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REVIEW ARTICLE

Oral Prolonged-Release Oxycodone/Naloxone for Managing Pain and Opioid-Induced Constipation: A Review of the Evidence

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■ **Abstract**

Background: Opioids provide effective relief from moderate-to-severe pain and should be prescribed as part of a multifaceted approach to pain management when other treatments have failed. Fixed-dose oxycodone/naloxone prolonged-release tablets (OXN PR) were designed to address the opioid class effect of opioid-induced constipation (OIC) by combining the analgesic efficacy of oxycodone with the opioid receptor antagonist, naloxone, which has negligible systemic availability when administered orally. This

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formulation has abuse-deterrent properties, since systemic exposure to naloxone by parenteral administration would antagonize the euphoric effects of oxycodone.

Methods: A literature search was conducted to assess the evidence base for OXN PR to treat moderate-to-severe pain and its impact on bowel function, based on published clinical trials and observational studies.

Results: Extensive data demonstrate that OXN PR provides effective analgesia and clinically relevant improvements in bowel function in patients with OIC and moderate-to-severe cancer-related pain and noncancer pain types such as low back pain, neuropathic pain, and musculoskeletal pain. OXN PR has also been found to improve bowel function in patients with OIC refractory to multiple types of laxatives, and improve Parkinson's disease–related pain. No unanticipated safety concerns have been reported in elderly patients.

Conclusions: Evidence from clinical trials and observational studies confirms that for selected patients OXN PR significantly improves moderate-to-severe chronic pain and provides relief from OIC. Treatment should be tailored to individual patients to establish the lowest effective dose. An absence of analgesic ceiling effect was seen across the clinically relevant dose range investigated (≤ 160/80 mg/day). ■

Key Words: narcotic antagonists, opioid analgesics, pain, opioid-related disorders

INTRODUCTION

Moderate-to-severe chronic pain is highly debilitating and has an estimated prevalence of approximately 20%.[1,2] In cancer patients, moderate-to-severe chronic pain is particularly common, affecting over half of individuals with advanced disease despite increased attention on pain assessment and management.[3] Analgesic drugs have a central role in managing chronic pain and are used as part of a multifaceted approach that integrates a variety of strategies, including interventional, psychological, physical, and complementary approaches, which together aim to improve pain treatment and enable rehabilitation.[4]

Selection of analgesic drugs should be governed by a comprehensive assessment of each patient in order to determine the pathophysiology of his or her pain, remembering that multiple pain types may be present. Evidence-based treatment guidelines for moderate-to-severe chronic pain indicate that opioid therapy can be very effective for carefully selected patients in whom pain has not responded to other measures.[5–7] However, use of opioid analgesics should be balanced against adverse effects that occur in most patients, as well as the risks for abuse and addiction.[5,7] Recent guidance from the European Pain Federation advocates that patients be fully informed about the potential risks and benefits of opioid therapy, and an individualized approach to patient care is undertaken.[7] This includes a therapeutic trial to establish whether or not opioid analgesia should be continued and regular clinical reviews to assess efficacy, compliance, physical, and psychological well-being of patients, adverse effects, and possible addiction/abuse or misuse.[7]

Opioid-induced bowel dysfunction (OIBD) is a common class effect of opioid analgesics. OIBD arises when exogenous opioids bind to enteric μ-opioid receptors present throughout the gastrointestinal tract, decreasing peristalsis and gastric emptying while elevating resting muscle tone and increasing nonpropulsive motility.[8] Up to 80% of patients receiving opioid analgesics report symptoms of OIBD, such as dry mouth, nausea, acid reflux, decreased appetite, abdominal pain, bloating, and constipation, with opioid-induced constipation (OIC) and straining to pass a bowel movement considered the most bothersome adverse effect.[9] Treatment guidelines recommend that laxatives be routinely prescribed to patients receiving opioid analgesia, but acknowledge that evidence supporting the prophylactic use of laxatives in this setting is lacking.[7,10–13] Several studies indicate that laxatives fail to address symptoms of OIC for some patients and can also be associated with troublesome adverse effects that can impact normal daily activities, such as bloating, flatulence, and sudden urge to defecate.[9,14–16] A recent pilot study in which patients were prescribed laxatives at the onset of opioid therapy concluded this paradigm was unlikely to prevent or treat OIC.[17] Laxatives can be ineffective for OIC due to the unique etiology of this condition compared with other types of constipation. Laxatives aid defecation via localized effects in the colon, while OIC arises from altered motility, secretion, and fluid resorption throughout the gastrointestinal tract following stimulation of enteric μ-opioid receptors.[18,19]

OIC does not appear to be correlated with the strength or dose of opioid, and management of OIC is further complicated by the fact that clinical measures of constipation, such as number of bowel movements per week, often do not correlate with patient experience.[15,20] Indeed, patient-assessment scales of constipation are advocated to ensure identification of affected individuals. Assessment tools validated in OIC include the Constipation Assessment Scale (CAS), Patient Assessment of Constipation Symptoms (PAC-SYM), Bowel Function Diary, and Bowel Function Index (BFI).[21–25] The CAS and PAC-SYM are well established, patient-completed tools that are considered to have

utility in clinical trials rather than in clinical practice, largely due to comprehension difficulties and the time taken to complete, respectively.[20] Further validation of the self-reported Bowel Function Diary is recommended along with adjustments to account for redundancies among items.[10,20] The BFI is a brief, physician-administered tool to assess patients' perception of OIC. It has been validated in several studies, with scores lower than 28.8 considered normal, based on nonconstipated patients with chronic pain.[20–22,26] BFI is recommended by the American Academy of Pain Medicine as the most appropriate tool for assessing OIC, stating that patients receiving opioid analgesics who have a BFI score of ≥ 30 should be considered for specific treatment to improve bowel function if they fail to respond to dietary and over-the-counter treatments.[10]

Oxycodone/naloxone prolonged-release tablets (OXN PR) are approved in Europe to treat severe pain that can only be adequately managed with opioids (starting daily dose 10/5 mg twice daily [bid] oxycodone/naloxone, maximum daily dose 160/80 mg) and severe idiopathic restless legs syndrome (starting daily dose 5/2.5 mg bid, maximum daily dose 60/30 mg).[27] OXN PR was designed to address OIBD by combining the analgesic efficacy of oxycodone (OXY) with selective blockade of enteric μ-opioid receptors by naloxone. While intravenous naloxone rapidly crosses the blood–brain barrier, the activity of oral naloxone (investigated dose range 5 to 120 mg) is principally confined to the gastrointestinal tract (bioavailability ≤ 2%) due to extensive first-pass hepatic metabolism.[28] As a result, oral naloxone can prevent or reverse OIC but does not reverse analgesia provided by OXY.[29,30] The fixed-dose combination of OXN PR is bioequivalent to OXY PR and naloxone PR given separately.[31] There is also limited clinical evidence indicating that ultralow doses of naloxone administered with morphine, buprenorphine, or tramadol may have an opioid-sparing effect, enhance analgesia, and/or reduce the severity of some OIBD symptoms.[32–39]

This review aims to assess the evidence base for OXN PR as a treatment for moderate-to-severe pain and the impact of this treatment on bowel function, based on published literature.

LITERATURE SEARCH

A search of PubMed was conducted (up to February 2, 2017) to identify clinical trials and observational studies investigating OXN PR for cancer-related pain and across nonmalignant pain settings. The search terms "random*", "observation*", and "pain" were each combined with "OXN PR" and "oxycodone AND naloxone". In total, 45 publications capturing 38 clinical trials and observational studies were identified that investigated OXN PR across a wide range of settings. Three additional congress abstracts detailing clinical studies on the analgesic use of OXN PR (not identified in the PubMed searches) were identified from a Mundipharma/Napp Pharmaceuticals database. This literature analysis also included 4 cost-effectiveness studies of OXN PR identified in the PubMed searches.

OXN PR for Chronic, Moderate-to-Severe Cancer-Related Pain

Evidence-based guidelines advocate the use of opioid analgesics to treat moderate-to-severe cancer-related pain, with oral morphine, OXY, or hydromorphone as the first choice treatment in this setting.[6] OXN PR has been investigated in a range of studies in patients with moderate-to-severe cancer-related pain (Table 1). These include 2 randomized controlled trials (RCTs) of double-blind treatment with OXN PR vs. OXY PR. The first reported RCT was a phase II study investigating OXN PR (≤ 120/60 mg/day) for 4 weeks, followed by an optional 24-week extension phase of open-label OXN PR.[40,41] OXN PR was associated with analgesic efficacy and safety that were comparable to those of OXY PR and provided clinically relevant improvements in bowel function measures that were maintained with long-term open-label OXN PR.[40,41] The second RCT was a recent 5-week phase III study with a 24-week open-label extension phase and included patients with OIC who required high-dose opioid to treat cancer-related or noncancer pain. OXN PR at daily doses of up to 160/80 mg provided effective analgesia and improved bowel function compared with OXY PR.[42,43] Subgroup analysis indicated greater pain relief in individuals receiving 140 to 160 mg/day compared with 100 to 120 mg/day, indicating absence of an analgesic ceiling effect at these doses. Outcomes in the subgroup of patients with cancer-related pain were comparable to those in the total population, and no additional safety concerns were identified.[42,43]

The findings from both RCTs are supported by open-label studies, including a 60-day observational study of 119 patients (78% with OIC [mean baseline BFI score > 29]) who required OXN PR at daily doses of ≥ 80/

Table 1. Summary of Clinical Trials, Observational Studies, and Case Studies Investigating OXN PR for Cancer-Related Pain

Reference	Study Overview	Key Outcomes
Ahmedzai et al.[40, 41]	Double-blind 4-week RCT of OXN PR (≤ 120/60 mg/day) vs. OXY PR (n = 185) followed by 24-week open-label extension phase (OXN PR, n = 128) in patients with moderate-to-severe cancer-related pain (OXN2001)	• OXN PR vs. OXY PR improved BFI scores ($P < 0.01$), constipation-related QoL assessments (EORTC QLQ-C30 subscore) and reduced laxative intake by 20% ($P = 0.17$) • OXN PR provided noninferior analgesia (BPI-SF) to OXY PR ($P < 0.01$) • Comparable safety profile with OXN PR and OXY PR • Long-term OXN PR provided sustained analgesia and bowel function • Patients who received OXY PR during the RCT experienced improved bowel function with open-label OXN PR
Amato et al.[44]	Observational 60-day study of patients with moderate-to-severe cancer-related pain despite analgesic treatment and/or opioid-related AEs (nausea, vomiting, or OIC) switched to OXN PR ≥ 80 mg/day to manage their pain; n = 119	• OXN PR reduced pain (≥ 30% decrease in average pain intensity, $P = 0.0001$), impact of pain on QoL (BPI-SF, $P < 0.0001$), and the mean number of daily breakthrough pain episodes ($P < 0.01$) from baseline (the proportion of patients reporting ≥ 1 breakthrough pain episode in the past 24 hours was not significantly different from baseline) • BFI scores improved from baseline ($P < 0.001$) and the proportion of patients receiving laxatives and/or enemas declined ($P < 0.001$) • Number of patients reporting AEs decreased from baseline ($P < 0.0001$)
Clemens et al.[47]	Open-label, 14-day, single-center study of OXN PR (titrated to adequate pain control) in patients with OIC; n = 26	• OXN PR was associated with significant improvements in BFI, stool consistency, spontaneous bowel movements, and Patient Global Impression (all $P < 0.0001$) • OXN PR provided effective analgesia for most (21/26) patients
Cuomo et al.[48]	Retrospective, single-center 28-day observational study of OXN PR (starting dose ≤ 10/5 mg bid). Patients had moderate-to-severe pain despite analgesic therapy or AEs requiring treatment modification; n = 206	• Switching to OXN PR provided significantly improved pain relief ($P < 0.0001$) without impairing bowel function (no clinically significant improvement in BFI) • No severe/unanticipated AEs were reported
De Santis et al.[46]	Open-label, 4-week observational study of OXN PR ≤ 80/40 mg/day) + pregabalin for patients with NSCLC and severe pain with a neuropathic component; n = 56	• OXN PR + pregabalin improved average pain intensity ($P < 0.0001$), BPI-SF ($P = 0.0002$), and episodes/intensity of breakthrough pain ($P \leq 0.005$) • Improvements in BFI ($P < 0.0001$) and other health-related PROs (HADS, $P \leq 0.0006$; SDS, $P < 0.001$) were also reported; 66% were satisfied/very satisfied with the therapy • Treatment was well tolerated
Dupoiron et al.[42,43]	Double-blind 5-week RCT of OXN PR (≤ 160/80 mg/day) vs. OXY PR (n = 243) followed by 24-week open-label extension phase (OXN PR ≤ 180/90 mg/day, n = 195) in patients with OIC and cancer-related or noncancer pain requiring doses ≥ 80 mg/day to manage their pain (OXN3506)	• Overall population: OXN PR vs. OXY PR was associated with noninferior analgesia ($P < 0.001$), greater reductions in BFI, less laxative use ($P = 0.006$), and more CSBM • Analgesia and bowel function were maintained long-term with open-label OXN PR • Comparable observations were reported in the subgroup of patients with cancer-related pain (n = 46)
Lazzari et al.[45]	Single-center, retrospective, observational, propensity matched study of OXN PR vs. OXY PR (5 to 20 mg/day starting dose); n = 146	• OXN PR and OXY PR provided similar analgesic efficacy • BFI improved from baseline with OXN PR but worsened with OXY PR ($P < 0.0001$) • ADRs were less frequent with OXN PR vs. OXY PR (8 vs. 29%, $P = 0.002$)

ADR, adverse drug reaction; AE, adverse event; BFI, bowel function index; bid, twice daily; BPI-SF, Brief Pain Inventory-Short Form; CSBM, complete, spontaneous bowel movement; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer QoL Questionnaire-Core 30; HADS, Hospital Anxiety and Depression Scale; NSCLC, non–small cell lung cancer; OIC, opioid-induced constipation; OXN PR, prolonged-release oxycodone/naloxone; OXY PR, prolonged-release oxycodone; QoL, quality of life; PRO, patient-reported outcome; RCT, randomized, controlled trial; SDS, Symptom Distress Scale.

40 mg to manage their cancer-related pain.[44] Compared with baseline (93% had received World Health Organization [WHO] stage III opioids) OXN PR reduced pain intensity, the impact of pain on quality of life (QoL), and the number of breakthrough pain episodes. Furthermore, by day 60, mean (SD) BFI scores (33.9 [21.8]) were near to normal values and substantially lower than reported at baseline (58.4 [29.9]) despite reduced use of laxatives/enemas.[44] A retrospective, propensity-matched study reported OXN PR to be associated with analgesic efficacy comparable to that of OXY PR and to provide significant improvements in BFI scores.[45] In a 4-week observational study of patients with non–small cell lung cancer and neuropathic pain, 82% responded to treatment (≥ 30% reduction in average pain intensity) with OXN PR plus pregabalin, with improved BFI and other health-related patient-reported outcomes (PROs).[46] A 14-day observational study of OXN PR in

cancer patients with OIC also reported significant improvements in pain intensity, BFI, and stool consistency.[47] A further observational study of cancer patients treated in an outpatient setting also reported significant improvements in pain scores with OXN PR, although no clinically significant change in BFI scores or laxative intake was observed compared with prior analgesic therapy (19% and 49% had received step II and step III WHO opioids, respectively).[48]

OXN PR for Moderate-to-Severe Noncancer Pain

Treatment guidelines recommend opioid therapy can be considered for chronic noncancer pain that has not responded to other treatments and is having an adverse impact on patients' QoL or daily functioning, and the therapeutic benefits are considered to outweigh potential harm.[5,7] Opioid analgesia should be initiated on a trial basis, with titration to the lowest effective dose, and therapy individualized according to each patient's health status, therapeutic goals, previous exposure to opioids, and predicted harms.[5,7] Our literature search identified a broad range of evidence for the role of OXN PR in moderate-to-severe noncancer pain settings, including low back pain, musculoskeletal pain, neuropathic pain, Parkinson's disease–related pain, and postoperative pain. These studies encompassed a variety of study designs, from phase 3 RCTs and large-scale, observational "real-world" studies to smaller pilot studies (Tables 2–6).

Table 2. Summary of Clinical Trials, Observational Studies, and Case Studies Investigating OXN PR for Low Back Pain

Reference	Study Overview	Key Outcomes
Baron et al.[67,68]	12-week RCT of tapentadol vs. OXN PR (starting dose 10/5 mg bid) in opioid-naïve patients with severe, chronic low back pain (neuropathic component); $n = 258$	• Tapentadol had noninferior analgesic efficacy and PAC-SYM vs. OXN PR (both, $P < 0.001$, primary endpoints) • Greater improvements in neuropathic pain-related symptoms ($P \leq 0.005$), global health status ($P = 0.005$), and HRQoL ($P \leq 0.017$) with tarpentadol vs. OXN PR • Tapentadol had better gastrointestinal tolerability (constipation and vomiting) vs. OXN PR ($P \leq 0.045$)
Cloutier et al.[61]	Canadian regulatory cross-over, 4-week RCT of OXN PR (starting dose 20/10 mg bid) vs. placebo for chronic low back pain; $n = 83$	• OXN PR significantly improved pain intensity scores ($P \leq 0.042$) and overall pain/sleep scores ($P = 0.005$) vs. placebo • Changes in BFI and stool consistency were comparable across treatment groups (most patients were not constipated at baseline) • Patients and investigators preferred OXN PR to placebo ($P \leq 0.02$) • Outcomes with OXN PR were maintained during a 6-month open-label extension

Ueberall et al.[62–64]	12-week, open-label, blinded endpoint study from Germany Pain Registry of adults with chronic low back pain; received (randomized 1:1:1 or physician decision) morphine, OXN PR, or OXY PR; $n = 901$ (PROBE)	• In randomized patients ($n = 453$) OXN PR provided significantly more responders for a combined measure of treatment continuation, analgesia, and bowel function ($P < 0.001$) and a lower risk of developing OIC vs. OXY PR and morphine ($P < 0.001$)
		• In all patients ($n = 901$):
		  • Normal BFI score was maintained in more patients receiving OXN PR vs. OXY and morphine ($P < 0.001$)
		  • OXN PR provided superior analgesia and treatment satisfaction (both, $P < 0.001$) and had a better tolerability profile vs. OXY and morphine
		  • Greatest gains in HRQoL observed with OXN PR ($P < 0.001$)

Ueberall & Mueller-Schwefe[65]	Randomly selected 12-week, open-label data from Germany Pain Registry of adults with chronic low back pain (neuropathic component) prescribed OXN PR ($n = 128$) or tapentadol ($n = 133$; PROBE 2)	• Noninferior benefit: risk profile of OXN PR vs. tapentadol • Greater composite analgesic/QoL efficacy (primary endpoint) for OXN PR ($P = 0.014$); between group differences increased in favor of OXN PR with stricter response definitions ($P \leq 0.017$) • OXN PR and tapentadol were similarly well tolerated
Vondrackova et al.[59]	12-week RCT of placebo, OXY PR or OXN PR (10/5 or 20/10 mg bid) in patients with chronic lower back pain; $n = 463$ (OXN3401)	• Comparable analgesia with OXY PR and OXN PR (superior to placebo, $P \leq 0.0003$) • Improved BFI and CSBM scores with OXN PR vs. OXY PR in patients with baseline moderate-to-severe OIC (BFI ≥ 50) • No unanticipated AEs with OXN PR • Efficacy and tolerability of OXN PR was maintained during 12-month open-label extension phase of pooled studies (OXN3001/OXN3401)[60]

AE, adverse event; bid, twice daily; BFI, Bowel Function Index; CSBM, complete, spontaneous bowel movement; HRQoL, health-related quality of life; OIC, opioid-induced constipation; OXN PR, prolonged-release oxycodone/naloxone; OXY, oxycodone; OXY PR, prolonged-release oxycodone; PAC-SYM, Patient Assessment of Constipation Symptoms; QoL, quality of life; RCT, randomized, controlled trial.

Table 3. Summary of Clinical Trials and Observational Studies Investigating OXN PR for Neuropathic Pain

Reference	Study Overview	Key Outcomes
Gatti et al.[76]	Retrospective, 2-month observational study of OXN PR (mean starting dose 15 mg bid, physician determined) in patients with constipation and chronic moderate-to-severe pain (~85% with neuropathic pain; gabapentin/pregabalin was permitted); $n = 1051$	• OXN PR reduced pain intensity ($P < 0.001$) and requirement for rescue medication from baseline ($P < 0.001$) • 84% rated PGIC as "very much" or "much" improved • BFI scores improved from baseline ($P < 0.001$) despite reduced use of laxatives ($P < 0.001$)
Hermanns et al.[74]	Observational study of 4-week OXN PR (dose determined by physician; 10/5 mg bid recommend for opioid-naïve patients); in patients with neuropathic pain; $n = 1488$	• OXN PR reduced pain intensity (BPI-SF, $P < 0.001$) and BFI scores (Week 4 mean BFI value reflected normal bowel function) vs. prior analgesic therapy ($P < 0.001$) • Pain-related functional impairment ($P < 0.001$) improved from baseline • Tolerability was "good/very good" in 89% of patients
Kang et al.[77]	4-week, single-arm study of OXN PR (20/10 mg bid starting dose) added to prior pregabalin or gabapentin in patients with chemotherapy-induced peripheral neuropathy ($n = 66$)	• OXN PR improved pain intensity scores ($P < 0.0001$) • OXN PR reduced numb/tingling hands ($P = 0.043$) and feet ($P < 0.0001$; FACT/GOG-Ntx) • ADRs included dizziness 21% and nausea 10%
Lazzari et al.[75]	Retrospective, observational, single-center study of open-label OXN PR (starting dose ≤ 30/15 mg/day) for 8 weeks in patients with constipation and neuropathic pain; $n = 200$ (all received concomitant gabapentin/pregabalin)	• OXN PR was associated with improved pain intensity and reduced use of rescue medication vs. baseline ($P < 0.0001$) • BFI improved ($P < 0.0001$) and laxative use decreased • For PGIC, 88% reported "much/extremely improved" • Findings were consistent regardless of age (≥ 65 vs. <65 years) or etiology of neuropathic pain

ADR, adverse drug reaction; AE, adverse event; BFI, Bowel Function Index; bid, twice daily; BPI-SF, Brief Pain Inventory Short Form; FACT/GOG-Ntx, Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group/Neurotoxicity; OXN PR, prolonged-release oxycodone/naloxone; PGIC, Patients' Global Impression of Change; QoL, quality of life; RCT, randomized, controlled trial.

Low Back Pain. Low back pain is thought to cause more disability worldwide than any other condition.[49] Unfortunately, improved understanding of the etiology of chronic low back pain has not translated into a decrease in prevalence or burden.[50] Indeed, an estimated 10% of individuals report chronic, impairing low back pain, of whom 84% seek health care.[51] When managing low back pain, it is recommended that pharmacological and interventional approaches be considered within a broader therapeutic framework, which includes physical and psychosocial strategies.[50,52] While consensus on the role of opioid analgesics to manage low back pain is lacking,[52,53] some treatment guidelines recommend opioids, sometimes for a limited duration, as an option for individuals who do not gain adequate relief from paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs).[54–57] Clinicians should also establish whether the source of low back pain is mechanical, neuropathic, or of mixed origin, as this may influence responsiveness to opioid therapy.[58]

While individuals with chronic, moderate-to-severe low back pain have been included in studies investigating OXN PR for a broad range of patients with noncancer pain, we identified 5 studies specifically investigating OXN PR in this setting (see Table 2). These include a large-scale ($n = 463$), 12-week, double-blind, placebo- and active-controlled RCT.[59] OXN PR (10/5 mg bid or 20/10 mg bid starting dose) was found to provide comparable analgesia to OXY PR in patients with moderate-to-severe, chronic low back pain, in tandem with improved bowel function in the subgroup of patients with substantial OIC at baseline (BFI score ≥ 50), as demonstrated by BFI and complete, spontaneous bowel movement (CSBM) scores.[59] The efficacy and tolerability of OXN PR was maintained during an open-label, 1-year extension phase of pooled studies.[60] Similar findings in this setting were reported in a smaller scale ($n = 83$) 4-week, placebo-controlled cross-over RCT, which showed significant improvements in sleep and analgesia with OXN PR that were maintained during a 6-month open-label evaluation.[61] While this study did not demonstrate improvements in BFI scores with OXN PR vs. placebo during the 4-week randomized treatment, most patients were not considered to be constipated at study baseline (mean [SD] daily bowel evacuation score of 1.0 [0.5]).

The utility of OXN PR for chronic, moderate-to-severe low back pain was also investigated in 2 multicenter 12-week observational studies based on the German Pain Registry (PROBE and PROBE 2; see Table 2). These studies were designed to reflect routine clinical practice in Germany and enrolled a broad

Table 4. Summary of Clinical Trials and Observational Studies Investigating OXN PR for Pain Associated with Osteoarthritis and Other Musculoskeletal Disorders

Reference	Study Overview	Key Outcomes
Blagden et al.[81]	Pooled analysis of 12-month extension phases of open-label OXN PR (≤ 120/60 mg/day) following two 12-week, double-blind RCTs of OXN PR vs. OXY PR in patients with moderate-to-severe chronic pain and OIC at baseline (OXN3001/OXN3006); *n* = 474 (~87% with musculoskeletal pain)	• OXN PR maintained analgesic efficacy and bowel function (BFI scores) observed in prior 12-week RCT for up to 12 months • Improvement in BFI scores was most marked in patients who received OXY PR during prior double-blind treatment • No new safety issues were observed with long-term OXN PR
Hesselbarth et al.[83, 84]	Prospective, observational 4 to 6 week study of OXN PR (dosed according to pain severity) vs. other opioids; *n* = 588 (~92% with moderate-to-severe musculoskeletal pain)	• Greater reductions in baseline pain intensity with OXN PR vs. other opioids ($P < 0.0001$) • Improvements BFI score were observed with OXN PR ($P < 0.0001$) but not other opioids (patients in "other opioid" group did not have constipation at baseline) • HRQoL gains (BPI-SF composite pain interference and EQ-5D scores) were more pronounced with OXN PR vs. other opioids • More patients rated the effectiveness (73% vs. 55%) and tolerability (84% vs. 69%) of OXN PR as "very good/good" vs. other opioids • Similar outcomes to the total population were observed in the OXN PR 40/20 mg/day cohort (*n* = 48) and in an opioid-naïve subgroup (*n* = 148)
Lowenstein et al.[72]	Double-blind, 12-week RCT of OXN PR (titrated to ≤ 80/40 mg/day) vs. OXY PR in patients with moderate-to-severe chronic pain and OIC; *n* = 278 (back pain 61%, OA ~29%, osteoporosis ~10%; OXN3006)	• Improvements in BFI scores observed with OXN PR vs. OXY PR after 1 week were maintained to week 12 ($P < 0.0001$) • More CSBM and lower laxative use ($P = 0.0009$) with OXN PR • Comparable analgesic efficacy with OXN PR and OXY PR • No unanticipated safety signals with OXN PR
Lowenstein et al.[80]	Pooled analysis of two 12-week, double-blind RCTs of OXN PR vs. OXY PR in patients with moderate-to-severe chronic pain and OIC (OXN3001/OXN3006); *n* = 587 (86% with musculoskeletal pain)	• Noninferior analgesia with OXN PR vs. OXY PR • Improved bowel function with OXN PR, including lower BFI scores and less laxative use ($P < 0.0001$) • Comparable general health (SF-36) and patient satisfaction (TSQM) with OXN PR vs. OXY PR • No unanticipated AEs with OXN PR
Rosa et al.[82]	Randomized, 4-week, single-center study of OXN PR vs. other opioid analgesics (OXY, transdermal fentanyl, hydromorphone) in patients with chronic osteoarticular pain; *n* = 60	• OXN PR was associated with shorter duration to titrate to effective analgesic dose (15 vs. 17 days), lower effective dose (72 vs. 80 mg), and longer duration of stable dose (77 vs. 58 days) vs. other opioids • OXN PR was also associated with improved BFI scores, which was not observed in the "other opioids" group
Schutter et al.[85]	Prospective, observational 4-week study of OXN PR (dose determined by treating physician) in patients with severe chronic pain; *n* = 7836 (86% musculoskeletal pain)	• OXN PR reduced strongest pain ($P < 0.001$) and increased the proportion of patients without pain in the prior 24 hours ($P < 0.001$) • BFI scores improved in all patients ($P < 0.001$); improved BFI was most marked in opioid-pretreated patients (opioid-naïve patients were not constipated at baseline) • Serious ADRs were reported by 2.3% • Efficacy and tolerability were considered "good" or "very good" by 84% and 87%, respectively
Simpson et al.[73]	Double blind, 12-week RCT of OXN PR (mean dose 33 mg/day) vs. OXY PR in patients with moderate-to-severe chronic pain and OIC; *n* = 322 (~72% with OA; OXN3001)	• Improved BFI scores with OXN PR vs. OXY PR were observed after 1 week and maintained ($P < 0.0001$) • More CSBM and lower laxative use with OXN PR ($P < 0.0001$) • Analgesic efficacy of OXN PR and OXY PR was comparable • No unanticipated AEs with OXN PR • Efficacy and tolerability was maintained during 12-month open-label extension phase of pooled studies (OXN3001/OXN3401)[60]

ADR, adverse drug reaction; AE, adverse event; BFI, Bowel Function Index; BPI-SF, Brief Pain Inventory Short Form; CSBM, complete, spontaneous bowel movement; HRQoL, health-related quality of life; OA, osteoarthritis; OIC, opioid-induced constipation; OXN PR, prolonged-release oxycodone/naloxone; OXY, oxycodone; OXY PR, prolonged-release oxycodone; RCT, randomized, controlled trial; SF-36, Short Form-36; TSQM, Treatment Satisfaction Questionnaire for Medicine.

spectrum of patients who required opioid analgesics to manage their pain. While these studies were of open-label treatment, analysis of study endpoints was blinded.[62–65] The PROBE study included 453 patients randomized to OXN PR, OXY PR, or morphine and 448 patients with opioid medication allocated based on physician decision. In the randomized cohort, significantly more patients receiving OXN PR were responders

Table 5. Clinical Studies Investigating OXN PR for Parkinson's Disease-Related Pain, Severe Bladder Pain, Pain in Elderly Patients, and in Laxative-Refractory Patients with Pain

Neurologic Disorders	Study Overview	Key Outcomes
Parkinson's disease–related pain		
Madeo et al.[89]	8-week single-center, uncontrolled study (OXN PR 5/2.5 mg bid) in Parkinson's disease–related pain; $n = 16$	• OXN PR provided analgesia ($P < 0.05$) • No adjustments to dopaminergic therapy were required • No detrimental effect on BFI scores or sleep • 2 patients (12.5%) discontinued due to AEs
Trenkwalder et al.[88]	Placebo-controlled, 16-week RCT (OXN PR 5/2.5 mg bid starting dose) followed by 4-week extension phase of open-label OXN PR in severe Parkinson's disease–related pain; $n = 202$ (OXN3502)	• Improvements in pain scores at weeks 4 to 12 ($P \leq 0.021$; week 16 primary endpoint was not met) and in the per protocol population at week 16 ($P = 0.010$) with OXN PR vs. placebo • Improvements in severe musculoskeletal pain and nocturnal pain at week 16 with OXN PR vs. placebo ($P \leq 0.023$) • There were more responders for CGI-I ($P = 0.02$) and reduction of baseline pain ($P = 0.02$) with OXN PR vs. placebo • No worsening of other nonmotor symptoms • Treatment-related AEs 57% in both groups and no unanticipated adverse effects
Severe bladder pain syndrome		
Goebell et al.[99,100]	Pilot RCT of OXN PR (≤ 20/10 mg bid) or placebo for 8 weeks followed by open-label OXN PR for 4 weeks in women with severe bladder pain syndrome; $n = 60$	• Greater improvements in pain scores with OXN PR vs. placebo at week 8, and further decreases during open-label OXN PR • Lower use of rescue ibuprofen with OXN PR vs. placebo • Lower impact of urinary and pain symptoms (ICSI, ICPI) with OXN PR vs. placebo ($P \leq 0.019$) • Fewer AEs with OXN PR vs. placebo
Elderly patients		
Guerriero et al.[107,108]	Open-label prospective study of OXN PR (starting dose 10/5 mg/day) in opioid-naïve patients ≥ 70 years of age with noncancer pain for 4 weeks, followed by 52-week extension phase; = 53	• OXN PR improved pain ($P < 0.0001$) and reduced the need for rescue paracetamol ($P < 0.0001$) at week 4 vs. baseline • No decline in cognitive (MMSE) or bowel (BFI) functions were reported at week 4 or week 52 • ≥ 30% reduction in baseline pain intensity without worsening bowel function was achieved at week 4 and week 52 by 78% and 96%, respectively ($P < 0.0001$) • OXN PR improved daily functioning at week 4 and week 52 (Barthel Index, $P \leq 0.01$) • OXN PR was generally well tolerated long-term
Petro et al.[109]	Prospective, open-label 45-day study of OXN PR (5/2.5 mg bid starting dose) in opioid-naïve patients > 65 years of age with musculoskeletal pain (94%) and cognitive impairment; $n = 53$	• OXN PR improved mean pain intensity ($P < 0.0001$) and daily functioning (Barthel Index, $P < 0.0001$) • Improvements in neuropsychiatric symptoms (Neuropsychiatric Inventory) were also reported ($P < 0.0001$) • OXN PR was well tolerated and did not worsen bowel function
Laxative-refractory patients		
Jones & Tripathi[111]	Single-center, observational study of OXN PR (mean starting dose 10.6/5.3 mg/day) in patients with chronic pain (54% low back pain) and OIC despite laxative use (31% ≥ 2 classes of laxatives); $n = 26$	• BFI scores improved from baseline at week 4 ($P < 0.001$), week 8 ($P < 0.05$), and week 12 ($P < 0.001$) • Reduction in pain scores were observed from baseline to week 12 ($P < 0.05$) • 83.3% indicated OXN PR as improvement on their prior medication • AEs reported by 23%
Koopmans et al.[110]	Pooled analysis of OXN PR (20/10 to 120/60 mg/day) for 4 weeks or 12 weeks in patients with cancer-related or noncancer pain and OIC refractory to ≥ 2 classes of laxatives (studies OXN2001, OXN9001); $n = 75$	• OXN PR improved BFI scores: mean reduction 21.2 points ($P \leq 0.0002$) • BFI was within normal range (≤ 28.8) in 43% of patients by day 15 • 36% of patients stopped using laxatives ($P < 0.001$) • Pain scores remained stable and no unanticipated AEs were reported
Mehta et al.[113]	Single-center, observational study of OXN PR (starting dose 10/5 mg/day) for 12 weeks in patients with noncancer pain and OIC unable to tolerate/not responded to laxatives; $n = 28$	• Mean baseline BFI score (79.3) reduced to within normal range (≤ 28.8) by week 1 ($P < 0.001$) and was maintained to week 12 ($P = 0.004$)

Table 5. (Continued)

Neurologic Disorders	Study Overview	Key Outcomes
		• Baseline PAC-QOL scores were improved from week 1 to week 12 ($P \leq 0.005$)
Poelaert et al.[112]	Observational study of OXN PR (median dose 20/10 mg/day) for 12 weeks in patients with noncancer pain (91%) and OIC refractory to ≥ 2 classes of laxatives; $n = 68$	• OXN PR was associated with improvements in pain ($P < 0.001$) and BFI (mean reduction 48.5 points, $P < 0.001$) vs. prior OXY PR • Improvements in EQ-5D QoL scores were reported ($P < 0.001$) • Laxative use reduced from baseline (96% vs. 39%, $P < 0.0001$) • AEs reported by 2.9%

AE, adverse event; bid, twice daily; BFI, Bowel Function Index; CGI-I, Clinical Global Impression-Improvement; ICPI, O'Leary-Sant Intestitial Cystitis Problem Index; ICSI, O'Leary-Sant Interstitial Cystitis Symptom Index; MMSE, Mini-Mental State Examination; OIC, opioid-induced constipation; OXN PR, prolonged-release oxycodone/naloxone; OXY PR, prolonged-release oxycodone; PAC-QOL, Patient Assessment of Constipation Quality of Life; QoL, quality of life; RCT, randomized, controlled trial.

for the primary endpoint comprising lack of premature treatment discontinuation, BFI worsening ≤ 50% from baseline, and ≥ 50% improvement from baseline in pain-related measures.[63] In the overall population ($n = 901$), more patients receiving OXN PR also reported ≥ 50% improvement in pain intensity, functional disability, and QoL measures and more maintained BFI scores within normal range compared with patients receiving morphine or OXY PR.[62–64] These findings are supported by PREFER, a 3-week, open-label study investigating patient preference for opioid therapy. Of 169 patients (62% had low back pain), OXN PR improved QoL measures, with most marked gains in individuals with OIC who were previously treated with WHO step II analgesics; greater patient preference for OXN PR compared with prior opioid analgesic therapy was also reported.[66]

PROBE 2, the second open-label, blinded endpoint, 12-week observational study, investigated the efficacy and tolerability of OXN PR and tapentadol, a μ-opioid receptor agonist and selective noradrenaline reuptake inhibitor, in patients with low back pain with a neuropathic component.[65] Using a composite endpoint that captured improvement in pain, pain-related disability, and QoL, the benefit:risk profile of OXN PR was shown to be noninferior to tapentadol, and to be superior to tapentadol when more stringent response criteria were applied. The safety/tolerability profiles of OXN PR and tapentadol were reported to be broadly comparable.[65] OXN PR (starting dose 10/5 mg bid) was also compared with tapentadol in a 12-week RCT of 258 opioid-naïve patients with chronic low back pain that included a neuropathic component. Noninferiority of the treatments in terms of analgesia and constipation was demonstrated.[67,68] This study suggested greater improvements in neuropathic pain-related symptoms and health-related QoL and a favorable safety profile with tapentadol vs. OXN PR.[67,68] This finding is in contrast to PROBE 2 and underlines the need for further head-to-head trials and to consider the individual safety profiles of therapies and optimal dosing strategies to personalize analgesic therapy.

Neuropathic Pain. Neuropathic pain, or pain arising as a direct consequence of a lesion or disease affecting the somatosensory system, can be very disabling and has numerous causes and manifestations.[69] For example, affected patients may include those with neuropathy due to diabetes, cancer patients receiving chemotherapy, patients with nerve lesions following trauma or surgery, and patients with central nervous system lesions such as stroke or spinal cord injury.[70] Unfortunately, more than two-thirds of patients with neuropathic pain are reported to obtain insufficient pain relief.[69] Treatment recommendations from the Special Interest Group on Neuropathic Pain (NeuPSIG) support the use of OXY and morphine as third-line therapy for individuals with inadequate pain relief using other agents, including anticonvulsants, tricyclic antidepressants, serotonin noradrenaline reuptake inhibitors, or lidocaine patches.[71]

While several RCTs of OXN PR have included some patients with moderate-to-severe neuropathic pain,[72,73] the effectiveness and tolerability of OXN PR in this setting was specifically investigated in 4 studies identified in our literature search (see Table 3). Two large-scale observational studies included a total of 1,688 patients with neuropathic pain, receiving OXN PR at mean starting doses of 24.4 mg/day and 16 mg/day, respectively (concomitant gabapentin/pregabalin was permitted).[74,75] In these "real-life" settings, OXN PR provided clinically relevant improvements in pain, functional impairment, and BFI scores compared with prior therapy, and was

Table 6. Clinical Studies Investigating OXN PR for Postsurgical Pain

Reference	Study Overview	Key Outcomes
Comelon et al.[91]	RCT of OXY PR vs. OXN PR (10/5 mg bid) for 3 days after laparoscopic hysterectomy; *n* = 85	• Comparable bowel function for OXY PR and OXN PR • Comparable analgesia and adverse effect profile for both groups • Few patients were dissatisfied with their pain medication (OXY PR 11%, OXN PR 5%)
Creamer et al.[97]	Open-label, single-center feasibility study of OXY PR vs. OXN PR (10/5 mg prior to anesthesia then 5/2.5 to 20/10 mg bid) until discharge from hospital for laparoscopic colorectal surgery; *n* = 50	• Return to gut function by day 3 may be similar with OXY PR vs. OXN PR (65% vs. 48%, $P > 0.05$) • OXN PR vs. OXY PR was associated with a shorter time to first bowel movement (87 vs. 111 hours, $P = 0.031$) • Total opioid consumption may be similar with OXY PR vs. OXN PR • (78 vs. 94 mg, $P > 0.05$)
Kampe et al.[92]	Single-center, retrospective study OXY PR vs. OXN PR (20/10 mg every 6 hours) administered with metamizole following thoracic surgery or thoracoscopy; *n* = 788	• OXN PR provided less effective analgesia than OXY PR on day 2 ($P \leq 0.01$) and comparable analgesia on days 5 and 6 • More patients receiving OXN PR vs. OXY PR received oral opioids following discharge from hospital ($P \leq 0.004$)
Kokki et al.[98]	RCT (single-blind) of OXY PR vs. OXN (10/5 mg bid) for 7 days following spinal surgery; *n* = 180 (opioid-naïve and on-opioid subgroups)	• Constipation was common at baseline: 29% and 48% of opioid-naïve and on-opioid patients, respectively • Opioid-naïve: day 7, constipation similar with OXN PR (57%) vs. OXN PR (58%) but was less prevalent at day 21 (20% vs. 7%) • On-opioid: constipation similar with OXN PR vs. OXY PR on day 7 (64% vs. 64%) and day 21 (16% vs. 17%) • Use of laxatives was lower with OXN PR vs. OXY PR in opioid-naïve and on-opioid subgroups • Analgesia was similarly effective for OXN PR vs. OXY PR in opioid-naïve and on-opioid subgroups
Kuusniemi et al.[93]	3 studies of OXN PR in postorthopedic surgery settings: • IPOP: RCT of OXN PR (20/10 mg bid or 10/5 mg bid) vs. OXY PR; *n* = 137 (OXN4505) • NIS: open-label, prospective study of OXN PR (dose determined by investigator) vs. other opioids; *n* = 80 (OXN9503) • QIP: open-label, prospective follow-up study of OXN PR (dose determined by investigator); *n* = 44	• IPOP: similar analgesic efficacies of OXN PR and OXY PR • NIS: OXN PR was associated with less restriction to carry out physiotherapy, lower use of laxatives (21% vs. 32%), and better tolerability vs. other opioids • QIP: OXN PR was associated with improved bowel function ($P \leq 0.04$) and ability to pass urine ($P = 0.03$) vs. baseline • No safety concerns were raised in any study
Oppermann et al.[94]	Prospective, noninterventional study of OXN PR (10/5 mg bid starting dose) vs. other opioids following total knee replacement; *n* = 80	• Similar analgesia with OXN PR vs. other opioids • OXN PR was associated with numerically better bowel function (mean BFI scores were within normal range) and better early functional outcomes (modified Larson score) vs. other opioids ($P = 0.018$) • OXN PR was generally better tolerated: ADRs 23% vs. 38%
Ruetzler et al.[95]	Randomized open-label, single-center study of OXN PR vs. patient-controlled IV morphine (equivalent starting doses) following cardiac surgery; *n* = 51	• Similar analgesia with OXN PR and morphine • Total opioid dose was lower for OXN PR vs. morphine (34 vs. 69 mg, $P < 0.001$) • OXN PR was generally better tolerated than morphine
Scardino et al.[96]	Retrospective single-center study of OXN PR (10/5 mg bid starting dose) with oral ketoprofen for 4 days after total hip replacement; *n* = 282	• Pain was well controlled during rest and movement (no patients had severe breakthrough pain) • 72% were "very satisfied" with their pain therapy • No patient reported severe pain or required IV morphine rescue

ADR, adverse drug reaction; BFI, Bowel Function Index; bid, twice daily; IPOP, immediate postoperative period; NIS, noninterventional study; OXN PR, prolonged-release oxycodone/naloxone; OXY PR, prolonged-release oxycodone; QIP, quality improvement program; RCT, randomized, controlled trial.

reported to be well tolerated.[74,75] These findings are supported by a third large-scale observational study of OXN PR (mean starting dose 15/7.5 mg/day; 19% received concomitant anticonvulsants) in 1,051 patients with constipation (37% had received prior opioid analgesia), of whom approximately 85% had chronic, moderate-to-severe neuropathic pain.[76] Furthermore, in a 4-week, single-arm study of 66 patients with chemotherapy-induced peripheral neuropathy inadequately controlled by pregabalin or gabapentin, additional OXN PR (20/10 mg/day starting dose) provided improved pain relief and neuropathic symptom control (reduced numbness/tingling of hands and feet).[77]

Pain Due to Osteoarthritis and Other Musculoskeletal Disorders. Osteoarthritis (OA) affects an estimated 27 million and 8.5 million adults in the United States and United Kingdom, respectively.[78] The prevalence of OA increases with age, affecting approximately one-third of individuals ≥ 65 years of age.[78] Pain is the hallmark symptom of OA and arises due to intra-articular and extra-articular factors.[78] Patients with OA are treated with a combination of nonpharmacologic and pharmacologic modalities, with opioid analgesics recommended for those who do not respond to acetaminophen, if NSAIDs and cyclooxygenase (COX)-2 inhibitors are contraindicated, and for patients with contraindications or unwilling to undergo total joint arthroplasty having failed medical therapy.[58,79]

Most studies identified in our literature search that investigated the impact of OXN PR on OA also included patients with other types of moderate-to-severe pain, including musculoskeletal conditions such as osteoporosis (see Table 4). These include two 12-week, double-blind RCTs in which patients with OIC received OXN PR at daily doses of up to 80/40 mg (1 study permitted up-titration to 120/60 mg/day for patients regularly taking > 2 doses of rescue medication).[72,73,80] In both studies, OXN PR was associated with comparable analgesia to OXY PR and better bowel function, including clinically relevant improvements in BFI score, increased number of CSBMs, and reduced laxative intake.[72,73,80] Pooled data from 12-month extension phases of both RCT studies, in which patients completing double-blind treatment with OXN PR or OXY PR received open-label OXN PR, demonstrated that pain control and bowel function with OXN PR was maintained long term, and no new safety issues were detected.[81] Similar findings were also reported in a 4-week, open-label randomized trial of 60 patients with osteoarticular pain. In this study, OXN PR provided a lower and more stable effective analgesic dose compared with other opioid analgesics (oxycodone, hydromorphone, and transdermal fentanyl) as well as improved BFI scores.[82]

The utility of OXN PR to treat moderate-to-severe musculoskeletal pain during routine clinical practice was investigated in 2 large-scale observational studies (see Table 4). These studies included 8,424 patients in total (> 86% had musculoskeletal pain, with causes of pain specified in 1 study only, which included degenerative spinal diseases, severe OA/arthritis, and osteoporosis).[83–85] Both studies found OXN PR provided more effective pain relief than prior analgesics, including other opioids, and had a positive impact on BFI scores. OXN PR was also considered "good/very good" in terms of efficacy and tolerability by ≥ 73% of patients.[83–85] Furthermore, 1 study reported that the therapeutic benefits of OXN PR in this setting were more pronounced compared with other opioids.[83,84]

Parkinson's Disease–Related Pain. In addition to the cardinal motor symptoms of Parkinson's disease, pain is a common nonmotor symptom that affects two-thirds of patients with this disease.[86] Parkinson's disease–related pain is a complex disorder and has a variety of manifestations, including musculoskeletal, visceral, nocturnal, orofacial, limb, and abdominal pain.[87] Low-dose OXN PR (5/2.5 mg bid starting dose) was investigated in 2 studies of Parkinson's disease–related pain (see Table 5). A phase II study of 202 patients with severe Parkinson's disease–related pain found that while the numerical reduction in 24-hour pain at week 16 was not statistically significant with OXN PR vs. placebo in the full analysis population, OXN PR was associated with significant improvements in average 24-hour pain at weeks 4, 8, and 12, and in the per protocol population at week 16.[88] Patients with severe musculoskeletal or nocturnal types of Parkinson's disease–related pain at baseline who received OXN PR reported significant improvements at week 16 compared with placebo.[88] Furthermore, OXN PR was not associated with worsening of other Parkinson's disease nonmotor symptoms, including mood and perceptual disorders, and there were no unanticipated adverse effects.[88] The findings from this study are supported by an 8-week observational study of OXN PR, which also reported clinically significant reductions in pain and no worsening of bowel function in 16 patients with moderate-to-severe Parkinson's disease–related pain.[89]

Postsurgical Pain. Guidelines recommend a tailored approach for the management of postoperative pain, and short-acting oral opioids are generally preferred over long-acting oral opioids for the immediate postoperative period, due in part to dose titration requirements.[90] Our literature search identified 8 studies investigating short-term administration of OXN PR to manage pain following surgery, including RCTs, open-label studies, and retrospective studies (see Table 6).[91–98] Together, the finding suggested broadly comparable analgesia with OXN PR vs. OXY PR, morphine, or other opioid analgesics, and some but not all studies also documented additional improvements in bowel function and early functional outcomes with

OXN PR.[91–98] High patient satisfaction (72% "very satisfied") with OXN PR plus oral ketoprofen was reported in a study of patients following hip replacement.[96] One study conducted in an orthopedic surgery setting investigated bladder function and reported less difficulty in passing urine with OXN PR vs. OXY PR.[93]

Bladder Pain. A pilot RCT of 60 women with severe pain due to bladder pain syndrome reported improvement in pain scores, lower use of rescue medication, and lower impact of urinary and pain symptoms with OXN PR at doses of up to 20/10 mg bid compared with placebo (see Table 5).[99,100]

Elderly Patients with Chronic Moderate-to-Severe Pain. Chronic moderate-to-severe pain is particularly prevalent in elderly individuals, due in part to age-related increases in the incidences of cancer and degenerative diseases such as OA. Given the demographic imperative of an aging population, addressing chronic pain in older individuals is a growing priority.[101] However, this can be complicated by age-related factors such as comorbidities, concomitant medications, physiological changes affecting drug bioavailability, and cognitive decline.[102] Evidence that NSAIDs and COX-2 inhibitors can lead to life-threatening adverse effects in older patients with gastrointestinal or cardiovascular disease has shifted attention to opioid analgesics.[103] While opioids are recommended for selected elderly patients with chronic, severe, cancer-related, and noncancer pain, careful management of therapy is cautioned and it is recommended that the safety profile of different opioids be considered when selecting opioids for this patient group.[103,104] It is widely recognized that constipation is more common in elderly patients, which may be due to reduced mobility, dietary factors, medical conditions, and/or concomitant medications.[105] Consequently, this population may be particularly vulnerable to OIC. Indeed, OIC was reported in 86% of older patients (mean age 61 years) receiving opioid analgesia in a large-scale observational study.[106]

While several RCTs of OXN have included a number of older patients,[41,72,88] our literature search also identified studies in which OXN PR (starting dose 10/5 mg/day) was specifically investigated in elderly individuals (see Table 5). In an open-label, prospective study of 53 opioid-naïve older patients (mean age 81 years) with chronic noncancer pain, OXN PR for up to 1 year significantly improved pain and functioning, and was generally well tolerated with no negative effects on cognitive functioning or BFI scores.[107,108] A second open-label, prospective study of 53 elderly patients with cognitive impairment and moderate-to-severe musculoskeletal pain also reported improved analgesia and daily functioning with OXN PR without worsening bowel function; interestingly, a significant improvement in dementia-associated symptoms was also observed.[109]

Laxative-Refractory Patients with Chronic Moderate-to-Severe Pain. Laxatives are effective for many (but not all) patients with idiopathic constipation, and the same holds true for patients with OIC.[9] Potential reasons for failure of laxatives include poor tolerance (including unpalatable taste and adverse effects such as bloating), unpredictable onset of action, and lack of efficacy. Indeed, some patients have OIC that is particularly difficult to treat, including individuals who experience no symptomatic relief despite taking several different types of laxatives. Small-scale studies and a retrospective analysis were identified in our literature search indicating that OXN PR may be an effective treatment option for these patients.[110–113]

A pooled analysis of RCTs investigating OXN PR vs. OXY PR for chronic moderate-to-severe pain included a subgroup of 75 patients with OIC who had not been treated satisfactorily with at least 2 classes of laxatives.[110] These patients experienced significant improvements in BFI scores from baseline, with 43% of individuals having a BFI score within the normal range by day 15.[110] Similar findings were reported in a small (n = 26), 12-week, single-center study of OXN PR in patients with OIC despite laxative therapy in which 83% of patients reported OXN PR was better than their previous opioid analgesia regimen.[111] Two 12-week observational studies of patients with laxative-refractory OIC also reported clinically relevant improvements in pain, bowel function, and QoL compared with prior treatments.[112,113]

Cost-Effectiveness Studies of OXN PR for Moderate-to-Severe Pain

Cost-utility studies were identified in our literature search, which together demonstrate that OXN PR is a cost-effective treatment compared with OXY PR for patients with moderate-to-severe pain and OIC. These studies included 3 analyses based on RCT data, performed in the United Kingdom, Canada, and Italy,

indicating that while analgesic costs are higher for OXN PR than OXY PR, drug cost is offset by lower use of laxatives, other healthcare resources, and greater QoL gains.[114–116] Indeed, the incremental cost-effectiveness ratio of OXN PR per quality-adjusted life-year gain was estimated to be £5,841, €475, and $2,178 to $7,732 CDN, and reported to be well below accepted cost-effectiveness thresholds.[114–116] An 8-week questionnaire-based observational study conducted in Sweden also indicated that switching from OXY PR and laxatives to OXN PR was associated with QoL gains and reduced need for healthcare visits, fewer hospitalizations due to pain or constipation, and reduced laxative use, which together translated into direct cost savings.[117] Tapentadol extended-release (ER) was reported to be slightly more cost-effective than OXN PR for treating OIC in 1 economic evaluation based on a meta-analysis of 3 RCTs, due to lower incidence of adverse events and fewer discontinuations.[116]

DISCUSSION

Extensive data from clinical trials and real-world studies demonstrate that OXN PR provides effective analgesia for moderate-to-severe cancer-related pain and noncancer pain types such as low back pain, neuropathic pain, musculoskeletal pain, Parkinson's disease–related pain, and postsurgical pain.[41,59,73,76,85,88,93] Furthermore, limited studies conducted specifically in elderly patients indicate that OXN PR is effective in this setting with no unanticipated safety concerns.[108] Given the substantial impact of OIC on patients' QoL and the economic burden of this condition, which has been attributed to increased healthcare utilization and reduced work productivity,[118,119] it is important to note that most studies of OXN PR demonstrated substantial improvements in bowel function in patients with OIC. This includes clinically significant reductions in BFI scores in patients with OIC refractory to at least 2 different types of laxatives[110] and BFI scores approaching nonconstipated values in several studies of patients with OIC at baseline.[44,81] The observation of effective analgesia in tandem with cognitive improvements in a small open-label study of patients with musculoskeletal pain and cognitive impairment was interesting; however, further RCTs are required to validate this finding.[109] In addition, while much of the published data on OXN PR across indications and treatment settings we identified were from double-blind RCTs or large-scale observational studies designed to reflect real-world practice,[41,63,80,85] the majority of this research was initiated by the pharmaceutical company that manufactures OXN PR.

All patients initiating opioid analgesia should be educated about OIBD, including OIC. To our knowledge, there are no RCTs suggesting that 1 particular laxative is most effective for managing OIC symptoms. Indeed, systematic reviews investigating laxatives in constipated palliative care patients, the majority of whom are receiving opioid analgesia, conclude that evidence for a role of laxatives in this setting is limited.[120,121] While laxatives are widely used as first-line therapy for OIC, several recent treatment guidelines recommend that opioid-antagonist-based therapies be considered either when initiating opioid therapy or for patients with OIC who fail to respond to laxatives, and provide a strong recommendation that OXN PR is more effective than oxycodone at avoiding OIC.[7,11,13] This is supported by several studies concluding that OXN PR is a cost-effective treatment compared with OXY PR, due to lower use of laxatives and healthcare resources, as well as QoL gains.[114–116] Based on available evidence, OXN PR represents a rationale treatment option for appropriately selected patients with moderate-to-severe pain, either to manage or avoid OIC. However, it should be remembered that patients receiving OXN PR may still require laxatives to address their constipation, which can be due to causes in addition to opioid therapy.

The fixed-dose combination formulation of OXN PR is associated with patient convenience and potential improved compliance compared with separate tablets of OXY PR and naloxone. However, disadvantages of a fixed dose include a lack of flexibility regarding the opioid:naloxone ratio, which may be suboptimal for some patients, as well as increased tablet cost compared with opioid plus laxatives. Further, while the available OXN PR 5/2.5 mg, 10/5 mg, 20/10 mg, and 40/20 mg tablets provide flexibility for dose titration, not all doses can be achieved. Initial studies of OXN PR were conducted across a limited dose range (up to 20/10 mg bid).[30,59] Based on growing experience with OXN PR and to meet the analgesic needs of a broader range of patients, this dose range was expanded in subsequent studies. OXN PR at doses of 5/2.5 mg bid is reported to provide effective analgesia in some settings, for example, in some elderly patients with noncancer pain and in individuals with severe types of Parkinson's disease–related pain.[88,107–109] However, many patients require higher doses of OXN PR to obtain sufficient pain relief. While the usual starting dose of OXN PR in opioid-

naïve patients is 10/5 mg bid, OXN PR is approved at daily doses of up to 160/80 mg for patients previously maintained on a stable daily dose who require increased analgesia.[27] Indeed, an RCT of OXN PR in patients with cancer-related and noncancer pain who required high doses to manage their pain demonstrated improved bowel function compared with OXY PR and effective analgesia with absence of an analgesic ceiling effect across the clinically relevant dose range investigated (up to 160/80 mg/day).[42] There are also case reports of OXN PR 180/90 mg/day reducing pain scores and improving QoL and OIC symptoms in patients with refractory pain.[122]

While OXN PR has considerable utility for moderate-to-severe pain while addressing OIC, as with other stong opioid analgesics it can be associated with significant adverse effects, which can include sedation and dizziness and gastrointestinal events.[27,123] As such, caution must be exercised when OXN PR is given to elderly or infirm patients or individuals with renal or hepatic impairment (OXN PR in contraindicated in patients with moderate-to-severe hepatic impairment).[27] Risk for potentially fatal respiratory depression is a particular concern when opioids are taken in excess.[27,123] Due in part to concerns about overdose, addiction, and misuse of opioid analgesics, undertreatment of chronic moderate-to-severe pain is common.[7,124,125] When opioid analgesics are used appropriately, the risk for addiction is generally considered to be low.[126] This is supported by studies indicating that adaptation of specific spinal and supraspinal molecular systems associated with chronic pain can decrease the reward effects of exogenous opioids, an effect that may be influenced by polymorphisms in opioid receptor and neuropeptide genes.[127] However, it is widely recognized that abuse and diversion of opioid analgesics is a significant public health challenge, despite screening tools designed to reduce the risk for misuse.[128] Abusers may manipulate opioid formulations to obtain faster absorption and a state of euphoria, for example, by nasal insufflation or intravenous administration of dissolved tablets. OXN PR has abuse-deterrent properties because increased systemic exposure to naloxone antagonizes the effects of OXY, which discourages tampering. Soluble OXN was shown to have significantly less drug-liking and rewarding effects in a randomized, placebo-controlled study of recreational opioid users, and reduced pharmacodynamic responses, drug-liking, and other measures of abuse potential have also been reported for OXN PR compared with OXY when chewed or administered intranasally.[129–131] Indeed, a fall in the rate of opioid-related deaths in recent years has been attributed in part to the introduction of abuse-deterrant formulations of opioid analgesics.[132] Despite the availability of abuse-deterrant formulations, clinicians continue to play a central role in the careful selection and comprehensive monitoring of patients receiving opioid analgesics, and must be adequately trained to look for signs of abuse and misuse.[133] Guidance for European healthcare professionals in the prevention, detection, and management of opioid analgesic dependence has recently been published.[134] Additional, large-scale studies are also required to provide further insight on the impact of OXN PR on deterring opioid abuse in Europe.

In summary, data from a wide variety of clinical trials and observational studies confirm that for selected patients, OXN PR can provide effective analgesia in a wide variety of moderate-to-severe pain settings. Treatment should be administered using a flexible dosing strategy that is tailored to the needs of individual patients. Consistent reports of improved bowel function associated with OXN PR in patients with OIC also underscores the rationale for combining the centrally acting opioid analgesic (OXY) and the locally acting antagonist (naloxone), which has demonstrated antagonism throughout the gut, to address the unique etiology of OIC.

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CONFLICT OF INTEREST

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