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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A B S T R A C T

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\textsuperscript{c} 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.

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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.\textsuperscript{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.\textsuperscript{2} Moderate and severe symptoms of pain are noted by approximately 60% and 25% of adults over the age of 65, respectively.\textsuperscript{3,4} Treatment of pain in the elderly (≥65 years) is complicated by physiological changes that accompany aging, including changes in the perception of pain.\textsuperscript{3,4} Chronic pain management among the elderly is complex and multifactorial, and frequently entails increased polypharmacy.\textsuperscript{5,6}

The World Health Organization’s 3-step pain ladder commonly serves as a framework for the pharmacological management of pain in adults.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.2,10 Hysingla® ER (Purdue Pharma LP., 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.11 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 time-point 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
Table 1
Patient characteristics at screening, prior and concomitant pain medications, and starting HYD dose.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>sex/age (years)/BMI (kg/m²)</th>
<th>Pain etiology and musculoskeletal pain</th>
<th>Other relevant medical condition</th>
<th>Relevant prior medications</th>
<th>Relevant concomitant medications</th>
<th>Pain scoreabc</th>
<th>Pain interference score</th>
<th>Screening opioid dose (mg/day)</th>
<th>Starting maintenance HYD dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>82/M/27.9</td>
<td>Osteoarthritis, arthralgia, and musculoskeletal pain</td>
<td>Gastroesophageal reflux disease, edema peripheral, arthralgia, venous insufficiency, and neuropathic peripheral</td>
<td>Diclofenac and glucosamine</td>
<td>Naproxen</td>
<td>3.8</td>
<td>3.5</td>
<td>2.9</td>
<td>0.4</td>
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<tr>
<td>Patient 2</td>
<td>81/M/31.1</td>
<td>Arthralgia</td>
<td>Atrial fibrillation, coronary artery disease, intermittent claudication, type 2 diabetes mellitus, diabetic neuropathy, hyperlipidemia, hypertension, bone erosion, osteolysis, insomnia, venous insufficiency, age-related macular degeneration, and edema peripheral</td>
<td>Acetaminophen/hydrocodone, paracetamol, zolpidem, and doxazosin</td>
<td>Zolpidem, nebivolol, insulin glargine, metformin, nefedipine, and atorvastatin</td>
<td>5.2</td>
<td>1.0</td>
<td>3.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Patient 3</td>
<td>81/F/23.1</td>
<td>Neck pain, musculoskeletal pain</td>
<td>Depression, glaucoma, osteoporosis, and hypothyroidism</td>
<td>Oxymorphone and venlafaxine</td>
<td>Venlafaxine, brimonidine, dorzolamide, methazolamide, timolol, and alprazolam</td>
<td>3.0</td>
<td>6.9</td>
<td>2.6</td>
<td>2.5</td>
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<tr>
<td>Patient 4</td>
<td>84/F/26.4</td>
<td>Back pain, intervertebral disc degeneration, lumbar spinal stenosis, spinal compression fracture, facet joint syndrome, and scoliosis</td>
<td>Anxiety, coronary artery disease, cardiac failure congestive, renal artery stenosis, dyslipidemia, facet joint syndrome, myocardial ischemia, mitral valve incompetence, pulmonary valve incompetence, tricuspid valve incompetence, osteoarthropathy, gastroesophageal reflux disease, and hypertension</td>
<td>Acetaminophen/hydrocodone and lorazepam</td>
<td>Acetaminophen/hydrocodone, lorazepam, atenolol, olmesartan, dexlansoprazole, atorvastatin, lisinopril, lorcaserine, glyceryl trinitrate, pantoprazole, and alprazolam</td>
<td>5.6</td>
<td>4.7</td>
<td>5.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Patient 5</td>
<td>78/M/26.4</td>
<td>Intervertebral disc degeneration, spinal pain, osteoarthritis, and arthralgia</td>
<td>Spinal nerve stimulator implantation, hypertension, cerebrovascular insufficiency, and blood cholesterol increased</td>
<td>Paracetamol</td>
<td>Paracetamol, rosvastatin, lisinopril, and clopidogrel</td>
<td>6.8</td>
<td>3.9</td>
<td>3.9</td>
<td>2.5</td>
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<tr>
<td>Patient 6</td>
<td>78/M/26.6</td>
<td>Back pain and osteoarthritis</td>
<td>Gastroesophageal reflux disease, hypercholesterolemia, hypertension, and peripheral vascular disorder</td>
<td>Celecoxib</td>
<td>Fentanyl, celecoxib, acetaminophen/hydrocodone, carotid angiography with stenting, heparin, midazolam, nicardipine, lisinopril, omeprazole, clopidogrel, pravastatin, and tamsulosin</td>
<td>8.3</td>
<td>2.9</td>
<td>0.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Patient 7</td>
<td>75/M/26.9</td>
<td>Osteoarthritis and arthralgia</td>
<td>Hyperlipidemia, aortic arteriosclerosis, and chronic obstructive pulmonary disease</td>
<td>Ibufprofen</td>
<td>Ibufprofen</td>
<td>6.3</td>
<td>5.0</td>
<td>4.7</td>
<td>2.6</td>
</tr>
<tr>
<td>Patient 8</td>
<td>77/M/24.4</td>
<td>Osteoarthritis and back pain</td>
<td>Pain in extremity, peroneal nerve palsy, pulmonary embolism, gastroesophageal reflux disease, and foot deformity</td>
<td>Ibufprofen</td>
<td>Fluoxetine, ibuprofen, morphine, oxycocet, paracetamol, warfarin, heparin, enoxaparin, and tamsulosin</td>
<td>7.3</td>
<td>4.0</td>
<td>5.7</td>
<td>3.2</td>
</tr>
</tbody>
</table>

(continued on next page)
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Sex/age (years)/BMI (kg/m²)</th>
<th>Pain etiology</th>
<th>Other relevant medical condition</th>
<th>Relevant prior medications</th>
<th>Relevant concomitant medications</th>
<th>Pain score</th>
<th>Pain interference score</th>
<th>Starting maintenance HYD dose (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 9</td>
<td>75/F/42.7</td>
<td>Arthralgia, joint range of motion decreased, back pain, and arthralgia</td>
<td>Atrial fibrillation, depression, gout, neuropathy peripheral, hyperlipidemia, hypertension, hypothyroidism, neuropathy peripheral, and restless legs syndrome</td>
<td>Cyclobenzaprine, gabapentin, acetaminophen/hydrocodone, ropinirole, sertraline, allopurinol, colchicine, furosemide, lisinopril, metoprolol, pravastatin, ropinirole, levorotatory, and warfarin</td>
<td>Cyclobenzaprine, gabapentin, acetaminophen/hydrocodone, ropinirole, sertraline, allopurinol, colchicine, furosemide, lisinopril, metoprolol, pravastatin, ropinirole, levorotatory, and warfarin</td>
<td>8.6</td>
<td>4.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Patient 10</td>
<td>77/M/24.3</td>
<td>Intervertebral disc degeneration</td>
<td>Gastroesophageal reflux disease and hypertension</td>
<td>Naproxen, gabapentin, and acetaminophen/hydrocodone</td>
<td>Naproxen, gabapentin, and acetaminophen/hydrocodone</td>
<td>6.9</td>
<td>–</td>
<td>2.6</td>
</tr>
<tr>
<td>Patient 11</td>
<td>77/F/31.5</td>
<td>Spinal osteoarthritis</td>
<td>Hyperlipidemia, hypothyroidism, and insomnia</td>
<td>Tramadol, ibuprofen, and zolpidem</td>
<td>Tramadol, ibuprofen, and zolpidem, and levorotatory</td>
<td>6.6</td>
<td>5.6</td>
<td>6.1</td>
</tr>
<tr>
<td>Patient 12</td>
<td>82/M/26.6</td>
<td>Spinal osteoarthritis and back pain</td>
<td>Atrial fibrillation</td>
<td>Acetaminophen/hydrocodone, methocarbamol, and warfarin</td>
<td>Acetaminophen/hydrocodone, methocarbamol, and warfarin</td>
<td>2.4</td>
<td>–</td>
<td>2.0</td>
</tr>
<tr>
<td>Patient 13</td>
<td>81/M/30.6</td>
<td>Back pain, arthralgia, and intervertebral disc protrusion</td>
<td>Headache, neck pain, hyperlipidemia, hypertension, and hypothyroidism</td>
<td>Butalbital with aspirin/caffeine and acetaminophen/hydrocodone</td>
<td>Butalbital with aspirin/caffeine, amiodipine, atenolol, levorotatory, and simvastatin</td>
<td>6.0</td>
<td>–</td>
<td>3.3</td>
</tr>
<tr>
<td>Patient 14</td>
<td>77/F/33.0</td>
<td>Osteoarthritis</td>
<td>Depression, hypertension, hypercholesterolemia, hypothyroidism, and osteopenia</td>
<td>Ibuprofen, chondroitin, and glucosamine</td>
<td>Ibuprofen, chondroitin, and glucosamine, enap-HL, simvastatin, and levorotatory</td>
<td>8.8</td>
<td>–</td>
<td>9.3</td>
</tr>
<tr>
<td>Patient 15</td>
<td>76/M/23.0</td>
<td>Back pain, osteoarthritis, and spinal osteoarthritis</td>
<td>Insomnia neuropathy peripheral, gastroesophageal reflux disease, coronary arterial stent insertion, hyperlipidemia, and hypertension</td>
<td>Acetaminophen/hydrocodone, ciclosporin, chondroitin w/glucosamine, temazepam, lisinopril, nicotinic acid, omeprazole and simvastatin</td>
<td>Acetaminophen/hydrocodone, ciclosporin, chondroitin w/glucosamine, temazepam, lisinopril, nicotinic acid, omeprazole and simvastatin</td>
<td>6.6</td>
<td>–</td>
<td>3.0</td>
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<tr>
<td>Patient 16</td>
<td>78/NA</td>
<td>Back pain and osteoarthritis</td>
<td>Muscle spasms</td>
<td>Paracetamol, chondroitin, and glucosamine</td>
<td>Paracetamol, chondroitin, and glucosamine, paracetamol, and omeprazole</td>
<td>4.1</td>
<td>0.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Patient 17</td>
<td>86/M/29.5</td>
<td>Osteoarthritis and back pain</td>
<td>Gout, atrial fibrillation, edema peripheral, hyperlipidemia, hypertension and Parkinson’s disease</td>
<td>Lorazepam, meloxicam, codine, phosphate, and venlafaxine</td>
<td>Lorazepam, meloxicam, venlafaxine, levorotatory, and levorotatory</td>
<td>5.3</td>
<td>–</td>
<td>5.1</td>
</tr>
<tr>
<td>Patient 18</td>
<td>76/F/35.8</td>
<td>Back pain and osteoarthritis</td>
<td>Depression, blood cholesterol increased, hypertension, and hypothyroidism</td>
<td>Meloxicam, lorazepam, venlafaxine, levorotatin, and levorotatory</td>
<td>Meloxicam, lorazepam, venlafaxine, levorotatin, and levorotatory</td>
<td>4.7</td>
<td>0.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Patient 19</td>
<td>77/M/26.6</td>
<td>Back pain</td>
<td>Anxiety, hypertension, angina pectoris, and, hyperkalemia</td>
<td>Clobenzaprine, meloxicam, enap-HL, simvastatin, and levorotatory</td>
<td>Clobenzaprine, meloxicam, enap-HL, simvastatin, and levorotatory</td>
<td>6.0</td>
<td>5.8</td>
<td>3.1</td>
</tr>
<tr>
<td>Patient 20</td>
<td>83/F/24.9</td>
<td>Intervertebral disc degeneration, back pain, and osteoarthritis</td>
<td>Neuritis hypertension, facet joint syndrome, and blood cholesterol increased</td>
<td>Oxycodone</td>
<td>Gabapentin, oxycodone, and amiodipine</td>
<td>7.6</td>
<td>6.7</td>
<td>4.4</td>
</tr>
<tr>
<td>Patient 21</td>
<td>77/M/33.6</td>
<td>Osteoarthritis and back pain</td>
<td>Hypertension</td>
<td>Naproxen</td>
<td>Amlodipine</td>
<td>5.0</td>
<td>2.0</td>
<td>2.6</td>
</tr>
</tbody>
</table>
used as required. The safety population included patients who received at least 1 dose of study drug during the study. Mean and standard deviations were calculated for continuous variables (age, weight, body mass index, screening “average pain over the last 14 days,” “average pain over the last 24 h” scores, and pain interference scores), while the number and percentage of patients were described for categorical variables (gender and previous opioid exposure). Patient characteristics were summarized and analyzed individually and by group. Safety and effectiveness were assessed by group. No imputation was performed.

Results

Patient characteristics

The demographics and baseline characteristics of the 24 elderly patients included in this post-hoc analysis are shown in Table 1. The mean age of the elderly cohort was 78.8 years (range, 75–86 years), and slightly under half of the cohort (45.8%, 11/24) was female. The overall elderly patient population was overweight (mean BMI = 28.4 kg/m²), and presented with moderate pain and associated functional interference at the initial screening visit (mean pain score = 6.09 on a 0–10 scale, and mean pain interference score = 4.97). A majority of the elderly patients had 6 or more comorbid conditions (92%, 22/24) at baseline, with a few patients having had as many as 24 active conditions. Some of the common comorbid conditions included hypertension (67%, 16/24), hyperlipidemia (42%, 10/24), hypothyroidism (33%, 8/24), gastroesophageal reflux disease (29%, 7/24), depression (21%, 5/24 subjects), hypercholesterolemia (21%, 5/24), insomnia (17%, 4/24 subjects), atrial fibrillation (17%, 4/24), and constipation (17%, 4/24). Less common comorbid conditions included coronary artery disease, anxiety, peripheral edema, peripheral vascular disorder, benign prostatic hyperplasia, and vulvitis.

A majority of the patients had 2 or more comorbid pain conditions (88%; 21/24) at baseline. Back pain (not otherwise specified [NOS]) (71%, 17/24) and osteoarthritis (NOS) (67%, 16/24) were the most frequent pain-related conditions observed among the elderly patients. Other pain conditions reported included arthritis (29%, 7/24), intervertebral disc degeneration (21%, 5/24), spinal osteoarthritis (17%, 4/24), musculoskeletal pain (13%, 3/24), and spinal compression fracture (4%, 1/24). Patients also reported depression (21%, 5/24) peripheral neuropathy (13%, 3/24), and insomnia (17%, 4/24), which may have influenced pain perception.

A majority of the elderly patients (75%, 18/24) received 5 or more medications at baseline, with a few patients receiving as many as 8 to 16 medications. Other than medication used for treatment of chronic pain, the most common of these medications included lipid modifying agents (17%, 25/24 patients), antithrombotic agents (75%, 18/24 patients), adrenergic beta-receptor blockers (38%, 9/24), angiotensin-converting-enzyme (ACE) inhibitors (38%, 9/24), drugs for acid-related disorders (13%, 8/24), urológicos (13%, 8/24), psycholeptics (29%, 7/24), and thyroid therapies (29%, 7/24). All patients received treatment for pain (opioid and/or non-opioid analgesics) prior to the start of the study; commonly prescribed medications were opioid plus non-opioid analgesic combination products (50%, 12/24), NSAIDs (42%, 10/24), opioids (25%, 6/24), and acetaminophen (17%, 4/24). In addition, antidepressants and gamma-aminobutyric acid receptor-modulating drugs may have provided pain relief in patients suffering from depression, insomnia, and anxiety prior to the commencement of the study. Patients also obtained pain relief using muscle relaxants (17%, 4/24) and supplements such as

### Table 1: Demographics and Baseline Characteristics of the 24 Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (y)</th>
<th>BMI (kg/m²)</th>
<th>Average Pain Over Last 24 h</th>
<th>Pain Interference</th>
<th>Primary Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>F</td>
<td>77</td>
<td>28.4</td>
<td>6.09</td>
<td>4.97</td>
<td>Opioid+Nsaids</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>76</td>
<td>28.2</td>
<td>7.60</td>
<td>5.00</td>
<td>Opioid+Nsaids</td>
</tr>
</tbody>
</table>

* BMI, body mass index.
glucosamine and chondroitin (17%, 4/24) before the study began. At the time of screening, 12 patients (50%) were considered opioid-naïve; the other 12 patients (50%) were considered opioid-experienced. The average screening opioid daily dose was equivalent to 14.1 mg hydrocodone.

Of the 24 patients ≥75 years enrolled in the study, 20 (83%) completed the titration period (Tables 1 and 2) and enrolled into the maintenance phase of the study, while 4 discontinued due to titration failure (3 patients due to AEs and 1 due to medical history not meeting entry criteria). Among patients entering the maintenance phase of the study, 70% (14/20 patients) completed the study while 6 patients withdrew from the study (Table 2). Of the 12 patients who were opioid-naïve at baseline, 7 (58%) completed the study. Of the 6 patients who did not complete the maintenance phase, 4 discontinued due to AEs, and 2 patients withdrew themselves from the study (1 patient could no longer keep the appointments, the other patient withdrew without explanation).

Among the 20 elderly patients who continued into the maintenance phase, the majority was receiving ≤40 mg HYD dose; 6 patients received 20 mg and 10 received 40 mg (Table 1). Four patients were treated at doses >60 mg HYD; 1 received 60 mg, 2 received 80 mg, and 1 received 120 mg. Patients who discontinued due to titration failure received HYD 20 mg (2 patients), 40 mg (1 patient), and 60 mg (1 patient). Among the patients who discontinued the study during maintenance, 3 received HYD 20 mg, while 2 received 40 mg, and 1 received 80 mg at the time of discontinuation. Of the 14 patients who completed the study, terminal HYD daily doses of 20, 40, 60, 80, and 120 mg were administered to 3, 5, 4, 1, and 1 patient(s), respectively.

During the study, all elderly patients received concomitant medications, and 8 (33%) patients received non-study opioid medications (vs 16 patients at baseline). Six of these 8 patients continued their pre-study opioid medications on an as-needed basis during the study; 2 patients (patients 6 and 8) were opioid-naïve at baseline and received non-study opioid medications during the study.

**HYD effectiveness**

Mean “pain over the last 24 h” scores decreased from moderate (6.1) to mild levels (3.9) by the end of the titration period, and levels remained mild throughout the maintenance phase until the end of study (3.6; Fig. 1). A decrease of 2.46 points in the mean “pain over the last 24 h” scores from baseline levels to the end of the study was demonstrated with HYD treatment. During the overall maintenance period, mean pain severity decreased by 2.3 and interference scores decreased by 2.0 points. A majority of patients were administered a single, stable HYD dosage throughout the maintenance phase (55%) (Fig. 2). Twenty percent of patients decreased their HYD dosage during the maintenance phase, while another 20% and 5% increased their HYD dosage by 1 level (eg, HYD 20–40 mg) and 2 levels (eg, HYD 20 to 40–60 mg), respectively.

The mean HYD dose administered increased from 24.2 mg to 40.8 mg during the titration period, and remained relatively stable (37.6–49.7 mg range) during the maintenance phase (Fig. 3). The use of non-study opioid analgesics decreased among study participants during the course of the study, declining from 7.5 mg to 1.9 mg in the titration phase and diminishing further during maintenance.

**Treatment satisfaction**

Of the 20 patients completing the titration period and entering the maintenance period of this study, 17 completed the treatment satisfaction questionnaire. Ninety-four percent (16/17) of patients indicated high levels of satisfaction (satisfied to extremely satisfied) with the study drug. All patients (100%) found it convenient to use HYD. 94% (16/17) of patients were satisfied with the ease and frequency of use of the study drug, and 88% of patients (15/17) were satisfied with the effectiveness of HYD at managing their pain. Overall, 94% (16/17) of patients were satisfied with the study drug, while all (100%) patients found it easy to plan HYD use.

**Safety**

Treatment-emergent AEs were reported by 71% of the patients (Table 3). The most frequently observed AEs were gastrointestinal disorders, including constipation (54%), nausea (17%), vomiting (8%), and dry mouth (4%). Overall, 7 of 24 patients (29%) discontinued due to an AE during the titration and maintenance periods (Table 2), with nausea and constipation being the only AEs leading to discontinuation that were reported in more than 1 patient. There was no incidence of falls. One patient reported hypogonadism, whereas hyperglycemia and immunosuppression were not assessed due to the lack of standardized testing. There were no deaths. Serious AEs were reported for 5 (21%) patients: 1 patient (patient 4) with a history of multiple cardiovascular disorders, including congestive heart failure and coronary artery disease, reported atypical chest pain; 1 patient (patient 6) with a history of peripheral vascular disorder and hypertension reported stenosis of the right internal carotid artery; 1 patient (patient 8) with a history of pulmonary embolism in the left lung reported bilateral pulmonary embolism, deep vein thrombosis in the left leg, and kidney stones; 1 patient (patient 22) with a history of pulmonary embolism reported lethargy and pneumonia; and 1 patient (patient 23) with a history of adenoiditis, mastoiditis, and vulvitis reported Methicillin-resistant *Staphylococcus aureus*-infected abscesses of perineum and buttocks. The serious AE of lethargy reported by 1 patient was the only serious AE to be considered by the investigator to be possibly study drug related. All other serious AEs were considered by the investigator to be not related to study drug.

**Discussion**

In this post-hoc analysis, HYD treatment was clinically effective in providing sustained reduction of pain scores over a 52-week period in the elderly patients with chronic pain. These reductions are considered clinically important (ie, a reduction in pain scores of ≥2 points and a reduction in BPI-SF pain interference scores of ≥1

### Table 2

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>Dose titration period (N = 24)</th>
<th>Maintenance period (N = 20)</th>
<th>Overall treatment period (N = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed period on HYD</td>
<td>20 (83)</td>
<td>14 (70)</td>
<td>14 (58)</td>
</tr>
<tr>
<td>Discontinued study</td>
<td>4 (17)</td>
<td>6 (30)</td>
<td>10 (42)</td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient's choice</td>
<td>3 (13)</td>
<td>4 (20)</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>0</td>
<td>2 (10)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Lack of therapeutic effect</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diversion</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Administrative</td>
<td>0</td>
<td>NA</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

HYD, hydrocodone bitartrate; N, number of patients in the population for the given period; n, number of patients with each individual response; NA, not available.
These patients achieved optimal treatment effects without requiring high doses of HYD (≤40 mg) and their HYD doses were stable throughout the 52-week maintenance period. Upon conversion to HYD treatment, these patients also reduced the use of other immediate-release or permitted short-acting opioids throughout the study. This elderly patient subgroup was also satisfied with the ease of use and convenience of HYD treatment. Overall these results of effectiveness of HYD treatment in the elderly patients was consistent with the results observed in the younger patient cohort (<65 years of age) and the overall study population from the primary study.14

The AE safety profile shown for HYD is consistent with those frequently seen in opioid analgesics in general.20,21 HYD treatment was generally well tolerated among the elderly patients in this study. The events rates for AEs observed in this study are consistent with a previous analysis among patients receiving opioid therapy for chronic nonmalignant pain.22 Although reports indicate that elderly patients taking opioid medications are at increased risk for falls and fractures,23,24 no falls were reported in this study. No other significant concerns reported with opioid use were evident in this study, such as hyperalgesia, endocrine dysfunction, and immunosuppression.25–27 In a separate analysis, the adverse event profile in this elderly subgroup was similar to that of younger patients <65 years of age.18,19 Although higher incidence of serious AEs were reported by the elderly group, compared to the younger cohort, all serious AEs were more likely a consequence of comorbid disease, and considered to be unrelated to the study drug with the exception of the serious AE of lethargy reported in 1 patient, which was considered to be possibly related to HYD use.

Once-daily HYD differs from the existing opioid formulations. Unlike the most frequently prescribed opioid hydrocodone-acetaminophen combination products,28 HYD does not contain a non-opioid component, therefore its dosage is not limited by potential toxicities associated with the non-opioid component in combination products, such as liver toxicity with acetaminophen. Although acetaminophen use is recommended as a first-line therapy for the treatment of pain and is generally considered safe, with a safety profile comparable between older (>65 years) and younger adults,2 acetaminophen-associated liver toxicity is the leading cause of acute liver failure in the US.29 In light of this association, the FDA has put forth a guidance to limit exposure to acetaminophen, especially when used chronically at higher doses, or when used in patients with liver insufficiency or alcohol use.30,31 In light of the current guidance, treatment of the elderly with acetaminophen should be closely monitored, since elderly patients taking medications which increase the activity of enzymes involved in phase I metabolism may be at increased risk for acetaminophen-induced hepatotoxicity.29

HYD is dosed every 24 h, affording once-daily dosing, which is associated with improved adherence rates relative to multiple daily doses.32 In addition, a study showed that after administration of HYD, the pharmacokinetic profile of hydrocodone in healthy elderly subjects (65–77 years) was similar to that in healthy younger subjects (20–45 years).11 Thus, conversion to HYD requires no additional dose adjustment other than those that are routinely recommended when converting from one opioid to another in an elderly population.5,7,33 Although the rates of opioid abuse or misuse among those 60 years of age or older are lower than that of a younger population,34 the problem of misuse and abuse among

**Fig. 1.** Mean “average pain over the last 24 h” scores. DT, dose titration period; SE, standard error.

**Fig. 2.** HYD dose changes during the maintenance period of the study.
ellderly patients is rapidly increasing. HYD is formulated with abuse-deterrent properties that are intended to deter tampering and misuse by certain avenues of administration.

This analysis of a subpopulation of a larger study is limited by its post-hoc nature and small population size. As such, this sub analysis was not designed to have the specificity that might have been used for a study of an exclusively older population. Of note, the results from this elderly patient subpopulation are similar to those seen with the entire patient population and the younger patient population from the same study.

An additional limitation of this study is the lack of a formal test for cognition. Pain report is the most reliable pain assessment source, yet many elderly patients can suffer from cognitive impairments that can lead to difficulties in accurately reporting pain levels or the incidence of AEs. Although no formal cognitive studies were conducted on the elderly population in this study, patients were enrolled in this study only if they were assessed by the investigator as capable of providing subjective assessments, and were able to read, understand and respond to questionnaires. Moreover, this study used an 11-point NRS to assess pain intensity, a measure that has been validated for use in elderly patient populations. Finally, although patients participating in this study had access to medication at no cost, it remains to be determined whether the availability of HYD in the real-world is affected by accessibility considerations.

Conclusions

In this post-hoc analysis of a long-term study, treatment with HYD resulted in reduced pain scores that were maintained over a 52-week period in geriatric patients, a growing and complex population to treat. Administration of HYD resulted in clinically meaningful reductions in mean “pain over the last 24 h” scores and pain interference scores, and provided significant pain relief to elderly patients for a duration of 52 weeks. A majority of patients received a stable dose of HYD during the maintenance period of the study. Additionally, these patients were able to achieve adequate analgesia without the use of supplemental non-study opioid medications at the end of the study. Furthermore, patients indicated high levels of satisfaction with HYD. The tolerability of HYD among geriatric patients was typical for an opioid, although no falls were observed in this study.

Conflicts of interest

This study was sponsored by Purdue Pharma L.P. (Stamford, CT). Kathleen Broglio is a consultant for Purdue Pharma L.P. Joseph Pergolizzi is a consultant for Purdue Pharma L.P. and Mundipharma. Mariibeth Kowalski and Ellie He are full-time employees of Purdue Pharma L.P. Warren Wen and Shau Yu Lynch were full-time employees of Purdue Pharma L.P. at the time this study was conducted. Editorial support was provided by Sameera Kongara, PhD, of QSci Communications and funded by Purdue Pharma L.P.
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