Brief Report

Oxymorphone Extended Release for the Treatment of Chronic Low Back Pain: A Retrospective Pooled Analysis of Enriched-Enrollment Clinical Trial Data Stratified According to Age, Sex, and Prior Opioid Use

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ABSTRACT

Objective: This study assessed the potential effects of age, sex, and prior opioid use on the response to oxymorphone extended release (ER) in patients with moderate to severe chronic low back pain.

Methods: Combined data from 2 placebo-controlled clinical trials with an enriched-enrollment, randomized-withdrawal design were analyzed. In patients aged ≥18 years with chronic low back pain, the dose of oxymorphone ER was titrated to a stable, tolerable, effective dose. Patients who completed titration were randomly assigned to a 12-week double-blind study period with oxymorphone ER or placebo. Oxymorphone immediate release 5 mg was permitted q4–6h, as needed for rescue medication or withdrawal symptoms, for 4 days after randomization and restricted to 10 mg/d thereafter. Pain intensity (100-mm visual analog scale [VAS]; 0 = no pain to 100 = worst pain imaginable) and time to study discontinuation due to lack of efficacy were compared with stratification by age (<65 vs ≥65 years), sex, and prior opioid use. Adverse events were categorized by severity and relation to study medication.

Results: Of 575 patients, 348 completed titration and 347 entered the double-blind study phase. There were no significant between-group differences in demographic variables, except that the mean age in the oxymorphone ER group was significantly higher (P = 0.04), and the proportion of men was significantly lower (P = 0.01). There was no significant age difference between the oxymorphone ER and placebo groups stratified by age (<65 vs ≥65 years). Fewer patients aged ≥65 years versus <65 years completed titration (45.0% [36/80] vs 63.0% [312/495]; P = 0.002). The least-squares mean (SEM) differences in VAS pain scores between the oxymorphone ER (n = 174) and placebo (n = 169) groups were significant at each postbaseline assessment (P < 0.001) and at study completion (12.3 [2.8] mm; P < 0.001) and was not significantly affected by age, sex, or prior opioid use. Age and sex had no significant influence on adverse events or discontinuations due to lack of efficacy. More discontinuations due to lack of efficacy occurred among patients in the placebo group (hazard ratio, 5.01; P < 0.001) and among opioid-experienced patients. The latter effect was limited to opioid-experienced patients who received placebo. The rates of discontinuation due to lack of efficacy were similar between oxymorphone ER–treated opioid-naive and opioid-experienced patients (11.4% vs 11.6%). The proportion of patients who experienced opioid-related adverse events was significantly greater in the oxymorphone ER group compared with the placebo group (25.7% vs 16.3%; P = 0.03). The most frequent treatment-emergent adverse events in the oxymorphone ER group were nausea (8.0%), constipation (6.3%), vomiting (4.6%), and diarrhea (4.0%); in the placebo group were nausea (5.8%), diarrhea (4.7%), and increased sweating (2.3%).

Conclusion: In the enriched population of patients who successfully titrated to oxymorphone ER, oxymorphone ER was effective and generally well tolerated, independent of patients' age, sex, or previous

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Key words: oxymorphone extended release, chronic low back pain, age, sex, opioid use.

INTRODUCTION

Chronic low back pain is a common, debilitating, and costly health problem.[1–4] Chronic low back pain is common in diverse populations, although the prevalence is higher in women[4,5] and increases with age.[4] Back pain is also the most common cause of activity limitation in adults aged <45 years, with a prevalence of 80.5 per 1000 population.[5] Given the potentially protracted and episodic course of chronic low back pain,[6] patient populations differ with respect to their history of exposure to pain pharmacotherapies. Patients experiencing chronic pain may have a history of treatment with multiple pharmacologic agents owing to inadequate analgesia, poor tolerability, and poor compliance.[7–10] Because of this inherent diversity among clinical populations with chronic low back pain, all treatments, including pharmacotherapies, must be individualized and flexible.

Opioid analgesics are well established in the treatment of cancer pain,[11] and they are gaining limited acceptance as a treatment for nonmalignant pain. Despite concerns about the potential for abuse, several systematic reviews of clinical trial data have concluded that opioid treatment is warranted in carefully selected, closely monitored patients with chronic nonmalignant pain.[12–14] In 2007, the American Pain Society and American College of Physicians issued joint clinical practice guidelines for the management of chronic low back pain that recommend the judicious use of opioid analgesics in patients with acute or chronic back pain who are unlikely to respond to acetaminophen or NSAIDs or who have contraindications to NSAIDs.[15] Several clinical trials have suggested the value of individualized titration of opioids in patients with chronic low back pain.[16–20] None of these trials, however, assessed whether major demographic variables, such as sex, age, and prior opioid treatment, influenced the efficacy and tolerability of opioid treatment. Older patients (aged ≥65 years) may require lower opioid doses than do younger patients to maintain effective analgesia,[21,22] are more sensitive to opioid-associated respiratory effects,[23] and are less susceptible to opioid-induced nausea.[23,24] Women may be more susceptible than men to opioid-induced nausea and vomiting[23] and to the analgesic effects of opioids, particularly κ-opioid receptor agonists, as shown in one study of women and men in their early 20s.[25] Patients with prior experience with opioid pain therapy have needed higher opioid doses to achieve effective analgesia.[16,17,26] Thus, differences in physiology[27,28] associated with age and sex, as well as neurobiologic changes resulting from previous opioid exposure,[29,30] may influence an individual's sensitivity to both the analgesic and adverse effects of opioids.

An extended-release (ER) formulation of the opioid oxymorphone* has shown efficacy in clinical trials enrolling patients with chronic moderate to severe pain.[31–34] In studies of patients with chronic cancer pain, oxymorphone ER was reported to be as effective as oxycodone controlled release (CR) in maintaining pain relief.[31,32] In noncancer pain, oxymorphone ER provided pain relief that was significantly greater than placebo in patients with chronic osteoarthritis pain[33,34] and provided pain relief that was similar to that of oxycodone CR[20] and significantly greater than placebo in patients with moderate to severe chronic low back pain.[16,17,20] Each of these studies examined oxymorphone ER in a cohort that included men and women of varying ages and with different degrees of prior exposure to pain pharmacotherapy.[16,17,20,31–34] The analgesic efficacy of oxymorphone ER across studies suggests that it may be effective across diverse subpopulations of patients; however, this question has not been systematically addressed. To further examine the potential effects of age, sex, and prior opioid use on the efficacy of oxymorphone ER, we performed a pooled analysis of data from 2 large clinical studies that assessed the efficacy of oxymorphone ER in the treatment of moderate to severe chronic low back pain.[16,17]

PATIENTS AND METHODS

Study Population

Patients eligible for the study included men and women aged ≥18 years with moderate to severe chronic low back pain.[16,17] Patients were deemed to have moderate to severe pain if their score on a 100-mm visual analog scale (VAS) (0 = no pain to 100 = worst pain imaginable) was ≥50 mm. In addition, patients were

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required to have moderate to severe pain that was present for a minimum of several hours per day for ≥3 months. Opioid-naive patients were eligible if they had been taking less than the equivalent of 5 mg/d oxycodone during the 14 days before screening. Opioid-experienced patients had been taking around-the-clock opioid pain medication (60–660 mg/d of oral morphine or equivalent) for 2 weeks before screening. All patients were required to continue (without change) all adjunctive therapies, such as physical therapy, biofeedback therapy, acupuncture, and herbal remedies.

Exclusion criteria included fibromyalgia, reflex sympathetic dystrophy or causalgia, acute spinal cord compression, cauda equina compression, acute nerve root compression, severe lower-extremity weakness or numbness, bowel or bladder dysfunction secondary to cauda equina compression, diabetic amyotrophy, meningitis, diskitis, back pain caused by secondary infection or tumor, and surgery to resolve back pain within 2 months (opioid-naive patients) or 6 months (opioid-experienced patients) of screening. Patients aged <18 years were excluded because oxymorphone ER was not approved for use in children, and pregnant or breastfeeding women were excluded because this population would have required special precautions or compromised ethical risk/benefit considerations. Additional criteria for study exclusion have been described in detail elsewhere.[16,17]

Institutional review board approval was obtained for the study protocol, and all patients provided written informed consent before study participation.

Design

This analysis used pooled data from 2 multicenter enriched-enrollment, randomized-withdrawal (EERW) clinical trials of oxymorphone ER conducted at 34 sites.[16,17] Both of these trials included a titration phase (the enrichment phase) and a 12-week, randomized, double-blind, placebo-controlled phase (the randomized-withdrawal phase). During the enrichment phase, patients who responded to oxymorphone ER were identified. Only this enriched population of responders was randomized to continue oxymorphone ER or to be switched to placebo. The EERW trial design was selected to approximate the conditions that treating physicians are likely to encounter in their practices. Traditional randomized controlled trials (RCTs) assess outcomes in an entire study population. RCTs may not accurately capture treatment effects because results for the entire study population represent an average of those patients who show the desired response and those who experience inadequate analgesia or intolerable adverse events. However, in clinical practice, patients who experience inadequate analgesia or intolerable adverse events would be expected to discontinue treatment. When only responders are randomized, treatment outcomes reflect efficacy and tolerability results in the patient population that would be most likely to continue treatment in clinical practice. Thus, for the present analysis, the open-label titration period allowed a comparison of response rates in subgroups stratified according to age, sex, and prior opioid use. The 12-week double-blind treatment period allowed an accurate quantification of response in a subgroup of patients for whom continued treatment was indicated.

Placebo was used as the comparator instead of another opioid to be consistent with the definition of EERW trial design recognized by the US Food and Drug Administration Center for Drug Evaluation and Research,[18] requiring the acquisition of data comparing new opioid analgesics to placebo. Furthermore, comparison to another opioid in addition to placebo would require a more complicated crossover study design. The EERW trials combined for this analysis were 2 of only a handful conducted to evaluate analgesics,[16,17,20,35–39] and oxymorphone ER is the only ER opioid evaluated in EERW trials. Therefore, inclusion of data from trials of other opioids in patients with chronic low back pain would be incompatible with the present analysis.

Interventions

The open-label titration period was intended to establish an individualized stable, effective, and well-tolerated dose of oxymorphone ER in patients who showed an initial response to the drug. Opioid-naive patients were considered to have reached a stabilized dose if they experienced adequate pain relief (eg, pain intensity ≤40 mm on a 100-mm VAS) for 3 of 5 consecutive days while receiving the same dose of study medication and if they required a minimum oxymorphone ER dose of 10 mg q12h (20 mg/d). Opioid-experienced patients were considered to have reached a stabilized dose if they met the same conditions as for opioid-naive patients and required no more than 2 doses of 5 mg oxymorphone immediate release (IR) as rescue medication each day.

During the titration period, oxymorphone ER was administered PO q12h, once early in the morning and once in the evening, without specific instructions regarding administration relative to ingestion of food. In opioid-naive patients, an initial dose of 5 mg PO q12h was administered for 2 days and then titrated upward in increments of 5 to 10 mg q12h at 3- to 7-day intervals until the dose was stabilized. Patients not requiring more than the initial 5 mg q12h were discontinued from the study because these patients did not have a sufficient level of baseline pain to allow detection of treatment effects. Opioid-experienced patients were first switched to a dose of oxymorphone ER that was approximately equal to their current opioid treatment, based on predefined conversion ratios and the investigator's judgment.[16,40] The oxymorphone ER dose could then be titrated as needed in 10-mg increments q12h at 3- to 7-day intervals until the dose was stabilized. Although opioid-naive patients were not permitted to use rescue medication during the open-label titration period, opioid-experienced patients were allowed to use oxymorphone IR prn (5 mg q4–6h). Patients had up to 1 month to reach their stabilized dose of oxymorphone ER.

Patients who met the criteria for dose stabilization were randomized to the 12-week double-blind treatment period, during which they either continued to receive oxymorphone ER q12h at the stabilized dose or were switched to matching placebo. To prevent opioid withdrawal, oxymorphone IR (5 mg q4–6h prn) was allowed during the first 4 days of double-blind treatment. Subsequent use of oxymorphone IR as rescue medication was limited to a maximum daily dose of 10 mg. To avoid confounding of opioid effects, NSAIDs and other concomitant analgesics were prohibited except to treat nonpain conditions (eg, fever, cardiovascular disease). All patients received an anti-constipation agent. Any patient who discontinued treatment prematurely, during either open-label titration or double-blind treatment, was reestablished on an appropriate pain medication.

All medications were provided to patients free of charge.

Study Assessments

Efficacy end points included the change in average daily pain intensity on a 100-mm VAS and the time (in days) to study discontinuation due to lack of efficacy. VAS pain intensity scores were collected at screening (before titration) and baseline (after titration and before randomization) and during double-blind study drug administration at days 4, 7, 14, 21, 28, 42, 56, 70, and 84. Additionally, data were collected on patients' and physicians' global assessments of pain medication (encompassing efficacy, tolerability, and overall satisfaction) rated on a categoric scale (poor, fair, good, very good, or excellent). Treatment-emergent adverse events were recorded at each study visit. Investigators graded the intensity of adverse events as mild, moderate, or severe and the relationship of an adverse event to the study medication as probable, possible, unlikely, or not related. *Mild* adverse events were usually transient, required no special treatment, and did not interfere with the patient's daily activities. *Moderate* adverse events introduced a low level of inconvenience or concern to the patient and may have interfered with daily activities, but were usually ameliorated by simple therapeutic measures. *Severe* adverse events interrupted a patient's usual daily activities and typically required systemic drug therapy or other treatment. A *probable* relationship indicated that a reasonable temporal sequence existed between the study medication and adverse event and, based on the investigator's clinical experience, an association between the adverse event and the study medication seemed likely. A *possible* relationship indicated that the association of the adverse event with the study treatment was unknown; however, the adverse event was not reasonably attributed to any other condition. An *unlikely* relationship indicated little or no likelihood that the study medication caused the adverse event; other factors, including disease progression or concurrent illnesses, were likely the cause.

Statistical Analyses

The 2 treatment groups were compared in terms of patients' demographic and baseline characteristics using t tests for continuous measures and χ^2 tests for categoric measures. The statistical analysis software used was SAS/STAT version 8.2 (SAS Institute Inc., Cary, North Carolina).

Mean VAS pain intensity scores were compared across the 2 groups using repeated-measures analysis of variance models that included treatment, visit, age group (<65 vs ≥65 years), sex, and prior opioid experience as main effects, with interaction terms for treatment by visit and age group. The least-squares (LS) means and SEMs were calculated for treatment

groups, as were the LS mean differences between treatments with corresponding *P* values for each visit.

Time to early discontinuation due to lack of efficacy was compared across the 2 treatment groups using proportional hazards regression models. The full model included treatment, age group (<65 vs ≥65 years), age group by treatment interaction, previous opioid experience, sex, baseline pain intensity, and screening pain intensity. The nonsignificant variables ($P > 0.05$) were removed from the full model, resulting in a final model that included treatment age group (<65 vs ≥65 years) and previous opioid experience. The *P* values reported herein are from the final model. Statistical analysis of adverse events consisted of χ^2 tests and logistic regression models that included treatment, age, and sex as factors.

RESULTS

Demographic Characteristics and Patient Disposition

The disposition of the study population is shown in **Figure 1**. Of the 575 patients enrolled, 348 (60.5%) completed open-label titration and 347 were randomized to a double-blind treatment group and began treatment (oxymorphone ER, n = 175; placebo, n = 172).

A numerically higher percentage of men compared with women (*P* = NS) and opioid-naive patients compared with opioid-experienced patients (*P* = NS) completed the titration period (**Table I**). Patients aged <65 years were significantly more likely to complete titration than those aged ≥65 years (63.0% [312/495] vs 45.0% [36/80]; $P = 0.002$). A total of 227 of 575 patients (39.5%) discontinued treatment. The most frequent reason for treatment discontinuation during titration was adverse events (18.4% [106/575]). The increased rate of discontinuation during titration among patients aged ≥65 years was entirely attributable to a higher rate of adverse events among patients ≥65 years (32/80 [40.0%] vs 73/495 [14.8%]). Adverse events caused discontinuation in 18.2% of opioid-naive patients (59/325) and 18.8% of opioid-experienced patients (47/250).[16,17] Other reasons for discontinuation were failure to reach a stabilized dose (7.0% [40/575]), withdrawal of consent (5.0% [29/575]), "other" (4.2% [24/575]), lack of efficacy (2.4% [14/575]), and loss to follow-up (2.4% [14/575]).[16,17] Lack of efficacy led to discontinuation in 1.2% (4/325) of opioid-naive patients and 4.0% (10/250) of opioid-experienced patients.[16,17]

The demographic and disposition characteristics of patients randomized to double-blind treatment are presented in **Table II**. The (mean [SD]) stabilized dose of oxymorphone ER in the patients assigned to continue oxymorphone ER or in those switched to placebo did not differ significantly (55.9 [47.21] vs 62.8 [51.01] mg/d), nor did the median dose of oxymorphone ER (40.0 mg/d in each group). Overall, patients with a history of opioid use, compared with opioid-naive patients, were stabilized on a higher mean dose of oxymorphone ER (87.2 [60.4] vs 40.0 [25.8] mg/d, respectively; $P < 0.001$).

The (mean [SD]) age of the oxymorphone ER group was significantly greater than that of the placebo group (50.0 [13.1] vs 47.2 [12.0] years; $P = 0.039$). However, when the patients were stratified by age (ie, <65 vs ≥65 years), the difference between the study groups was not significant. More than 85% of the patients in each treatment group were aged <65 years. The proportion of men was significantly lower in the oxymorphone ER group than in the placebo group (43.4% [76/175] vs 57.0% [98/172]; $P = 0.01$). There were no between-group differences in ethnicity; >85% of the patients in each group were white.

Degenerative disc disease, herniated disc, osteoarthritis, and trauma were the most common causes of chronic low back pain, with no significant differences between treatment groups. Categoric ratings of pain intensity at screening in the oxymorphone ER group (74.3% [130/175] moderate; 25.7% [45/175] severe) and placebo group (77.3% [133/172] moderate; 22.7% [39/172] severe) did not differ significantly. No significant differences were found between the oxymorphone ER and placebo groups in mean VAS-rated pain intensity at screening or baseline. In both groups, the mean VAS decreased from ~69 mm at screening to 21 mm at baseline ($P < 0.001$).

The proportion of patients who completed the 12-week double-blind study drug administration period was significantly higher in the oxymorphone ER group than in the placebo group (69.0% [120/174] vs 38.5% [65/169]; $P < 0.001$) (**Figure 1**). As described in detail in this section, the major difference in discontinuations between treatment groups was the result of fewer discontinuations due to lack of efficacy in patients randomized to oxymorphone (11.5% [20/174] vs 42.6% [72/169]; $P < 0.001$). The rates of discontinuation due to adverse events were low and not

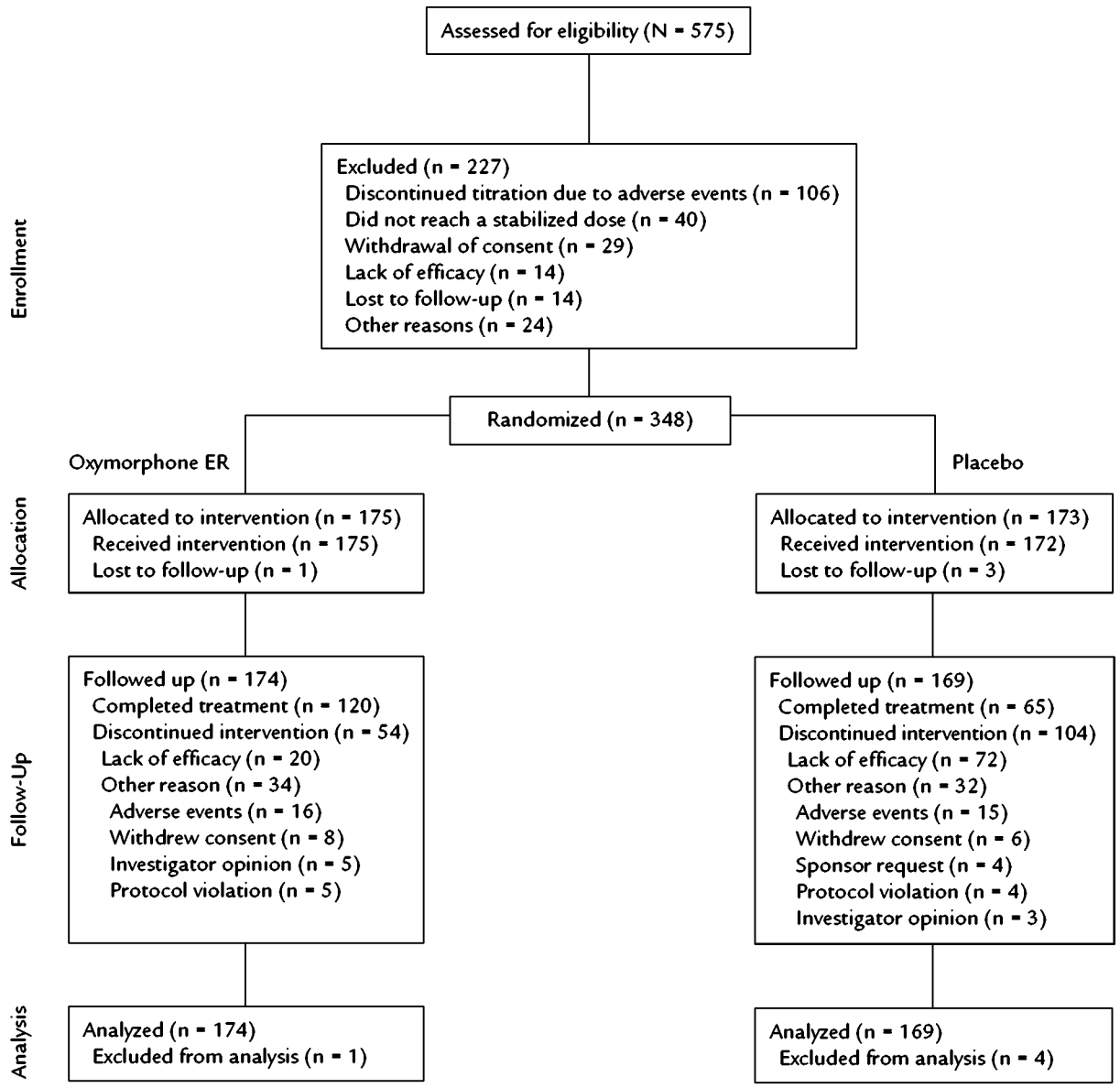

Figure 1. Disposition of the study population with chronic low back pain randomized to receive double-blind administration of oxymorphine extended release (ER) or placebo.

significantly different between the oxymorphone ER and placebo groups (9.2% [16/174] vs 8.9% [15/169]). Discontinuations for reasons unrelated to efficacy were reported in 34 patients (19.5%) in the oxymorphone ER group and 32 patients (18.9%) in the placebo group (P = NS).

Efficacy

Pain Intensity on Visual Analog Scale

A total of 343 patients (oxymorphone ER, n = 174; placebo, n = 169) were included in the efficacy analyses. Patients who were lost to follow-up or did not receive double-blind treatment were excluded. During

Table I. Characteristics of patients with chronic low back pain randomized to receive double-blind administration of oxymorphone extended release or placebo.

Characteristic	Patients Enrolled,* No. (%)	Patients Completing Titration, No. (%) by Category
Sex		
Female	297 (51.7)	174 (58.6)
Male	278 (48.3)	174 (62.6)
Age†		
<65 y	495 (86.1)	312 (63.0)
≥65 y	80 (13.9)	36 (45.0)
Opioid history		
Naive	325 (56.5)	205 (63.1)
Experienced	250 (43.5)	143 (57.2)

*Patients enrolled and receiving treatment (N = 575).
† $P < 0.002$ for relation of characteristic to likelihood of completing titration period.

the double-blind treatment period, (mean [SD]) VAS pain-intensity scores remained relatively constant in the oxymorphone ER group (baseline, 20.8 [0.90] mm; week 12, 20.9 [1.61] mm), but VAS was significantly increased in the placebo group (baseline, 20.6 [0.85] mm; week 12, 32.7 [3.32] mm; $P < 0.001$). Significant effects were found for treatment, visit, and the interaction of treatment with visit on VAS pain intensity (all, $P < 0.001$). Differences in the mean VAS pain-intensity scores between oxymorphone ER and placebo are illustrated in **Figure 2**. Significant differences in the LS means were observed at each visit after baseline when age group, prior opioid experience, and sex were included as main effects ($P < 0.001$ for all visits after baseline). The LS mean (SEM) difference in VAS pain scores between the oxymorphone ER and placebo groups at study completion was 12.3 (2.8) mm ($P < 0.001$). There were no significant effects of age, sex, prior opioid experience, or age by treatment interaction on VAS pain intensity.

Discontinuations Due to Lack of Efficacy

As noted previously, discontinuations for reasons other than lack of efficacy were not significantly different between the oxymorphone ER and placebo groups (19.5% [34/174] vs 18.9% [32/169]). In contrast, the percentage of patients discontinuing because of lack of efficacy during double-blind treatment was ~4-fold greater in the placebo group than in the oxymorphone ER group (42.6% [72/169] vs 11.5% [20/174]; $P < 0.001$).

Survival analyses indicated a significant effect of treatment on discontinuation due to lack of efficacy (**Figure 3**), such that patients in the placebo group were ~5-fold more likely to discontinue because of lack of efficacy during the study (hazard ratio = 5.01; $P < 0.001$). Accordingly, the mean (SD) durations of administration in the double-blind period were 66.8 (30.6) days (median, 84.0 days) in the oxymorphone ER group and 39.3 (37.4) days (median, 11.5 days) in the placebo group ($P < 0.001$); this difference was largely attributable to discontinuations due to lack of efficacy.

Previous opioid experience was associated with an increased risk for discontinuation due to lack of efficacy ($P = 0.01$), but this overall risk increase was due entirely to differences between opioid-naive and opioid-experienced patients in the placebo group. Discontinuation due to lack of efficacy among patients who received placebo was reported in 35.7% of opioid-naive patients (35/98) and 54.9% of opioid-experienced patients (39/71) ($P = 0.01$). In contrast, the proportions of patients who discontinued treatment with oxymorphone ER because of lack of efficacy were 11.4% (12/105) in opioid-naive patients and 11.6% (8/69) in opioid-experienced patients (P = NS). Thus, prior opioid use had no apparent effect on the percentage of patients who discontinued because of lack of efficacy in the oxymorphone ER group. Age, sex, and baseline and screening VAS pain scores exhibited no significant effect on time to discontinuation due to lack of efficacy in either group.

Tolerability

A significantly higher proportion of patients who received oxymorphone ER versus placebo reported treatment-emergent opioid-related adverse events (25.7% [45/175] vs 16.3% [28/172]; $P = 0.03$). However, a significantly greater proportion of adverse events were of mild or moderate severity in the oxymorphone ER group compared with the placebo group (97.8% [44/45] vs 85.7% [24/28]; $P = 0.01$). According to a logistic regression analysis of adverse

Table II. Demographic and disposition data in patients with chronic low back pain randomized to double-blind treatment with oxymorphone extended release (ER) or placebo.

Characteristic	Oxymorphone ER (n = 175)	Placebo (n = 172)
Age		
Mean (SD), y	50.0 (13.1)*	47.2 (12.0)
<65 y, no. (%)	152 (86.9)	159 (92.4)
Male sex, no. (%)	76 (43.4)†	98 (57.0)
Ethnicity, no. (%)		
White	152 (86.9)	155 (90.1)
Black	17 (9.7)	10 (5.8)
Hispanic	6 (3.4)	5 (2.9)
Other	0	2 (1.2)
Opioid experienced, no. (%)	70 (40.0)	72 (41.9)
Pain etiology/category, no. (%)		
Degenerative disc disease	64 (36.6)	51 (29.7)
Osteoarthritis	42 (24.0)	39 (22.7)
Trauma	32 (18.3)	39 (22.7)
Herniated disc	17 (9.7)	20 (11.6)
Spinal stenosis	10 (5.7)	4 (2.3)
Other	43 (24.6)	50 (29.1)
Pain intensity		
Screening: moderate, no. (%)	130 (74.3)	133 (77.3)
Screening: severe, no. (%)	45 (25.7)	39 (22.7)
Screening: VAS, mm, mean (SEM)	69.1 (1.09)	69.6 (1.05)
Baseline: VAS, mm, mean (SEM)	20.8 (0.90)	20.6 (0.85)
Oxymorphone ER stabilized dose, mg/d		
Mean (SD)	55.9 (47.21)	62.8 (51.01)
Median	40.0	40.0
Range	10.0–220.0	10.0–260.0

VAS = visual analog scale.
*P = 0.039 versus placebo (t test).
†P = 0.012 versus placebo (χ^2 test).

events, the odds ratio that patients treated with oxymorphone ER would experience opioid-related adverse events was 1.66 (P = 0.02). Differences in the occurrence of adverse events according to age and sex were not statistically significant (both, P = NS) (**Table III**).

Adverse event rates were generally similar between opioid-naive and opioid-experienced patients, although there were some exceptions.[16,17] Constipation occurred more frequently in opioid-naive patients during titration (26.2% [85/325] vs 11.6% [29/250]; P = 0.003), but percentages were not significantly different during double-blind treatment for opioid-naive patients and opioid-experienced patients (6.7% [7/105] vs 5.7% [4/70]; P = NS). Opioid-experienced patients were receiving bowel treatment regimens when they entered the study and were required to continue them throughout oxymorphone ER treatment, whereas opioid-naive patients initiated bowel regimens only after entering the study. Neither vomiting nor dizziness was reported during double-blind

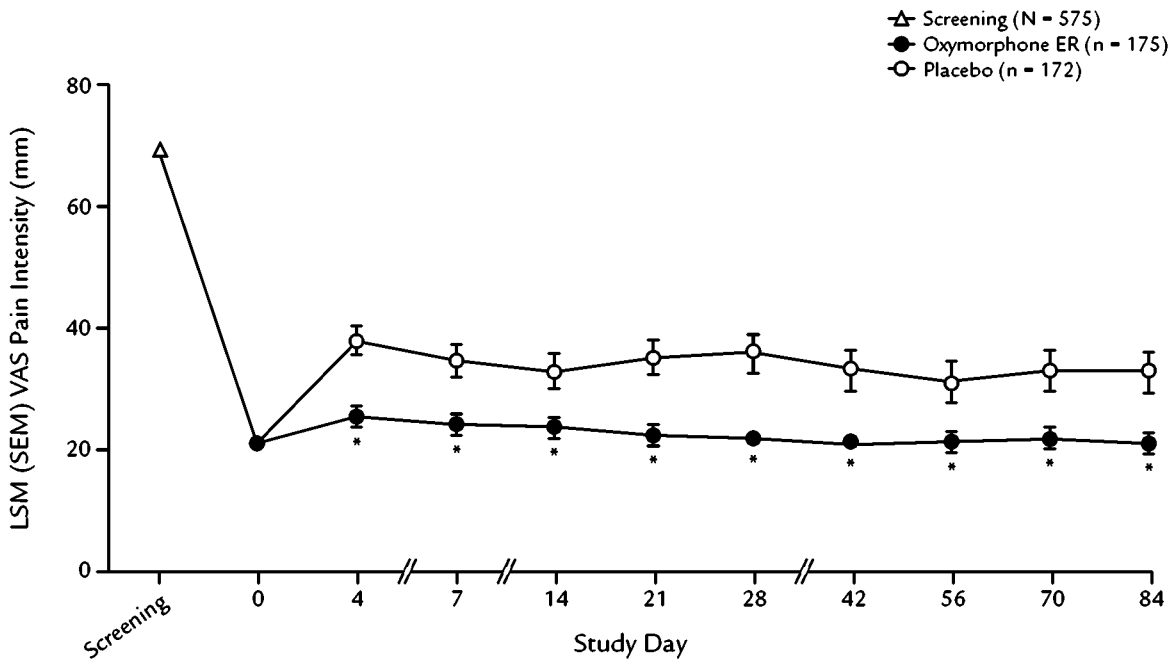

Figure 2. Least-squares mean (LSM) (SEM) pain intensity on visual analog scale (VAS) by visit among patients with chronic low back pain during administration of oxymorphone extended release (ER) or placebo. Screening = visit before enrollment; day 0 = baseline before randomization. All subsequent visit days are referenced to baseline. *$P < 0.001$ versus placebo.

treatment in any opioid-experienced patient; vomiting was reported in 7.6% (8/105) and dizziness was reported in 4.8% (5/105) of opioid-naive patients. Thus, opioid-naive status was associated with an increase in the frequency of specific adverse events, but these rates were low and decreased with ongoing treatment as patients acclimated to oxymorphone ER.

Treatment-emergent opioid-related adverse events reported by at least 1% of the patients in either treatment group during double-blind treatment are presented in **Table III**. The most frequent treatment-emergent adverse events in the oxymorphone ER group were nausea (8.0%), constipation (6.3%), vomiting (4.6%), and diarrhea (4.0%); in the placebo group were nausea (5.8%), diarrhea (4.7%), and increased sweating (2.3%).

DISCUSSION

Oxymorphone ER has been reported to be efficacious in treating moderate to severe pain resulting from diverse causes, including chronic low back pain,[16,17,20] osteoarthritis,[32,34,41] and cancer.[31,32] In the present analysis, we assessed data from 2 EERW studies to determine whether certain demographic variables affected the treatment response to oxymorphone ER in patients with chronic low back pain. The EERW design was chosen to gauge the level of response to oxymorphone ER in a population of responders similar to those who would be likely to receive oxymorphone ER for an extended period in clinical practice. During the titration phase, we found no significant association between sex or previous opioid experience with initial response to oxymorphone ER, but patients aged <65 years were more likely to complete titration than were those aged ≥65 years. This finding was entirely attributed to an increased rate of adverse events among patients aged ≥65 years. Although seniors have been found to be proportionally more likely than younger patients to suffer adverse events with opioids[42] and other medications,[43] among patients who had successful titration to an effective, well-tolerated dose, reductions in VAS-rated pain intensity during treatment with oxymorphone ER were durably main-

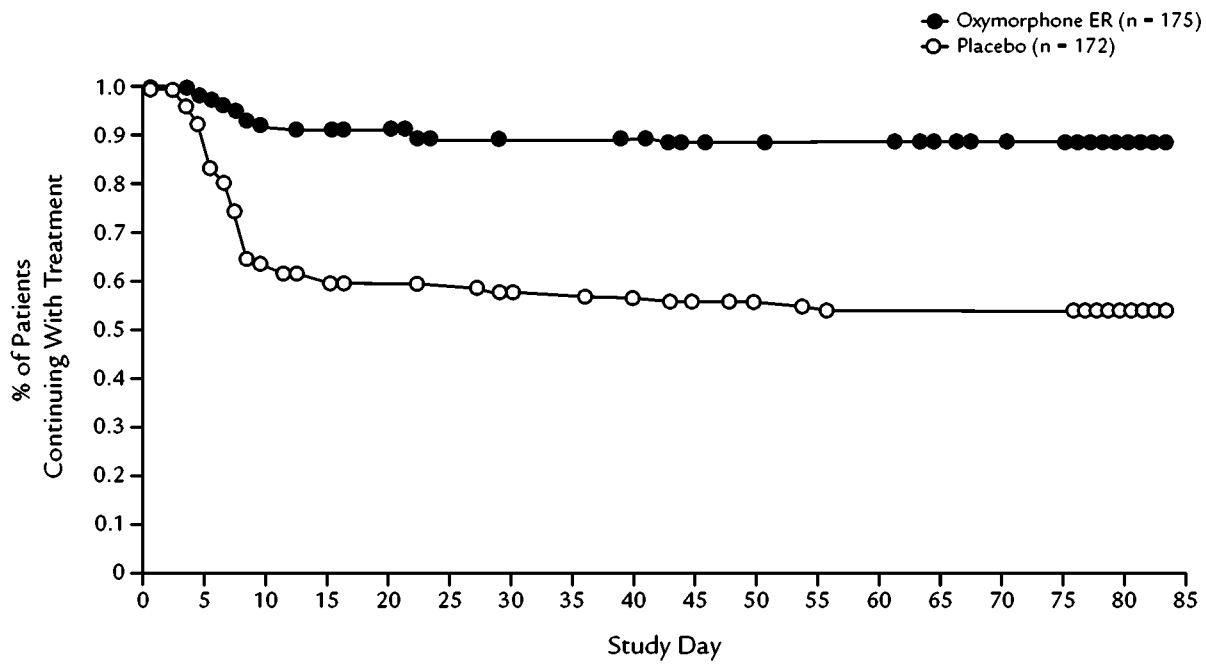

Figure 3. Kaplan-Meier survival curves depicting time (in days) to study discontinuation due to lack of efficacy among patients with chronic low back pain being administered oxymorphone extended release (ER) or placebo.

Table III. Treatment-emergent opioid-related adverse events reported by at least 1% of patients with chronic low back pain in either group during double-blind administration of oxymorphone extended release (ER) or placebo. Values are no. (%).

Adverse Event	Oxymorphone ER (n = 175)	Placebo (n = 172)	*P*
Total no. of adverse events	92 (52.5)	71 (41.3)	0.04*
Nausea	14 (8.0)	10 (5.8)	NS
Constipation	11 (6.3)	2 (1.2)	0.01*
Vomiting NOS	8 (4.6)	2 (1.2)	NS
Diarrhea NOS	7 (4.0)	8 (4.7)	NS
Headache NOS	6 (3.4)	2 (1.2)	NS
Dizziness (except vertigo)	5 (2.9)	3 (1.7)	NS
Insomnia NEC	4 (2.3)	2 (1.2)	NS
Somnolence	4 (2.3)	0	0.05*
Increased sweating	3 (1.7)	4 (2.3)	NS
Pruritus	3 (1.7)	1 (0.6)	NS
Fatigue	1 (0.6)	2 (1.2)	NS
Dry mouth	1 (0.6)	1 (0.6)	NS

NOS = not otherwise specified; NEC = not elsewhere classified.
*Differences for these adverse events commonly associated with opioids.

tained over a 12-week double-blind treatment period, regardless of age, sex, or opioid experience.

Discontinuations due to lack of efficacy were also assessed as an index of the overall efficacy of oxymorphone ER. Significant effects were observed for treatment, such that patients who were randomized to receive placebo were ~5-fold more likely to discontinue because of lack of efficacy than those who continued on their stable dose of oxymorphone ER. These results are consistent with those from previous reports[20,34] and were not found to be influenced by age or sex. A history of prior opioid use increased the probability of discontinuations due to lack of efficacy, but only in patients randomized to receive placebo. No significant differences were found in discontinuations due to lack of efficacy between opioid-naive and opioid-experienced patients who continued their stable dose of oxymorphone ER. Thus, the efficacy of oxymorphone ER appeared to be unaffected by prior opioid use in this population.

Other investigators have reported that variables such as age,[21,22] sex,[25] and prior opioid experience[26] affected the response to opioids. In the present study, opioid-experienced patients entered the double-blind period receiving a higher mean daily dose of oxymorphone ER when compared with opioid-naive patients (87.2 vs 40.0 mg, respectively). More advanced disease state, progressing age, and other factors may also affect the doses required for efficacy. Although demographic characteristics may affect a patient's sensitivity to opioids, such differences need not limit efficacy and tolerability. In both trials considered here, the titration period allowed optimization of each patient's dose. Careful titration to an individualized dose might have facilitated drug efficacy across the diverse patient population. One percent of opioid-naive patients and 4% of opioid-experienced patients discontinued titration because of lack of efficacy.[16,17]

Titration with oxymorphone ER might have improved tolerability in this diverse population. In all, 18.2% of opioid-naive and 18.9% of opioid-experienced patients discontinued titration because of adverse events.[16,17] Adverse events occurred with moderate frequency (41.3% of patients receiving placebo and 52.5% of patients receiving oxymorphone ER) (**Table III**) during double-blind treatment, were generally mild to moderate in intensity, and did not differ significantly according to age or sex. Adverse event rates during double-blind treatment were also generally similar between opioid-naive and opioid-experienced patients. Some adverse events, such as constipation, were more common in opioid-naive patients during titration, but the frequency declined during double-blind treatment after patients were acclimated to treatment. Although the adverse events reported in this analysis were typical of those reported for other opioids[44,45] and with oxymorphone ER specifically,[20,32,41] the rates were lower than those that were reported with other opioids in a 2004 meta-analysis of 15 clinical trials.[13]

Nonetheless, the population included in the present analysis was not large enough to allow extrapolation to the general population of patients with chronic low back pain. Data included in the analysis were derived from 2 studies that used flexible titration schedules and an EERW design. Few opioid trials use these design features, and this fact limited the number of patients who could be combined for analyses. Given its small population sample, the present analysis can be viewed as helping to establish 2 hypotheses for future study: namely, that individualized titration of a strong opioid can enhance both analgesia and tolerability and that oxymorphone ER may be a suitable opioid option in diverse populations of individuals with moderate to severe chronic low back pain who have a history of suboptimal analgesia or intolerable adverse events during opioid treatment. These hypotheses require confirmation in large, prospective studies.

CONCLUSIONS

This study included adults with moderate to severe chronic low back pain who had inadequate response or were unable to tolerate previous opioid or nonopioid medication. Patients showing an initial response to oxymorphone ER were randomized to continue oxymorphone ER or to be switched to placebo for 12 weeks. In this enriched population of responders, oxymorphone ER provided effective analgesia and was generally well tolerated, independent of patients' age, sex, or previous opioid use.

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REFERENCES

1. Collins JJ, Baase CM, Sharda CE, et al. The assessment of chronic health conditions on work performance, absence, and total economic impact for employers. *J Occup Environ Med.* 2005;47:547-557.
2. Centers for Disease Control and Prevention (CDC). Prevalence of disabilities and associated health conditions—United States, 1999 [published correction appears in *MMWR Morb Mortal Wkly Rep.* 2001;50:149]. *MMWR Morb Mortal Wkly Rep.* 2001;50:120-125.
3. Vogt MT, Kwoh CK, Cope DK, et al. Analgesic usage for low back pain: Impact on health care costs and service use. *Spine.* 2005;30:1075-1081.
4. Mapel DW, Shainline M, Paez K, Gunter M. Hospital, pharmacy, and outpatient costs for osteoarthritis and chronic back pain. *J Rheumatol.* 2004;31:573-583.
5. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet.* 1999;354:581-585.
6. Wasiak R, Kim J, Pransky G. Work disability and costs caused by recurrence of low back pain: Longer and more costly than in first episodes. *Spine.* 2006;31:219-225.
7. Quang-Cantagrel ND, Wallace MS, Magnuson SK. Opioid substitution to improve the effectiveness of chronic noncancer pain control: A chart review. *Anesth Analg.* 2000;90:933-937.
8. Grilo RM, Bertin P, Scotto di Fazano C, et al. Opioid rotation in the treatment of joint pain. A review of 67 cases. *Joint Bone Spine.* 2002;69:491-494.
9. Palangio M, Northfelt DW, Portenoy RK, et al. Dose conversion and titration with a novel, once-daily, OROS osmotic technology, extended-release hydromorphone formulation in the treatment of chronic malignant or nonmalignant pain. *J Pain Symptom Manage.* 2002;23:355-368.
10. Portenoy RK, Moulin DE, Rogers A, et al. I.V. infusion of opioids for cancer pain: Clinical review and guidelines for use. *Cancer Treat Rep.* 1986;70:575-581.
11. World Health Organization. *Cancer Pain Relief.* 2nd ed. Geneva, Switzerland: WHO Office of Publication; 1996.
12. Bartleson JD. Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: A review. *Pain Med.* 2002;3:260-271.
13. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain.* 2004;112:372-380.
14. Portenoy RK. Opioid therapy for chronic nonmalignant pain: A review of the critical issues. *J Pain Symptom Manage.* 1996;11:203-217.
15. Chou R, Qaseem A, Snow V, et al, for the 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 [published correction appears in *Ann Intern Med.* 2008;148:247-248]. *Ann Intern Med.* 2007;147:478-491. Summary for patients in *Ann Intern Med.* 2007;147:I45.
16. Hale ME, Ahdieh H, Ma T, Rauck R, for the Oxymorphone ER Study Group 1. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: A 12-week, randomized, double-blind, placebo-controlled study. *J Pain.* 2007;8:175-184.
17. Katz N, Rauck R, Ahdieh H, et al. A 12-week randomized placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. *Curr Med Res Opin.* 2007;23:117-128.
18. Temple RJ. Where protocol design has been a critical success factor in success or failure [CDER Web site]. http://www.fda.gov/cder/present/DIA2004/Temple.ppt. Accessed January 30, 2009.
19. Gabrail NY, Dvergsten C, Ma T, et al. Oxymorphone extended-release (ER) provides safe, effective, and rapid analgesia during opioid rotation: Results of a randomized, double-blind, crossover, comparative study with oxycodone controlled-release (CR). Presented at: American Society of Clinical Oncology 2003 Annual Meeting; May 31-June 3, 2003; Chicago, Ill.
20. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: Results of a randomized, double-blind, placebo- and active-controlled phase III study. *J Pain.* 2005;6:21-28.
21. Hall S, Gallagher RM, Gracely E, et al. The terminal cancer patient: Effects of age, gender, and primary tumor site on opioid dose. *Pain Med.* 2003;4:125-134.
22. Viganó A, Bruera E, Suarez-Almazor ME. Age, pain intensity, and opioid dose in patients with advanced cancer. *Cancer.* 1998;83:1244-1250.
23. Cepeda MS, Farrar JT, Baumgarten M, et al. Side effects of opioids during short-term administration: Effect of age, gender, and race. *Clin Pharmacol Ther.* 2003;74:102-112.
24. Mercadante S, Casuccio A, Pumo S, Fulfaro F. Factors influencing the opioid response in advanced cancer patients with pain followed at home: The effects of age and gender. *Support Care Cancer.* 2000;8:123-130.

25. Gear RW, Miaskowski C, Gordon NC, et al. Kappa-opioids produce significantly greater analgesia in women than in men. *Nat Med.* 1996;2:1248-1250.
26. Rapp SE, Ready LB, Nessly ML. Acute pain management in patients with prior opioid consumption: A case-controlled retrospective review. *Pain.* 1995;61:195-201.
27. Stamer UM, Bayerer B, Stüber F. Genetics and variability in opioid response. *Eur J Pain.* 2005;9:101-104.
28. Zubieta JK, Dannals RF, Frost JJ. Gender and age influences on human brain mu-opioid receptor binding measured by PET. *Am J Psychiatry.* 1999;156:842-848.
29. Zuo Z. The role of opioid receptor internalization and beta-arrestins in the development of opioid tolerance. *Anesth Analg.* 2005;101:728-734.
30. Gintzler AR, Chakrabarti S. Post-opioid receptor adaptations to chronic morphine: Altered functionality and associations of signaling molecules. *Life Sci.* 2006;79:717-722.
31. Gabrail NY, Dvergsten C, Ahdieh H. Establishing the dosage equivalency of oxymorphone extended release and oxycodone controlled release in patients with cancer pain: A randomized controlled study. *Curr Med Res Opin.* 2004;20:911-918.
32. Sloan P, Slatkin N, Ahdieh H. Effectiveness and safety of oral extended-release oxymorphone for the treatment of cancer pain: A pilot study. *Support Care Cancer.* 2005;13:57-65.
33. Kivitz A, Ma C, Ahdieh H, Galer BS. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, Phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. *Clin Ther.* 2006;28:352-364.
34. Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: Results of a randomized, double-blind, placebo- and active-controlled Phase III trial. *Pain Med.* 2005;6:357-366.
35. Byas-Smith MG, Max MB, Muir J, Kingman A. Transdermal clonidine compared to placebo in painful diabetic neuropathy using a two-stage 'enriched enrollment' design. *Pain.* 1995;60:267-274.
36. Galer BS, Rowbotham MC, Perander J, Friedman E. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: Results of an enriched enrollment study. *Pain.* 1999;80:533-538.
37. Lynch ME, Clark AJ, Sawynok J. Intravenous adenosine alleviates neuropathic pain: A double blind placebo controlled crossover trial using an enriched enrollment design. *Pain.* 2003;103:111-117.
38. Russell I, Kamin M, Bennett R, et al. Efficacy of tramadol in treatment of pain in fibromyalgia. *J Clin Rheumatol.* 2000;6:250-257.
39. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol.* 2000;27:772-778.
40. Anderson R, Saiers JH, Abram S, Schlicht C. Accuracy in equianalgesic dosing. Conversion dilemmas. *J Pain Symptom Manage.* 2001;21:397-406.
41. McIlwain H, Ahdieh H. Safety, tolerability, and effectiveness of oxymorphone extended release for moderate to severe osteoarthritis pain: A one-year study. *Am J Ther.* 2005;12:106-112.
42. Guay DR. Use of oral oxymorphone in the elderly. *Consult Pharm.* 2007;22:417-430.
43. Wysowski DK, Swartz L. Adverse drug event surveillance and drug withdrawals in the United States, 1969-2002. *Arch Intern Med.* 2005;165:1363-1369.
44. Cherny N, Ripamonti C, Pereira J, et al, for the Expert Working Group of the European Association of Palliative Care Network. Strategies to manage the adverse effects of oral morphine: An evidence-based report. *J Clin Oncol.* 2001;19:2542-2554.
45. Davis MP, Srivastava M. Demographics, assessment and management of pain in the elderly. *Drugs Aging.* 2003;20:23-57.

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