylation by cytochrome P450 (CYP) 3A4 [44, 45]. Very little naloxone reaches the systemic circulation, accounting for its very low oral bioavailability (2–3%). Thus, clinically significant systemic exposure does not occur following oral administration, allowing localized gastrointestinal antagonism without reversal of analgesia [20, 46]. Nevertheless, prior experience with immediate-release (IR) formulations of naloxone indicated precipitation of withdrawal symptoms, even at low doses [20, 47, 48]. It has been proposed that naloxone IR may saturate metabolism capacity, facilitating systemic absorption and reversal of opioid agonism [10, 13]. Consequently, OXN uses a PR formulation for both oxycodone and naloxone, which may limit systemic exposure of naloxone. Naloxone demonstrably reduces colonic transit time, and studies have indicated bioavailability equivalence between the individual components and the FDC [6, 49, 50]. An optimized balance of efficacy for OIC and limiting undesired gastrointestinal symptoms (e.g., abdominal pain, diarrhea) occurs with an oxycodone to naloxone ratio of 2:1 [13, 51].

OXN underwent several key randomized controlled trials (RCTs) in Europe demonstrating similar analgesic outcomes to oxycodone PR as well as efficacy for OIC (see Table 1 for key studies). Most studies included patients with chronic nonmalignant pain [13, 52–55]. RCTs compared OXN to placebo and oxycodone PR, but comparisons to other PR opioid analgesics have not been performed. OXN impact on OIC was primarily demonstrated by improved scores on the Bowel Function Index (BFI), as well as other measures including complete spontaneous bowel movements (CSBM), Patient Assessment of Opioid-Induced Constipation, Patient Assessment of Constipation Symptoms, frequency of laxative use, and stool consistency on the Bristol Stool Form scale [13, 52–54, 56]. A BFI score is the mean of three patient-scored components for bowel dysfunction (1–100), with higher scores indicating greater dysfunction [57]. Differences between OXN and its comparators were assessed

Table 1 A summary of clinical studies for OXN

Study	Study type	Population	Intervention	Dose limit (mg/day)	Laxative regimen	Primary endpoint(s)	Results
OXN3401 (Clinicaltrials.gov #NCT01971632) [52]	Randomized controlled study	463 patients with chronic nonmalignant pain receiving opioids for at least 2 weeks prior to the study	Pre-randomization: Conversion and titration for OC 12-week double-blind phase: OXN, OC PR, or placebo 1-year extension phase: Open-label OXN	40	Laxative use allowed but not specifically described	Analgesia: Time from initial dose to recurrent pain events (inadequate pain control)	Analgesia: A statistically significant ($P < 0.0001$–0.0003) difference was found for time to pain events between OXN and placebo groups. Pain event incidence was similar for OXN compared to OC
OXN3001 (Clinicaltrials.gov #NCT00412152) [53]	Randomized controlled study	322 patients with chronic nonmalignant pain and OIC, requiring OC 20–50 mg/day	Pre-randomization: Conversion and titration for OC 12-week double-blind phase: OXN or OC PR 52-week extension phase: Open-label OXN	50	Oral bisacodyl was allowed but not specifically described	Bowel function: BFI after 4 weeks	Bowel function: Mean BFI improved by −26.9 points (from 61.8 to 34.9) for OXN group and −9.4 points (from 61.0 to 51.6) for OC PR group ($P < 0.0001$) after 4 weeks
OXN3006 (Clinicaltrials.gov #NCT00412100) [54]	Randomized controlled study	265 patients with chronic nonmalignant pain and OIC, requiring OC 60–80 mg/day	Pre-randomization: Conversion and titration for OC 12-week double-blind phase: OXN or OC PR 52-week extension phase: Open-label OXN	120	Laxatives allowed only after 72 h following last bowel movement or if patient experienced discomfort. Bisacodyl 10 mg allowed up to 5/day for 7 consecutive days. If no bowel movement occurred in 24 h following two doses of bisacodyl (total 48 h), an enema was allowed	Bowel function: BFI	Bowel function: Mean BFI improved by −26.5 points (from 67.4 to 40.9) for OXN group and −10.8 points (from 64.1 to 53.3) for OC PR group after 4 weeks. Difference in mean BFI scores between two groups throughout 4 weeks was statistically significant (−14.9, $P < 0.0001$), and was observed after 1 week of treatment
(Clinicaltrials.gov #NCT00412100, #NCT00412152) [61]	Pooled analysis of two randomized controlled studies	581 patients with chronic nonmalignant pain; pooled data for OXN3001 and OXN3006	Pre-randomization: Conversion and titration for OC 12-week double-blind phase: OXN or OC PR	120	Oral bisacodyl 5–10 mg after 72 h following last bowel movement or if patient experienced discomfort	Analgesia: Average pain over last 24 h (Pain Intensity Scale) over 12 weeks	Analgesia: Mean pain intensity scores were stable throughout the double-blind phase and similar between treatment groups. No statistically significant differences were observed ($P = 0.3197$, noninferiority $P < 0.0001$)

Table 1 continued

Study	Study type	Population	Intervention	Dose limit (mg/day)	Laxative regimen	Primary endpoint(s)	Results
(Clinicaltrials.gov #NCT01971632, #NCT00412152) [60]	Observational extension study	379 patients with chronic nonmalignant pain; extensions of OXN 3401 and OXN3001	Open label OXN up to 52 weeks	80	Bisacodyl oral during first 7 days; thereafter, other laxatives were allowed as needed after consultation with investigator	Analgesia: BPI-SF; Change in OXN dose; Average pain over last 24 h (Pain Intensity Scale);Frequency of analgesic rescue dose/day Bowel function: BFI Safety	Analgesia: BPI-SF items were low and stable over course of study. 53.8% patients remained on same OXN dose received during double-blind phase. Mean total daily dose of oxycodone increased from 35.6 to 43.7 mg at end of study Bowel function: Persistent effect on BFI from 35.6 to 20.6 (average 15-point reduction in score) Safety: Adverse effects were similar to opioid therapy, with no additional safety concerns identified

BFI Bowel Function Index, *BPI-SF* Brief Pain Inventory-Short Form, *NX* naloxone, *OC* oxycodone, *OIC* opioid-induced constipation, *OXN* oxycodone/naloxone, *PR* prolonged-release

for impact on OIC based on statistical significance and also clinical relevance: a BFI score >28.8 represents constipation, while a reduction ≥12 has been validated as a clinically meaningful change [57, 58]. CSBMs should exceed three per week, with fewer representing constipation based on Rome III criteria [59]. Phase 3 trials indicated both statistically significant and clinically relevant gains in bowel function with OXN, with three trials indicating benefit within the first week of treatment [13, 53, 54, 56]. An extended and persistent benefit of OXN for bowel dysfunction has been demonstrated during open-label treatment for 12 months, with mean BFI score further lowered below levels associated with constipation (from 35.6 to 20.6) [60]. In all RCTs except one [13], mean BFI score following 4 to 12 weeks of treatment with OXN was still higher than 28.8, indicating persistence of symptoms [13, 53, 54, 56, 61]. It is important to note some patients had very high BFI scores prior to treatment with OXN and experienced substantial decreases in this parameter overall. Though OXN may have mitigated OIC, constipation may have persisted in some patients due to confounding factors such as metabolic disorders, hydration status, age, comorbidities, and medications [31]. Likewise, OXN treatment decreased but did not eliminate need for laxatives, with 34–70% of patients presenting with OIC still requiring adjunct therapy after 4 weeks of OXN [13, 53, 54, 61]. Prolonged treatment may facilitate reductions in laxative dependence, as 16% of patients in the extension phase used laxatives with only 8.7% reporting regular laxative use [60]. Use of laxatives between treatment arms did not achieve statistically significant differences in RCTs enrolling patients with cancer pain or those lacking constipation at baseline [56, 62].

Although results of RCTs indicate comparable analgesic efficacy of OXN to oxycodone PR, noninferiority has not been unequivocally demonstrated. Four trials attempted to demonstrate noninferiority of OXN or co-administration of oxycodone and naloxone for analgesia, but failed to establish the boundary for inferiority or achieve adequate power in study design [13, 56, 61, 63]. Calculated *P* values between treatment arms of OXN and oxycodone PR did not achieve statistical significance, indicating failure to reject the null hypothesis for superiority rather than illustrating equivalence or noninferiority [64, 65]. Despite this limitation, patient and provider preference for efficacy and tolerability indicate preference for OXN versus oxycodone PR [55]. Several observational studies have demonstrated successful use of OXN in clinical practice for a large number of patients, including geriatric populations [9, 60, 66–70].

OXN is an effective analgesic for treatment of neuropathic pain, which is notoriously difficult to treat [62, 67, 69]. Three published studies have addressed use of OXN for postoperative pain following orthopedic, gynecological, and cardiac surgery, with mixed results [63, 71, 72]. Improvement in bowel function has not been unequivocally demonstrated, potentially complicated by the low doses and brief treatment courses used and impact of gastrointestinal surgery on bowel function; analgesia was similar to intravenous (IV) opioids [63, 71, 72]. OXN is not recommended before surgery or for 12 to 24 h in the immediate postoperative period [46]. Three studies to date have focused on patients with cancer pain, with only one designed as a RCT [56] and two as observational studies [9, 68]. Although OXN exhibited favorable outcomes for analgesic efficacy, several questions have been raised regarding its place in therapy for this indication.

Patients treated for cancer pain may require high doses and rapid titration, and the maximum OXN dose of 80/40 mg per day may preclude effective treatment [9, 73]. Furthermore, constipation in cancer patients is often multifactorial, and the benefit of OXN for ameliorating symptoms of OIBD may be limited [10, 12]. An observational study by Cuomo et al. [68] demonstrated that 4 weeks of treatment with OXN for cancer pain did little to improve BFI scores, although it did not worsen pre-existing bowel dysfunction.

The primary adverse effect associated with OXN was gastrointestinal in nature (e.g., diarrhea, constipation, abdominal pain, and nausea). Symptoms exhibited a dose-related increase in prevalence over placebo and oxycodone PR in RCTs, but OXN has an overall adverse effect and safety profile similar to oxycodone PR at doses studied [13, 52–54]. Gastrointestinal symptoms may represent a return of bowel function and have been described following treatment with methylnaltrexone [13, 38]. Four RCTs [52, 54, 56, 62] and one observational study [60] monitored opioid withdrawal symptoms via the modified Subjective Opioid Withdrawal Scale; the addition of naloxone does not appear to precipitate opioid withdrawal, and adverse effects consistent with withdrawal were generally comparable between groups. Open-label extension studies up to 52 weeks have maintained a favorable tolerability profile, with higher rates of adverse effects observed in the first 3 months and few serious adverse effects [60, 61].

PHARMACOECONOMIC CONSIDERATIONS

Results from industry-sponsored cost-effectiveness analyses favored OXN over oxycodone PR in the United Kingdom (UK), Germany, Spain, Belgium, and the Netherlands [74–78]. The German study [76, 77] used a noninterventional design and compared treatment with OXN versus other strong opioids (World Health Organization Step III), yielding an incremental cost-effectiveness ratio (ICER) that demonstrated greater cost effectiveness with OXN. Broad applicability of these results may be limited, given that annual acquisition costs were higher for other opioids compared to OXN and no statistically significant difference was noted in quality-adjusted life years in the 6-month interim analysis [76, 77]. Despite higher direct costs of OXN treatment in the UK and Spain, both studies demonstrated ICER values below thresholds used to determine cost efficiency [74, 75]; similar findings were published for Belgium and the Netherlands [78]. These studies support that overall cost savings may be achieved when OXN is selected for some patients with OIC, as the cost of drug acquisition may be offset by costs associated with complications of OIBD. Of note, data were pulled from previous clinical trials which restricted laxative use [74, 78]. Recommendations for scheduled laxatives with chronic opioid therapy are routine but not always followed [19]. Published RCT protocols deviated from this standard of care [53, 54], but may better reflect real-world scenarios in which laxatives are frequently used reactively [19, 74]. A direct cost comparison of OXN to a regimen with PR opioids and scheduled laxatives has not been performed [13, 53–56].

PLACE IN THERAPY

Overall, OXN appears to exhibit a favorable risk/benefit profile for achieving analgesic efficacy while preventing and treating—but not completely alleviating—symptoms of OIC. Clinical trials indicate improved outcomes for OIC when patients are constipated at baseline,

but there may be questionable benefit in patients with limited or no symptoms of OIC. Only two RCTs included patients who did not have OIC at baseline [52, 62]. OXN treatment did not achieve statistically significant outcomes on bowel function in either study, but neither used BFI score as a primary endpoint and constipation may not have been related to opioid use in one study [52, 62]. The number needed to treat (NNT) for patients with existing OIC to achieve at least 3 CSBMs per week was 3.8 to 4 in clinical trials [53, 54], whereas the NNT for patients with mild or no existing OIC was 14 [52, 79]. While prophylaxis with a laxative-based bowel regimen (the current standard of care) may not always be effective, the NNT for preventing a ≥72 h period without a CSBM has been demonstrated between 2.9 and 4.8; however, magnesium oxide was the most common laxative used in these trials, in contrast to senna or bisacodyl which are the most conventional laxatives used in the US [22, 80]. Clinicians must weigh the risks and benefits of treating patients prophylactically with OXN for as-yet-undeveloped OIC, although some experts have recommended prevention with OXN [18, 81].

There is insufficient data to evaluate whether patients requiring high doses of opioids may be effectively treated with OXN. Earlier studies in patients with nonmalignant pain investigated lower doses (typically a maximum of 40/20 mg to 80/40 mg per day) [9, 13, 52, 53, 55, 60, 66]. Only two RCTs have investigated doses up to 120/60 mg/day [54, 56], and one observational study maximized doses at 160/80 mg [68]. Oxycodone CR may be given as supplemental doses up to 400 mg/day when analgesic requirements are increased, but this may negate the benefit of naloxone for OIC [46]. Although studies of naloxone 5–120 mg have demonstrated bioavailability of ≤2%, concern exists surrounding the notion that increased doses may facilitate greater absorption of naloxone, precipitating opioid withdrawal or loss of analgesia [82, 83]. Two case reports of treatment failure with OXN have been published. In the first case [73], conversion and titration from oxycodone PR 40 mg/day to OXN 240/120 mg/day over 4 days resulted in poor analgesia, possibly indicating a role for high-dose OXN or rapid titration in treatment failure [84, 85]. In the second report [86], poor analgesia and symptoms of withdrawal were documented in a patient with portal vein thrombosis after converting oxycodone PR to OXN 20/10 mg/day. The authors hypothesized that absorption of naloxone via portosystemic collateral channels bypassed first-pass hepatic metabolism, resulting in increased bioavailability of naloxone [86]. These cases support employing vigilance when prescribing OXN to patients requiring high doses or rapid titration. OXN is contraindicated in patients with moderate to severe hepatic impairment as systemic exposure with naloxone may be increased. Additionally, OXN has not been studied in pregnant or lactating women. Naloxone crosses the placenta, and fetal exposure could result in opioid withdrawal [46].

OXN use has been explored for other conditions, including restless leg syndrome symptoms refractory to first-line dopaminergic treatment [87]. Studies for use with other indications have been recently completed or are underway (e.g., Clinicaltrials.gov #NCT01197261, #NCT01374763, #NCT01816581, #NCT01439100, #NCT00944697).

OPIOID MISUSE AND ABUSE DETERRENCE

In light of increasing levels of nonmedical use, the risks and benefits of prescribing controlled

substances must always be carefully considered [88, 89]. Individuals may abuse opioids via several different modes of administration, with oral, IV, and intranasal identified as the most common routes [90]. Some formulations readily lend themselves to overuse via the intended route (e.g., IR oxycodone and hydrocodone). Other medications are appealing due to the ability of users to overcome the PR mechanisms to achieve a better "high" by administration through an alternative route. Experienced opioid abusers are known to tamper with formulations to accelerate drug delivery by injection or insufflation, but the oral route is preferred by the vast majority (up to 97% of abusers) [90]. Abusers have identified oxycodone as a drug of preference due to its variety of available formulations [91]; consequently, abuse-deterrent formulations such as OXN may be of great clinical importance.

Abuse-deterrent strategies are typically targeted at discouraging tampering attempts and limiting administration by non-approved routes such as injection, which may carry increased risks to the abuser (e.g., overdose, infection, drug dependence) [92]. Tamper resistance (i.e., physical barriers), inclusion of irritants, aversive components, formulation of a prodrug, and unique delivery systems are all employed in efforts to dissuade abuse [93, 94]. Combining an opioid agonist with an antagonist may discourage tampering or administration by unapproved routes [90, 94]. It is important to note that abuse-deterrent mechanisms do not preclude all forms of abuse and may lead to unpredictable upswings in abuse of other drugs [95, 96]. Furthermore, the addition of an orally inactive antagonist may not discourage abuse by oral ingestion [97]. Abuse-deterrent mechanisms are, however, an important component of efforts to dissuade nonmedical use and limit ingestion by high-risk routes of administration. It has been suggested that OXN may provide abuse deterrence, though no peer-reviewed studies are available as of this writing. It has been suggested that increased systemic exposure of naloxone, antagonism of opioid effects, and reduced drug liking when the drug is chewed or administered via intranasal and IV routes may reduce the appeal of OXN for experienced opioid abusers [98–101]. The manufacturer is seeking language about abuse deterrence on the product label in the US [7].

CONCLUSIONS

OXN is a promising addition to the armamentarium of treatment options for chronic pain of cancer and nonmalignant etiology. Naloxone does not appear to impair analgesic efficacy for the vast majority of patients, and benefit for the treatment of OIC has been clearly demonstrated. The role for OXN in OIC prevention compared to standard prophylaxis with laxatives has yet to be determined. OXN use for prevention in at-risk populations may be prudent given the high burden and relative under-appreciation of OIC's impact, and provide greater cost efficiency by reducing costs associated with OIC. As prescription drug misuse with oxycodone and other opioids has grown to epidemic proportions in the US, the presence of naloxone as an abuse-deterrent feature may potentially confer additional benefit, particularly for oxycodone abusers who prefer non-oral routes of ingestion. It is unclear how the presence of naloxone will affect abusers who prefer to ingest large quantities of the drug orally. More research on the impact of abuse deterrence for this formulation is needed.

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Conflict of interest. Anne Z. DePriest and Katie Miller declare that they have no conflict of interest.

Compliance with ethics guidelines. This review does not contain any new studies with human or animal subjects performed by any of the authors.

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