Impact of Prolonged-release Oxycodone/Naloxone on Outcomes Affecting Patients' Daily Functioning in Comparison With Extended-release Tapentadol: A Systematic Review

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ABSTRACT

Purpose: The objective of this systematic review was to assess the clinical efficacy, safety, tolerability, and health-related quality of life outcomes associated with management of moderate-to-severe chronic pain with oxycodone/naloxone and tapentadol, focusing on the effect of these treatments on patients' daily functioning.

Methods: Literature from a wide range of sources, including Embase, MEDLINE, MEDLINE In-Process, and the Cochrane Central Register of Controlled Trials, was searched to identify randomized controlled trials investigating tapentadol or oxycodone/naloxone for the treatment of patients with chronic pain. A network meta-analysis was conducted to determine the relative efficacy and safety profiles of these treatments.

Findings: Oxycodone/naloxone was significantly better than tapentadol with respect to the Patient Assessment of Constipation Symptoms total score (risk ratio = −3.60; 95% credible interval, −5.36 to −2.11) and revealed a significantly lower risk of dizziness (risk ratio = 0.72; 95% credible interval, 0.42–0.98). Oxycodone/naloxone was directionally favored, although not significantly superior to tapentadol for headache, fatigue, dry mouth, dyspepsia, and withdrawals due to lack of efficacy. For the AE outcomes of constipation, nausea, and vomiting, as well as pain efficacy and all-cause withdrawals from studies, tapentadol was directionally favored without any statistical difference from oxycodone/naloxone. However, the two treatments were not wholly comparable for the evaluation of pain efficacy because of differences in on-study rescue medication and a higher baseline pain severity in the tapentadol studies.

Implications: Oxycodone/naloxone offers significant improvements in Patient Assessment of Constipation Symptoms total score and dizziness and was directionally favored for fatigue and headache compared with extended-release tapentadol, which may translate to improved patient daily functioning and health-related quality of life. (*Clin Ther.* 2015;37:212–224) © 2015 The Authors. Published by Elsevier HS Journals, Inc.

Key words: chronic pain, constipation, dizziness, oxycodone/naloxone, tapentadol.

INTRODUCTION

Chronic pain is associated with a wide range of conditions, including cancer, neuropathic pain, osteoarthritis, and other musculoskeletal disorders, and represents a considerable burden on patients and health care systems. Prevalence of moderate-to-severe chronic pain is high, and in a large-scale computer-assisted telephone survey of 46,394 adults in the general population across Europe and Israel, 19% of respondents reported having moderate-to-severe chronic pain.[1] Health care costs associated with chronic pain are significant; therefore, the overall management of chronic pain represents a substantial burden to health care systems. In the United States, chronic pain was estimated to affect approximately 100 million people in 2008 and was associated with an annual national cost of between $560 billion and $635 billion.[2,3] Studies conducted in Europe also report a considerable economic burden due to chronic

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pain, as indicated by a retrospective study from the United Kingdom in which patients with chronic lower back pain reported costs more than double those incurred by matched controls without chronic lower back pain (£1074 vs £516, $P<0.05$).[4] Taken together, patients with chronic pain in the United Kingdom were reported to account for 4.6 million medical appointments per year in 2002, which incurred an overall annual cost of £69 million to the National Healthcare System.[5]

The biopsychosocial model of chronic pain is widely accepted and considers the social and psychological effects of a condition in addition to a purely biological perspective. Indeed, chronic pain may involve a complex combination of physical dysfunction with the beliefs, coping strategies, illness behaviors, and social interactions of the patient. Therefore, treatment of chronic pain is often multidisciplinary and multimodal, with the aim of maximizing pain relief and increasing patient motility, independence, and quality of life (QoL). Pharmacotherapy, including opioids, forms an important part of this multimodal approach.

US guidelines for chronic pain from the Institute for Clinical Systems Improvement from 2013 recommend opioids for the treatment of patients with persistent moderate-to-severe pain in individuals whose pain is not responsive to initial therapies, as part of an overall pain management program, and when there is a favorable risk-benefit profile of prescribing opioids.[6] This recommendation was in accordance with the World Health Organization 3-step ladder treatment paradigm (developed specifically for treatment of chronic pain in patients with cancer), which recommends administering aspirin, acetaminophen, and nonsteroidal anti-inflammatory drugs for mild pain, then escalating treatment to weak opioids (such as codeine or dihydrocodeine) and finally to stronger opioids (such as oxycodone, morphine, or hydromorphone) as necessary with increasing pain severity.

As a result, opioids are the main treatment option for patients with moderate-to-severe pain, and a number of strong opioids are clinically available; for example, morphine, oxycodone, tapentadol (where available), hydromorphone, fentanyl, and buprenorphine are all widely used. One key drawback of opioid treatment is the adverse effect (AE) profile, including headache, dizziness, and fatigue, which can affect daily functioning and patient QoL.[7–9] Another frequent AE of opioid treatment is opioid-induced bowel dysfunction (OIBD), an umbrella term used to describe the gastrointestinal AEs of opioids, including constipation, hard dry stools, bloating and abdominal distension, and abdominal cramps and spasms.[10] In a multinational, Internet-based study of 322 patients taking daily opioids (PROBE 1), constipation was reported as the most common AE in 81% of patients, and it was considered to be the AE that was most bothersome and most often reported as severe, despite the use of laxatives in all patients. Because laxatives do not target the cause of OIBD, they have limited efficacy in this setting.[11] In a survey of OIBD by Pappagallo[12] and Kumar et al,[13] more than half (54%) of patients treated with laxatives did not achieve the desired symptomatic improvement at least 50% of the time. The AEs experienced by patients treated with opioids, such as constipation, may lead to dose reduction (which can affect the effectiveness of their pain relief), reduced patient adherence, or treatment discontinuation to switch to a different opioid. Therefore, a need exists for opioid treatments that offer improved tolerability with fewer AEs.

Oxycodone is an opioid receptor agonist commonly used for the treatment of patients with moderate-to-severe pain. As with other opioids, when used as a monotherapy, oxycodone stimulates opioid receptors in the gastrointestinal tract, disrupting normal bowel activity and reducing gut motility, resulting in constipation.[14] Naloxone is an opioid antagonist that binds to opioid receptors in the gut with a higher affinity than oxycodone, thereby outcompeting oxycodone and acting directly to prevent AEs, such as constipation and bowel dysfunction, caused by binding of oxycodone at these receptors.[15] Because of the extensive first-pass metabolism of naloxone in the liver, <3% of the naloxone dose reaches the systemic circulation and therefore does not interfere with the analgesic efficacy of oxycodone. Studies of oxycodone/naloxone (2:1) have found comparable analgesic efficacy compared with oxycodone alone.[16] The oxycodone/naloxone combination therefore combines effective analgesia with improvements in opioid-induced bowel AEs, such as constipation.[15,17] Prolonged-release (PR) oxycodone* can be given in a fixed-dose combination with naloxone at a ratio of 2:1.[15]

*Trademark: Targinact®, Targin®, or Targiniq® (Napp Pharmaceuticals Ltd, Cambridge, United Kingdom).