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Clinical Paper

Long-term effectiveness and safety of once-daily, single-entity, extended-release hydrocodone in patients of ≥75 years of age with moderate to severe nonmalignant and nonneuropathic pain

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ABSTRACT

In elderly (≥75 years) individuals, age-associated physiologic changes and a higher prevalence of comorbidities, polypharmacy, and increased susceptibility to medication-induced side effects complicate pain management. Hysingla® ER (HYD) is a once-daily, single-entity, extended-release hydrocodone formulation approved for the treatment of chronic pain that is insufficiently controlled by alternative treatments. In this post-hoc analysis of a previously reported study, the effectiveness and safety of HYD for the treatment of moderate-to-severe chronic pain among the elderly (≥75 years) for a 52-week duration was investigated. HYD dose administered during the maintenance period-remained relatively stable and provided clinically meaningful decreases in mean "pain over the last 24 h" and pain interference scores. Patients achieved pain control without additional non-study opioid use at the end of the study. Adverse events were typical of opioids. In summary, HYD provided clinically meaningful reduction of pain scores in elderly patients that were maintained over a 52-week period.

Introduction

Improvements in medicine have prolonged the lives of Americans over the past century, and Americans 65 years of age and older now constitute 13.7% of the United States (US) population (43.1 million in 2012), with approximately 45% of them being 75 years or older.[1] Aging is often accompanied by a proliferation of health issues; a significant proportion of the growing elderly population has multiple chronic conditions including arthritis, diabetes, respiratory disease, hypertension, and heart disease. Chronic pain is also a prevalent condition among the elderly, reported to affect 81.1% of those 78 years of age and 56.3% of those 85 years of age.[2] Moderate and severe symptoms of pain are noted by approximately 60% and 25% of adults over the age of 65, respectively.[3] Treatment of pain in the elderly (>65 years) is complicated by physiological changes that accompany aging, including changes in the perception of pain.[3,4] Chronic pain management among the elderly is complex and multifactorial, and frequently entails increased polypharmacy.[5,6]

The World Health Organization's 3-step pain ladder commonly serves as a framework for the pharmacological management of pain in adults.[6] Treatment of low-intensity pain typically involves the administration of non-opioid analgesics such as acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), with or without adjuvants (Step 1). For moderate-intensity pain, a non-opioid analgesic, together with a mild opioid such as tramadol and hydrocodone, is generally administered (Step 2). For patients experiencing severe pain, treatment with a strong opioid such as morphine, oxycodone, or fentanyl is considered appropriate (Step 3).

However, although the WHO analgesic ladder has been adapted for pain management in the elderly,[7] pain management in this vulnerable population is different from the general population in many ways. Due to a lack of clinical trial data in the elderly, pain management guidelines need to be adapted to address the issues of increased concurrent illnesses, polypharmacy, susceptibility to adverse events (AEs), and physiological changes that impact efficacy of treatment.[6–9] The elderly patient's condition is often

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complicated further by the underreporting of pain.[6,7] Optimal pain management in the elderly, therefore, requires a multidisciplinary approach including pharmacotherapy and nonpharmacological interventions such as physical therapy, and cognitive therapy. Nonpharmacological interventions such as physical therapy, and cognitive therapy should be considered for elderly patients with chronic pain, although combined treatment with pharmacotherapy is generally more effective.[6]

The complex and multimodal interactions of aging, concurrent comorbidities, and polypharmacy present a substantial challenge to the medical management of pain in the elderly and frail patient subgroup whose pain control is consequently often found to be suboptimal.[6,7,10] Hysingla® ER (Purdue Pharma L.P., Stamford, CT; hereafter HYD) is a once-daily, single-entity, extended-release hydrocodone bitartrate tablet with abuse-deterrent properties. In November 2014, HYD was approved for use in the US for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.[11] In a previously reported phase 3 multicenter, double-blind, placebo-controlled trial, HYD was demonstrated to be an effective analgesic for the treatment of chronic lower back pain over a 12-week duration,[12] consistent with Food and Drug Administration (FDA) requirements for opioid analgesics used for chronic pain.[13] Simultaneously with the randomized controlled trial, a separate open-label phase 3 multicenter study established the safety and effectiveness of HYD over a 52-week period in treating patients with persistent, moderate-to-severe nonmalignant and non-neuropathic pain.[14] While it is recognized that non-drug therapies play an important part in the management of chronic pain, this report presents a post-hoc analysis of this open-label study of an opioid analgesic, performed to examine the long-term effectiveness and tolerability of HYD among a subpopulation of elderly study participants ≥75 years of age who were experiencing chronic pain.

Material and methods

Study design

This was a post-hoc analysis of data from an open-label, multicenter study that assessed the long-term safety and effectiveness of HYD 20–120 mg tablets, taken once-daily in opioid-naïve and opioid-experienced patients with chronic, moderate-to-severe nonmalignant and non-neuropathic pain (ClinicalTrials.gov, NCT01400139).[14] In the study, eligible patients received a starting HYD dose of 20 mg, 40 mg, 60 mg, or 80 mg, depending upon their incoming opioid dose. Hydrocodone-equivalent total opioid daily dose was calculated using conversion factors employed in the study protocol.[14] If more than 1 incoming opioid had been used, the overall total daily dose was the sum of all individual opioid daily hydrocodone-equivalents. HYD dose adjustments (up to 120 mg) were permitted during a 45-day titration period. Patients achieving a stable dose were enrolled into a 52-week maintenance period, and continued treatment at the stable dose. The dose of HYD that was administered for at least 7 days and provided acceptable pain relief and tolerability was regarded as the stable dose. Dose alterations were permitted as necessary throughout the maintenance period.

Patients

In this post-hoc analysis, the long-term safety and analgesic effectiveness of HYD among a subpopulation of elderly (≥75 years of age) patients were drawn from the patient population of a primary study, which enrolled eligible patients who were 18 years of age or older. Patients were eligible to participate in the primary study if they were experiencing chronic, moderate-to-severe nonmalignant and non-neuropathic pain over several hours a day, for at least 3 months prior to the start of screening. Patients could have been either opioid-naïve (ie, patients with an incoming opioid dose equivalent to <5 mg/day of oxycodone) or opioid-experienced. Patients taking ≥120 mg oxycodone equivalent opioid analgesics within 14 days of the screening visit were excluded. Patients with neuropathic pain, an underlying gastrointestinal condition, uncontrolled gout, pseudogout, psoriatic arthritis, active Lyme disease, rheumatoid arthritis or other inflammatory arthritis, uncontrolled psychiatric disorders, unstable cardiac or respiratory disease, impaired liver or renal function, or a history of substance abuse were not eligible for this study. Patients were included in the primary study if they were capable of subjective evaluation (ie, pain scores); were able to read and understand questionnaires; were willing and able to use an electronic diary; and were able to read, understand and sign the written informed consent form. All patients participating in the study provided written informed consent.

Assessments

At the start of the screening period, baseline information was documented. The patient's demographic information, medical history and current medical conditions, pain history and etiology, and pain rating ("average pain over the last 14 days" measured on an 11-point numerical rating scale [NRS] where 0 = no pain and 10 = worst pain imaginable) were recorded. The use of NRS to assess pain intensity in an elderly cohort has been validated.[10,15] In addition, the patient's medications were recorded, as were non-drug therapies used over the previous 30 days. Patients recorded "average pain over the last 24 h" scores in an electronic diary, at approximately 8 PM every day. Pain interference with activities of daily living (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep) was also assessed using the Brief Pain Inventory – short form (BPI-SF) survey on a 0 to 10 scale, where a higher score indicates more interference. BPI-SF has been validated and used in populations that include those 65 years of age or older.[15] A treatment satisfaction questionnaire was administered to patients at week 4 of the maintenance period (or the end of study/early discontinuation for patients who discontinued study prior to week 4); week 4 was chosen as the administration timepoint so that patients could reasonably be expected to compare their satisfaction of HYD to that of their baseline regimen. Safety measures included AEs, clinical laboratory test results (complete blood count with differential, urinalysis, blood chemistry panel), vital sign measurements, and electrocardiogram findings.

Other medications

The use of supplemental opioid (excluding controlled-release or long-acting medications) and non-opioid analgesics was permitted throughout the study. Non-opioid analgesics were permitted if maintained at a stable regimen throughout the duration of the study. Medications that were started before the first dose of HYD was administered were considered prior medications, regardless of whether their use was continued into the study period or not. Medications taken after the first dose of HYD was administered were considered concomitant medications, irrespective of the duration of their use.

Statistical analysis

Statistical Analysis System (SAS®) version 9.3 was used to conduct statistical analyses. Other validated statistical software was