

# Developments in managing severe chronic pain: role of oxycodone–naloxone extended release

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**Abstract:** Chronic pain is a highly disabling condition, which can significantly reduce patients' quality of life. Prevalence of moderate and severe chronic pain is high in the general population, and it increases significantly in patients with advanced cancer and older than 65 years. Guidelines for the management of chronic pain recommend opioids for the treatment of moderate-to-severe pain in patients whose pain is not responsive to initial therapies with paracetamol and/or nonsteroidal anti-inflammatory drugs. Despite their analgesic efficacy being well recognized, adverse events can affect daily functioning and patient quality of life. Opioid-induced constipation (OIC) occurs in 40% of opioid-treated patients. Laxatives are the most common drugs used to prevent and treat OIC. Laxatives do not address the underlying mechanisms of OIC; for this reason, they are not really effective in OIC treatment. Naloxone is an opioid receptor antagonist with low systemic bioavailability. When administered orally, naloxone antagonizes the opioid receptors in the gut wall, while its extensive first-pass hepatic metabolism ensures the lack of antagonist influence on the central-mediated analgesic effect of the opioids. A prolonged-release formulation consisting of oxycodone and naloxone in a 2:1 ratio was developed trying to reduce the incidence of OIC maintaining the analgesic effect compared with use of the sole oxycodone. This review includes evidence related to use of oxycodone and naloxone in the long-term management of chronic non-cancer pain and OIC.

**Keywords:** chronic pain, opioid-induced constipation, opioids, oxycodone–naloxone

## Introduction

Chronic pain is a highly disabling condition, which can significantly reduce patients' quality of life. Typically, chronic pain results in depression, anxiety, and loss of independence.<sup>1–4</sup>

Chronic pain is associated with a wide range of cancer and non-cancer pain conditions including neuropathic pain and osteoarthritis. Prevalence of moderate and severe chronic pain is high in the general population, and in a large survey conducted by Breivik et al in more than 46,000 adults in Europe and Israel, 19% of respondents reported having chronic pain.<sup>5</sup> The incidence of pain increases significantly in patients with advanced cancer; in fact, up to 70% of them have been reported to experience chronic pain.<sup>6,7</sup>

The aim of the treatment of chronic pain is to increase the quality of life of the patient with a multidisciplinary and multimodal approach. The pharmacological agents currently used to treat chronic pain include non-opioid analgesics, in particular paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. Guidelines for the management of chronic pain recommend opioids for the treatment of moderate-to-severe pain in patients whose pain is not responsive to initial therapies with paracetamol and/or NSAIDs.<sup>8</sup> Despite their analgesic efficacy being

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well recognized, adverse events (AEs) related to the opioid therapy which include headache, dizziness, fatigue, and especially the opioid-induced bowel dysfunction (OIBD) can affect daily functioning and patient quality of life.<sup>9–12</sup> Opioid-induced constipation (OIC), which is part of OIBD, occurs in 40% of opioid-treated patients.<sup>13</sup> In contrast with the adverse effects mediated through the central opioid receptors, which occur at the start of treatment and usually rapidly disappear, OIC is mediated through intestinal opioid receptors and often persists.<sup>5,13</sup>

Laxatives are the most common drugs used to prevent and treat OIC. Laxatives do not address the underlying mechanisms of OIC, and for this reason, they result ineffective in the majority of patients with OIC.<sup>14,15</sup> In a survey of OIBD conducted by Pappagallo<sup>14</sup> and Kumar et al<sup>16</sup> 54% of patients treated with laxatives did not report the desired improvement at least 50% of the time. One strategy to minimize or prevent OIC while maintaining analgesic efficacy is blocking the intestinal opioid receptor while allowing the activation of the central one.<sup>17,18</sup> Oxycodone is an opioid receptor agonist commonly used for the treatment of patients with moderate-to-severe pain. Oxycodone stimulates opioid receptors in the gastrointestinal tract, modifying normal bowel activity and reducing gut motility, potentially resulting in constipation.<sup>19</sup> Naloxone is an opioid receptor antagonist with low systemic bioavailability. When administered orally, naloxone antagonizes the opioid receptors in the gut wall, while its extensive first-pass hepatic metabolism ensures the lack of antagonist influence on the central-mediated analgesic effect.<sup>20</sup> A prolonged-release formulation consisting of oxycodone and naloxone (PR OXN) in a 2:1 ratio was developed trying to reduce the incidence of OIC maintaining the analgesic effect compared to use of the sole oxycodone.<sup>19</sup>

In this review, we focus on the specific role of PR OXN in the management of chronic pain and OIC in non-cancer patients.

## Methods

A literature search was conducted in the PubMed database using the term “oxycodone and naloxone” through April 2015. All clinical and pharmacokinetic studies and reviews of PR OXN were included. The PubMed search generated 223 results, with 45 containing clinically relevant information of PR OXN. 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 have been increasingly being used in the last decade for the treatment of chronic cancer and non-cancer pain.<sup>21–23</sup> Despite proven analgesic efficacy, their use is associated with constipation that can significantly have an impact on patients' quality of life even more than the pain itself.<sup>24</sup> In a multinational study conducted on more than 300 patients taking daily opioids (PROBE 1), constipation was the most common AE reported by 81% of patients, and it was often reported as severe.<sup>25</sup> OIC is attributed to the activation of the mu-opioid receptors present in the gut wall that lead to decreased gastric motility as well as decreased gastrointestinal, biliary, and pancreatic secretions.<sup>13,26</sup> Additionally, propulsion in the small and large intestines is inhibited, whereas non-propulsive contractions are increased. Bowel dysfunction in patients with OIC, however, is not caused exclusively by the opioid medication. Factors such as pain, medications other than opioids, diet, and underlying disease factors play an important role.<sup>27</sup>

The Bowel Function Index (BFI) is a validated, clinician-administered, patient-reported questionnaire. BFI is designed to evaluate OIC in cancer and non-cancer chronic pain patients, and it uses a numerical scale from 0 (easy) to 100 (severe) to record a patient's subjective assessment of three items related to OIC: ease of defecation, feeling of incomplete evacuation, and patient personal judgment of constipation. A lower score indicates a better bowel function; a score of <28.8 is considered a normal bowel function with respect to OIC, and a BFI change of >12 points is considered a clinically relevant change.<sup>28–32</sup>

Strategies for the management of OIC symptoms include the use of laxatives and treatment with opioid antagonists. Laxatives are commonly used medication to reduce the constipation induced by the chronic use of opioids.<sup>33</sup> Despite the fact that laxatives can be useful in some circumstances, including delayed colonic transit, since OIC has a unique etiology, they are not really effective in its treatment.<sup>25</sup> The interaction between opioids and opioid receptors present throughout the gut can affect numerous gastrointestinal functions, including neural activity, motility, secretion, resorption of fluid, and blood flow.<sup>13,26</sup> Consequently, opioids delay gastric emptying and prolong transit time throughout the small and large intestines. For these reasons, laxatives, which predominantly act on the colon, frequently do not address the symptoms of OIC. No single laxative is considered optimal for OIC. Moreover, there are no direct comparative data on different laxatives in the prevention or treatment of OIC, resulting in a lack of generally accepted guidelines regarding

laxative use for this condition.<sup>34</sup> Furthermore, laxatives are associated with potential side effects including bloating, gas, and gastroesophageal reflux and may be associated with tolerability.<sup>35</sup>

## Oxycodone–naloxone in the prevention–treatment of OIC

The OIBD arise from opioid-mediated actions on the central nervous system (CNS) and gastrointestinal tract.<sup>36</sup> In the CNS, opioids interact with four receptor subtypes ( $\mu$ ,  $\delta$ ,  $\kappa$ , and opioid receptor-like-1) inducing analgesia and reducing the gastrointestinal propulsion due to an alteration of autonomic outflow from the CNS.<sup>36</sup> Nevertheless, the high density of  $\mu$  receptors in the enteric system appears to mediate most of opioid gastrointestinal effects.<sup>37</sup> Studies of the human intestine suggest that  $\delta$  and  $\kappa$  receptors make a lesser contribution to OIC.<sup>37</sup> The incidence of constipation related to the opioid therapy can be reduced using opioid antagonists, such as methylnaltrexone, alvimopan, naloxegol, and naloxone.<sup>38</sup> The aim of using opioid antagonist in patients with OIC is to try to inhibit the actions of the opioids in the gut without affecting their central effect and maintaining their analgesic action.<sup>17</sup> The subcutaneous injection of methylnaltrexone was initially approved only for palliative care in patients with advanced cancer when traditional oral laxatives fail.<sup>39</sup> Methylnaltrexone is, in fact, approved to treat OIC in chronic non-cancer pain too.<sup>40</sup> Alvimopan is approved and indicated for short-term use to accelerate postoperative recovery of upper and lower gastrointestinal tracts after surgeries, but its use is actually characterized by cardiovascular safety concerns.<sup>40</sup> Oral naloxegol was approved in 2014 by the US Food and Drug Administration as an add-on to existing pain therapy, and it has shown to be effective in increasing bowel movements.<sup>40</sup> Naloxegol is a pegylated naloxone molecule with  $\mu$ -opioid antagonist activity, reduced central permeability, and oral bioavailability. Trials showed long-term safety and at least 12 weeks of effectiveness in patients with OIC including patients not previously responding to laxative use.<sup>41</sup> Naloxone is a competitive opioid antagonist at opioid receptors inside and outside the CNS primarily used intravenously for the treatment of opioid overdose. After systemic administration, it reverses both centrally and peripherally mediated opioid effects with a half-life amounting to 1–1.5 hours. Elimination is primarily by glucuronidation in the liver. When administered orally, naloxone antagonizes the opioid receptors in the gut wall, potentially reducing OIC, while its extensive first-pass hepatic metabolism ensures the lack of antagonist influence

on the central analgesic effect.<sup>42</sup> To minimize or prevent OIC while maintaining analgesic efficacy, a prolonged-release tablet consisting of oxycodone and naloxone in a 2:1 ratio was developed.<sup>43</sup> Several randomized controlled trials (RCTs) have reported on the comparable analgesic efficacy of PR OXN and prolonged-release oxycodone (PR OXY), with a clinically relevant improvement in OIC in various types of pain.<sup>44–46</sup> Recently, a noninterventional, observational, real-life study evaluating the pain relief and OIC with PR OXN treatment in daily practice in patients with chronic severe pain compared with previous PR OXY treatment was published.<sup>47</sup> Patients enrolled in this study were treated with PR OXY for at least the last 30 days before PR OXN treatment, and in particular, they reported OIC despite the use of at least two laxatives with different mechanisms of action. Patients were switched immediately from PR OXY to PR OXN with equal oxycodone doses.<sup>47</sup> The study found that PR OXN was superior to PR OXY in terms of pain relief, OIC, and quality of life in patients with chronic pain previously treated with PR OXY and experiencing OIC despite the use of at least two different laxatives.<sup>47</sup> This study confirmed that PR OXN clinically improves OIC even in patients experiencing laxative-refractory OIC. Furthermore, the average BFI was  $<28.8$  after 6 weeks of PR OXN treatment, indicating that most patients were no longer constipated despite opioid treatment.<sup>47</sup> The observed improved pain relief during the study period was not related to an increased dose or increased use of analgesic, and it was probably due to a better adherence to the opioid therapy due to improved OIC.<sup>47</sup>

## Oxycodone–naloxone in the treatment of chronic non-cancer pain

Osteoarthritis and spine pain are two of the leading causes of pain and disability worldwide.<sup>48</sup> Pain in these patients can reduce function and affects a person's ability to carry out his/her daily activities. Guidelines usually recommend the prescription of paracetamol as the first-line analgesic for these conditions.<sup>49–53</sup> Recently, a systematic review and meta-analysis published by Machado et al evaluating the efficacy and safety of paracetamol for spinal pain and osteoarthritis raised doubts related to the place of this medication as a first analgesic choice to treat such conditions.<sup>54</sup> Machado reports that there is “high-quality” evidence that paracetamol does not have a clinical effect as pain medication in patients with low back pain or osteoarthritis.<sup>54</sup> These findings confirmed what was already underlined in the first draft of the new National Institute for Health and Care Excellence guidelines on the

management of osteoarthritis; that is, paracetamol should not be routinely offered to patients as it might not be effective and was potentially associated with side effects when used at high doses for a long period of time.<sup>55</sup> This decision was reversed due to the fact that the Royal College of General Practitioners, the Primary Care Rheumatology Society, and the British Society for Rheumatology raised concerns that removing paracetamol as an analgesia option could result in the increased use of oral NSAIDs and opioids.<sup>56</sup> Despite the limited availability of strong scientific evidence to support long-term opioid therapy for chronic non-cancer pain, use of opioids has increased substantially through the years.<sup>57</sup> In the case of long-term opioid prescription to treat patient with spine pain or osteoarthritis, guidelines are in agreement with regard to providing adequate patient evaluation, judicious opioid dosing, and careful patient monitoring to minimize the risks of AEs and abuse.<sup>57</sup> Oxycodone has been shown to be an effective analgesic in various types of pain, and its combination with naloxone in a fixed 2:1 ratio was tested in terms of analgesic efficacy and gastrointestinal tolerability in a number of clinical studies including RCTs.<sup>44–46</sup>

Due to the degenerative nature of chronic pain in particular in patients with osteoarthritis, effective pain management often requires prolonged therapy. Consequently, the long-term effects of opioid treatments must be established.<sup>57</sup> The effectiveness as pain medication of the fixed combination of oxycodone–naloxone prolonged-release tablets was already demonstrated in studies of short duration (12 weeks).<sup>43,45,46</sup> Recently, a pooled analysis related to two 52-week extension phases evaluating the efficacy and the safety of PR OXN was published.<sup>58</sup> The extension phases, during which all the patients received PR OXN, followed two RCTs conducted in patients with moderate-to-severe non-cancer pain and OIC to compare the efficacy and safety of the combination of oxycodone–naloxone versus oxycodone alone. The pooled analysis showed that pain control was maintained with PR OXN throughout the 12-month study period.<sup>56</sup> Improvement in bowel function, indicated by a decrease in BFI scores, throughout the extension phase was significant in patients who switched from receiving PR OXY in the previous studies to PR OXN at the start of the extension phases. Forty-six percent of the patients experienced treatment-related AEs.<sup>58</sup> Eight percent of the patients experienced constipation that was classified as possibly, probably, or definitely related to study drug. Diarrhea was considered possibly, probably, or definitely related to study drug in only 13 patients, and was considered unlikely related to study medication in five patients.<sup>58</sup>

## Oxycodone–naloxone in older patients

Chronic pain due to osteoarthritis increases dramatically with age, affecting approximately 60% of people aged over 65.<sup>59</sup> Opioids are recommended as part of a multiparmacological pain management for older patients to treat moderate-to-severe chronic pain impairing their daily quality of life. Limits of opioids use in this population are represented by a higher incidence of opioid-related side effects.<sup>60–62</sup> A 4-week, single-center, prospective observational study investigating the analgesic efficacy and tolerability of PR OXN in patients older than 70 years naïve to strong opioids was published by Guerriero et al.<sup>63</sup> The effects of PR OXN on functional and cognitive status, mood, and quality of life were also analyzed. Twenty-six percent of the patients enrolled in this study complained of constipation at baseline, but almost all had BFI values >29, indicating some degree of bowel dysfunction.<sup>63</sup> The administration of PR OXN was associated with a clinically nonsignificant decrease in BFI values throughout the study; otherwise, at the last follow-up visit, fewer patients were still complaining of constipation.<sup>63</sup> Overall, PR OXN was well tolerated during the 28 days of treatment. Out of the 53 patients who started treatment, only one patient experienced a severe AE leading to PR OXN discontinuation within the first week.<sup>63</sup> One of the major concerns of the opioid therapy in the older patients is their potential negative effect on the cognitive function. The impairment of the cognitive function seems to be related to an increase in the daily dose and not with stable doses of opioids.<sup>64–66</sup> In the study by Guerriero et al low dose of PR OXN did not impact negatively on the overall cognitive status of the study population.<sup>63</sup>

## Conclusion

Opioids are routinely used in the treatment of moderate-to-severe pain in a wide range of conditions. Despite their analgesic efficacy, chronic management with opioids is often compromised by adverse effects which include nausea, sedation, euphoria/dysphoria, itching, and what is called OIBD. OIBD comprises several gastrointestinal AEs including constipation that can significantly reduce quality of life. Laxatives are the most commonly used treatments for OIBD, although they are not very effective, since they are not mechanism based. Naloxone is an opioid receptor antagonist with low systemic bioavailability (<3%). If administered orally, naloxone antagonizes the opioid receptors in the gut wall, while its extensive first-pass hepatic metabolism ensures the lack of antagonist influence on the central opioids receptor. Naloxone does not appear to impair



the opioid analgesic effect in the majority of patients. The combination oxycodone–naloxone has been shown to be effective as pain medication and in the prevention–treatment of OIC improving adherence at the opioids pain therapy and the quality of life even after a 12-month therapy and in the older patients.

## Disclosure

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## References

- Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. *Pain*. 2001;89(2–3):127–134.
- Johannes CB, Le TK, Zhou X, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of an Internet-based survey. *J Pain*. 2010;11(11):1230–1239.
- Toblin RL, Mack KA, Perveen G, Paulozzi LJ. A population-based survey of chronic pain and its treatment with prescription drugs. *Pain*. 2011;152(6):1249–1255.
- Vetter TR. A primer on the prevalence of pain in patients with cancer: a systematic review of the past 40 years of health-related quality of life in chronic pain medicine. *Anesth Analg*. 2007;104(3):703–718.
- Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10:287–333.
- Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F. Management of cancer pain: ESMO clinical practice guidelines. *Ann Oncol*. 2012;7:139–154.
- van den Beuken-van Everdingen MH, de Rijke JM, Kessels AG, Schouten HC, van Kleef M, Patijn J. Prevalence of pain in patients with cancer: a systematic review of the past 40 years. *Ann Oncol*. 2007;18(9):1437–1449.
- Hooten W, Timming R, Belgrade M, et al. *Assessment and Management of Chronic Pain*. Bloomington: MN: Institute for Clinical Systems Improvement; 2013.
- Terwindt G, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of headache on quality of life in the general population: the GEM study. *Neurology*. 2000;55(5):624–629.
- Grimby A, Rosenthal U. Health-related quality of life and dizziness in old age. *Gerontology*. 1995;41:286–298.
- Flehtner H, Bottomley A. Fatigue and quality of life: lessons from the real world. *Oncologist*. 2003;8(suppl 1):5–9.
- Panchal SJ, Müller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract*. 2007;61:1181–1187.
- Holzer P, Ahmedzai SH, Niederle N, et al. Opioid-induced bowel dysfunction in cancer related pain: causes, consequences, and a novel approach for its management. *J Opioid Manag*. 2009;5(3):145–151.
- Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg*. 2001;182:11S–18S.
- Ahmedzai SH, Boland J. Constipation in people prescribed opioids. *BMJ Clin Evid*. 2010;6:2010.
- Kumar L, Barker C, Emmanuel A. Opioid-induced constipation: pathophysiology, clinical consequences, and management. *Gastroenterol Res Pract*. 2014;2014:141737.
- Camilleri M. Opioid-induced constipation: challenges and therapeutic opportunities. *Am J Gastroenterol*. 2011;106(5):835–842.
- Choi YS, Billings JA. Opioid antagonists: a review of their role in palliative care, focusing on use in opioid-related constipation. *J Pain Symptom Manage*. 2002;24(1):71–90.
- Riley J, Eisenberg E, Müller-Schwefe G, Drewes AM, Arendt-Nielsen L. Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin*. 2008;24:175–192.
- Mercadante S, Giarratano A. Combined oral prolonged-release oxycodone and naloxone in chronic pain management. *Expert Opin Investig Drugs*. 2013;22:161–166.
- de Leon-Casasola OA. Opioids for chronic pain: new evidence, new strategies, safe prescribing. *Am J Med*. 2013;126(3 suppl 1):S3–S11.
- American Society of Anesthesiologists Task Force on Chronic Pain Management; American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: an updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology*. 2010;112(4):810–833.
- Franklin GM. Opioids for chronic noncancer pain: a position paper of the American Academy of Neurology. *Neurology*. 2014;83(14):1277–1284.
- Bell T, Annunziata K, Leslie JB. Opioid-induced constipation negatively impacts pain management, productivity, and health-related quality of life: findings from the National Health and Wellness Survey. *J Opioid Manag*. 2009;5:137–144.
- Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE1). *Pain Med*. 2009;10:35–42.
- Clemens KE, Quednau I, Klaschik E. Bowel function during pain therapy with oxycodone/naloxone prolonged-release tablets in patients with advanced cancer. *Int J Clin Pract*. 2011;65(4):472–478.
- Dennison C, Prasad M, Lloyd A, Bhattacharyya SK, Dhawan R, Coyne K. The health-related quality of life and economic burden of constipation. *Pharmacoeconomics*. 2005;23(5):461–476.
- Rentz AM, Yu R, Müller-Lissner S, Leyendecker P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. *J Med Econ*. 2009;12(4):371–383.
- Rentz AM, van Hanswijck de Jonge P, Leyendecker P, Hopp M. Observational, nonintervention, multi center study for validation of the Bowel Function Index for constipation in European countries. *Curr Med Res Opin*. 2011;27(1):35–44.
- Coffin B, Causse C. Constipation assessment scales in adults: a literature review including the new Bowel Function Index. *Expert Rev Gastroenterol Hepatol*. 2011;5(5):601–613.
- Ueherall MA, Müller-Lissner S, Buschmann-Kramm C, Bosse B. The Bowel Function Index for evaluating constipation in pain patients: definition of a reference range for a non-constipated population of pain patients. *J Int Med Res*. 2011;39(1):41–50.
- Ducrotte P, Causse C. The Bowel Function Index: a new validated scale for assessing opioid-induced constipation. *Curr Med Res Opin*. 2012;28(3):457–466.
- Tamayo AC, Diaz-Zuluaga PA. Management of opioid-induced bowel dysfunction in cancer patients. *Support Care Cancer*. 2004;12(9):613–618.
- Holzer P. Non-analgesic effects of opioids: Management of opioid-induced constipation by peripheral opioid receptor antagonists: prevention or withdrawal? *Curr Pharmaceutical Design*. 2012;18:6010–6020.
- Tack J. Current and future therapies for chronic constipation. *Best Pract Res Clin Gastroenterol*. 2011;25(1):151–158.
- Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. *Pain Physician*. 2008;11(2):S105–S120.
- Holzer P. Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans. *Neurosci Lett*. 2004;361(1–3):192–195.
- Poulsen JL, Brock C, Olesen AE, Nilsson M, Drewes AM. Clinical potential of naloxegol in the management of opioid-induced bowel dysfunction. *Clin Exp Gastroenterol*. 2014;7:345–358.

39. Bader S, Durk T, Becker G. Methylnaltrexone for the treatment of opioid-induced constipation. *Expert Rev Gastroenterol Hepatol*. 2013;7(1):13–26.
40. Leppert W. Emerging therapies for patients with symptoms of opioid-induced bowel dysfunction. *Drug Des Devel Ther*. 2015;9:2215–2231.
41. Leonard J, Baker DE. Naloxegol: treatment for opioid-induced constipation in chronic non-cancer pain. *Ann Pharmacother*. 2015;49(3):360–365.
42. Smith K, Hopp M, Mundin G, et al. Low absolute bioavailability of oral naloxone in healthy subjects. *Int J Clin Pharmacol Ther*. 2012;50(5):360–367.
43. Löwenstein O, Leyendecker P, Lux EA, et al. Efficacy and safety of combined prolonged release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. *BMC Clin Pharmacol*. 2010;10:12.
44. Vondrackova D, Leyendecker P, Meissner W, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain*. 2008;9(12):1144–1154.
45. Simpson K, Leyendecker P, Hopp M, et al. Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate-to-severe noncancer pain. *Curr Med Res Opin*. 2008;24(12):3503–3512.
46. Löwenstein O, Leyendecker P, Hopp M, et al. Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: a randomised controlled trial. *Expert Opin Pharmacother*. 2009;10(4):531–543.
47. Poelaert J, Koopmans-Klein G, Dioh A, et al. Treatment with prolonged-release oxycodone/naloxone improves pain relief and opioid-induced constipation compared with prolonged-release oxycodone in patients with chronic severe pain and laxative-refractory constipation. *Clin Ther*. 2015;37(4):784–792.
48. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163–2196.
49. Chou R, Qaseem A, Snow V, et al; Clinical Efficacy Assessment Subcommittee of the American College of Physicians; American College of Physicians; American Pain Society Low Back Pain Guidelines Panel. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. *Ann Intern Med*. 2007;147:478–491.
50. Zhang W, Doherty M, Arden N, et al; EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). EULAR evidence based recommendations for the management of hip osteoarthritis: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis*. 2005;64:669–681.
51. Jordan KM, Arden NK, Doherty M, et al; Standing Committee for International Clinical Studies Including Therapeutic Trials ESCISIT. EULAR recommendations 2003: an evidence based approach to the management of knee osteoarthritis: report of a Task Force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCSIT). *Ann Rheum Dis*. 2003;62:1145–1155.
52. Hochberg MC, Altman RD, April KT, et al; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res*. 2012;64:465–474.
53. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014;22:363–388.
54. Machado GC, Maher CG, Ferreira PH, et al. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. *BMJ*. 2015;350:h1225.
55. National Institute for Health and Care Excellence. *Osteoarthritis: Care and Management in Adults*. NICE; 2014. Available from: [www.nice.org.uk/guidance/cg177](http://www.nice.org.uk/guidance/cg177)
56. Mallen C, Hay E. Managing back pain and osteoarthritis without paracetamol. *BMJ*. 2015;350:h1352.
57. Cheung CW, Qiu Q, Choi SW, Moore B, Goucke R, Irwin M. Chronic opioid therapy for chronic non-cancer pain: a review and comparison of treatment guidelines. *Pain Physician*. 2014;17(5):401–414.
58. Blagden M, Hafer J, Duerr H, Hopp M, Bosse B. Long-term evaluation of combined prolonged-release oxycodone and naloxone in patients with moderate-to-severe chronic pain: pooled analysis of extension phases of two Phase III trials. *Neurogastroenterol Motil*. 2014;26(12):1792–1801.
59. Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. *Drugs Aging*. 2003;20(1):23–57.
60. Gibson SJ, Lussier D. Prevalence and relevance of pain in older persons. *Pain Med*. 2012;13(suppl 2):S23–S26.
61. Chai E, Horton JR. Managing pain in the elderly population: pearls and pitfalls. *Curr Pain Headache Rep*. 2010;14(6):409–417.
62. Abdulla A, Bone M, Adams N, et al. Evidence-based clinical practice guidelines on management of pain in older people. *Age Ageing*. 2013;42(2):151–153.
63. Guerriero F, Sgarlata C, Marcassa C, Ricevuti G, Rollone M. Efficacy and tolerability of low-dose oral prolonged-release oxycodone/naloxone for chronic nononcological pain in older patients. *Clin Interv Aging*. 2014;10:1–11.31.
64. Chapman SL, Byas-Smith MG, Reed BA. Effects of intermediate- and long-term use of opioids on cognition in patients with chronic pain. *Clin J Pain*. 2002;18(suppl 4):S83–S90.
65. Kamboj SK, Tookman A, Jones L, Curran HV. The effects of immediate-release morphine on cognitive functioning in patients receiving chronic opioid therapy in palliative care. *Pain*. 2005;117(3):388–395.
66. Tassain V, Attal N, Fletcher D, et al. Long term effects of oral sustained release morphine on neuropsychological performance in patients with chronic non-cancer pain. *Pain*. 2003;104(1–2):389–400.

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