Pain Physician 2010; 13:561-573 • ISSN 1533-3159

Randomized Trial

Reduced Cognitive and Psychomotor Impairment with Extended-Release Oxymorphone Versus Controlled-Release Oxycodone

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Disclaimer: This study was funded by Endo Pharmaceuticals, Inc.
Conflict of interest: This study was conducted by Kendle Early Stage on behalf of Endo Pharmaceuticals, Inc., who provided funding. Kerri A. Schoedel, Bijan Chakraborty, and Edward M. Sellers are employees of Kendle Early Stage. Kathleen Zerbe, RN, and Stephen McMorn, PhD, are employees of Endo Pharmaceuticals, Inc., and both own stock in Endo Pharmaceuticals, Inc.

Manuscript received: 08/16/2010
Revised manuscript received: 10/28/2010
Accepted for publication: 11/01/2010

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Background: Opioids provide effective pain control, yet have risks including adverse events (AEs) (e.g., constipation, nausea/vomiting, sedation) and cognitive/psychomotor effects.

Objective: To compare cognitive and psychomotor effects of oxymorphone extended release (OM-ER) versus oxycodone controlled release (OC-CR).

Study design: Randomized, double-blind, 5-way crossover

Setting: Single inpatient research unit

Methods: Nondependent recreational opioid users were administered single intact oral tablets of placebo, OM-ER (15 and 30 mg), and OC-CR (30 and 60 mg), separated by a 7- to 21-day washout. The divided attention (DA) test measured psychomotor impairment (e.g., manual tracking [e.g., percentage over road], target accuracy [e.g., target hits], reaction time [hit latency]). Visual analog scales measured alertness/drowsiness, agitation/relaxation, and dizziness. Sedative, stimulant, and dysphoric effects were measured using the Addiction Research Center Inventory Pentobarbital-Chlorpromazine-Alcohol (PCAG), Benzedrine Group (BG), and Lysergic Acid Diethylamide (LSD) scales, respectively. Comparisons were made between equianalgesic doses (OM-ER 15 mg vs OC-CR 30 mg; OM-ER 30 mg vs OC-CR 60 mg), within active drug doses, and between active drugs and placebo using least squares (LS) mean difference of the peak maximum (Emax) or minimum (Emin) effect using linear mixed model analysis of covariance.

Results: Thirty-five participants received all 5 treatments. Peak cognitive and psychomotor impairment (LS mean [SE]) was less with OM-ER than equianalgesic doses of OC-CR for reaction time (Emax hit latency, longer if impaired; 571.2 [13.4] vs 588.1 ms [13.4], P=0.03 for OM-ER 15 mg vs OC-CR 30 mg, respectively; 572.4 [13.4] vs 604.3 ms [13.4], P<0.001 for OM-ER 30 mg vs OC-CR 60 mg, respectively); tracking accuracy (Emin percentage over road, lower if impaired; 71.4 [2.4] vs 65.3 [2.4], P=0.007; 69.9 [2.4] vs 59.4 [2.4], P<0.001), and target accuracy (Emin target hits percentage, lower if impaired; 81.0 [3.1] vs 74.5 [3.1], P=0.02; 79.4 [3.1] vs 66.1 [3.1], P<0.001). Several other DA measures showed that OC-CR, especially 60 mg, produced more psychomotor impairment than equianalgesic OM-ER. Compared to OM-ER, OC-CR produced more dizziness (Emax, P<0.001 for OM-ER 15 mg vs OC-CR 30 mg and for OM-ER 30 mg vs OC-CR 60 mg), drowsiness (Emax, P<0.001 for both equianalgesic dose groups), relaxation (Emin, P=0.003 for OM-ER 15 mg vs OC-CR 30 mg; P=0.001 for OM-ER 30 mg vs OC-CR 60 mg), dysphoria (Emax LSD, P<0.001 for both equianalgesic dose groups), and sedation (Emax, PCAG; P<0.001 for both equianalgesic dose groups) and less stimulation (BG, Emin; P=0.01 for OM-ER 15 mg vs OC-CR mg; P<0.001 for OM-ER 30 mg vs OC-CR 60 mg). Several AEs occurred more commonly with OC-CR than OM-ER (e.g., euphoria, nausea, somnolence, vomiting, dizziness).

Limitations: Participants were young, healthy volunteer nondependent recreational drug users, and only single doses were evaluated. The effects of tampering or higher doses were not assessed.

Conclusions: Single oral intact low and high doses of OM-ER produced less cognitive and psychomotor impairment plus less sedation than equianalgesic OC-CR in this exploratory study.

ClinicalTrials.gov registration NCT00955110

Key words: opioid, cognitive effects, psychomotor effects, sedation, dysphoria, oxymorphone, oxycodone, long-acting opioids

Pain Physician 2010; 13:561-573

Opioids are frequently used for postoperative pain (1), cancer pain (2), and chronic noncancer pain that is moderate to severe (3,4). Although effective for pain control, opioids are not without risks. Prominent among these risks are opioid abuse and dependence. Large increases in nonmedical use/abuse of opioids and in misuse-related deaths have been documented over the last decade, a time during which the therapeutic use of opioids has expanded (5).Other potential risks include adverse events (AEs) (e.g., constipation, nausea/vomiting, sedation, delirium) (6) and cognitive and psychomotor effects, especially with larger doses (7,8). Opioid-induced sedation and/or delirium might affect cognitive and psychomotor abilities, potentially leading to increased accidents. Several recent studies found that opioid users were more likely to have severe automobile accidents (9,10). Although these particular studies only looked retrospectively at accidents in opioid users, the cognitive and sedative effects of opioids could be contributing factors to the increased rate of severe or fatal car crashes.

Several studies support acute changes in cognitive abilities with opioid use. One study found that higher doses of opioids, such as oxycodone, subjectively reduced alertness and heightened sedation, making driving more of an effort, although objective driving test performance was not adversely affected (11). However, that study used the lowest available doses of oxycodone (5 and 10 mg), and it is known that higher doses (20 or 30 mg) cause greater sedation and greater psychomotor and cognitive impairment in eye-hand coordination tests (7). A recent German health economics study (12), which was designed to model the cost of injuries from falls and opioid-induced AEs (e.g., dizziness, sedation), showed that over a set time period and using a defined daily dose, oxycodone had larger costs per patient from falls/injuries versus other opioids. The German authors suggest that these data are important because the population is aging and opioids are being prescribed more frequently to treat cancer and noncancer pain in the elderly, a population that may be more likely to experience opioid AEs and already has lower bone density and increased risk of falling (12). Based on the German experience, Hass and colleagues (12) suggest that physicians should consider the potential for cognitive and psychomotor impairment when prescribing an opioid.

Cognitive, psychomotor, and subjective effects can be compared between opioids using validated instruments and methods that quantify these effects (7,13). Long-acting opioid formulations are used to provide sustained, around-the-clock pain control. One of the most recently approved long-acting opioids is oxymorphone extended release (OM-ER) (OPANA ER, Endo Pharmaceuticals, Inc., Chadds Ford, PA), which entered the US market in 2006. OM-ER uses a unique technology that decreases peak-to-trough drug fluctuations (TIMERx®, Penwest Pharmaceuticals Co., Danbury, CT, USA). Anecdotal reports by clinicians and patients suggested that OM-ER is associated with fewer cognitive effects than oxycodone controlled release (OC-CR) (OxyContin, Purdue Pharma L.P., Stamford, CT), but confirmed clinical proof is lacking. This exploratory study compared single, intact, equianalgesic doses of OM-ER and OC-CR for cognitive and psychomotor impairment in healthy volunteer nondependent recreational opioid users. The doses chosen for this study were in the middle range of those used for chronic pain treatment (14-16). Higher doses or multiple sequential doses over several days were not tested. Furthermore, the study was not designed to evaluate the effects of tampering with either formulation.

Methods

Study Design

The study followed the guidelines for Good Clinical Practice published by the International Conference on Harmonisation. Health Canada and institutional review board (IRB Services, Aurora, ON, Canada) approvals were obtained for the study protocol, informed consent form, and other relevant study documents. All participants provided written informed consent before any study-related procedures were performed. The study was conducted from May to September 2009 by Kendle Early Stage (Toronto, ON, Canada) at a single inpatient research unit.

The study was divided into 2 phases in which participants were randomized and received over-encapsulated blinded drugs (both placebo and active comparators); the investigators were also blinded to the treatment allocations. The first phase was a qualification phase to determine which volunteers could tolerate and discriminate 8-mg hydromorphone from placebo using Visual Analog Scales (VAS) and Addiction Research Center Inventory (ARCI) scales. Hydromorphone 8 mg was used to avoid bias in selecting participants showing stronger effects for either of the study drugs. For the participants who could differentiate blinded hydromorphone 8 mg and placebo, the next phase was initiated. Before

entry into the treatment phase, participants were randomized to one of 10 treatment sequences according to two 5 X 5 Williams squares. After randomization, they received a single intact dose of blinded OM-ER (15 and 30 mg), OC-CR (30 and 60 mg), and placebo.

Participants

Healthy adu;t participants were recruited using the research site's participant database and local advertisements. The study enrolled male and female volunteers who were experienced, nondependent, recreational opioid users because they could tolerate the use of opioids at pharmacologic doses (i.e., regularly used for pain control) without needing a naltrexone cover. Inclusion criteria were a body mass index (BMI) between 19.0 and 29.0 kg/m^2; a weight above 50.0 kg; ability to read and speak English; and willingness to conform to all study procedures. Women were either abstinent or used preapproved birth control for one month before the study start to one month after the end of the study. Negative pregnancy tests were verified before each crossover period. Exclusion criteria included a history of alcohol or drug dependence; history of asthma, neurologic disorders, Addison disease, or psychiatric illness; clinically significant disorders on physical examination; using monoamine oxidase inhibitors within 14 days of the study; excessive cigarette (>20 per d) or cigar (>2 per d) smoking or unwillingness to abstain from smoking for 14 hours surrounding the study procedures; or investigational drug use within 30 days of screening. Participants were restricted from using recreational drugs or binge drinking (>5 drinks) during the study, and negative urine drug screen/breath alcohol tests were confirmed prior to each dosing.

Drug Treatments

During the qualification phase of the study, blinded hydromorphone 8 mg and placebo were given on days 1 and 2, and participants remained in the inpatient research unit from day 0 until day 3. During the treatment phase, participants were randomized to a treatment sequence, which included placebo, OM-ER (15 and 30 mg), and OC-CR (30 and 60 mg). The doses of OM-ER and OC-CR were based on the opioid conversion table in the OM-ER prescribing information (17) and were chosen because they were representative of mid-range doses used for chronic pain (14-16). Only a single, blinded, intact, oral dose of drug was tested during each crossover period (7–21-d washout). Testing was not done on higher or multiple doses over consecutive days. No outside food was allowed during treatment and standardized meals were provided at approximately the same time during each treatment period; a light breakfast was consumed 2 to 3 hours predose and a standardized lunch followed the completion of all 4-hour postdose assessments. Participants were on a restricted diet during the study (e.g., no grapefruit juice throughout the study, no caffeine within 24 hours of taking a study drug). Water was prohibited for one hour before to one hour after drug administration. Health products and over-the-counter and prescription medicines were restricted within one week of each treatment period. Drinking alcohol was prohibited within 48 hours before each period.

Pharmacodynamic Assessments During the Treatment Phase

Tests for Sedation and Cognitive/Psychomotor Effects

Standardized tests evaluating the subjective, cognitive, and psychomotor effects of opioids were applied (8,18). The divided attention (DA) test monitored psychomotor performance, attention, and accuracy by using a computer simulation of an airplane flying over a curvy road. During the DA test, the road curves randomly and the participant is presented with a total of 16 targets per trial, which appear quickly and arbitrarily. Using a joystick and a trigger button, the participant tries to keep the plane over the road while responding to the presented targets. Each test is composed of 3 one-minute trials on different road courses. The following DA parameters were evaluated: farthest root mean square (RMS) diagonal distance from the center of the road, percentage of time over road, and mean farthest distance from the center of the road (manual tracking variables); hit latency (reaction time in ms); and number of false alarms and percentage of target hits (accuracy/attention).

Three scales from the ARCI questionnaire (19) were used to measure sedation and mood effects. Sedation and stimulation, respectively, were assessed by the ARCI Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) (scale, 0–15) and the Benzedrine Group (BG, scale (0–13). The PCAG contains items such as "My speech is slurred," "I feel dizzy," and "I am not as active as usual"; the BG scale contains items such as "I feel more clear headed than dreamy," "My movements are faster than normal," and "I have better control over myself than usual." Somatic complaints and dysphoria were measured using

the ARCI Lysergic Acid Diethylamide (LSD) group scale (0–14). Multiple VAS measured alertness/drowsiness (A/D) and agitation/relaxation (0 = very drowsy/relaxed and 100 = very alert/agitated), as well as negative effects (e.g., dizziness [0 = definitely no and 100 = definitely so]). Assessments for the DA test were performed predose and at 1, 2, 3, 4, 6, 8, 12, and 24 hours postdose; ARCI and VAS were assessed at predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose. Pharmacodynamic measures were administered on laptops using validated 21 Code of Federal Regulations Part 11 compliant software (Scheduled Measurement System, Kendle Early Stage, Toronto, ON, Canada).

Pupillometry

Pupil diameters were measured under mesopic lighting using an optical scanner that combined an infrared light and a digital camera (which took approximately 41 digital images over 3 seconds and computed a mean pupil diameter). Miosis was assessed predose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours postdose.

Safety

All participants who received any investigational treatment were monitored for safety. This included measuring vital signs, completion of physical examination by the study doctor, and monitoring AEs. For all participants who completed the study, the final safety visit occurred 3 to 7 days after the last dose of study medication.

Statistical Analysis

Statistical analyses were performed using SAS Version 9.1.3 (SAS Institute, Cary, NC). Sample size calculations indicated that 30 participants would be needed to complete the study with an 80% power to detect a minimal clinically relevant difference between drugs; planned enrollment was for 40 participants to ensure that 30 completed the study. Data from participants with no major protocol violations and who completed all 5 crossover periods were used for the statistical analyses. Significance was set at 0.05; all tests were 2-sided. Missing values were not imputed. The primary comparisons in the study were between equianalgesic doses: OM-ER 15 mg versus OC-CR 30 mg and OM-ER 30 mg versus OC-CR 60 mg. Secondary analyses were performed on different doses of the same active drug (OM-ER 15 mg vs 30 mg; OC-CR 30 mg vs 60 mg) and between active drugs and placebo.

Pharmacodynamic endpoints at each time point were summarized using descriptive statistics (n, mean, SD, median, range) and for the peak minimum (E_{min}) and maximum effect (E_{max}). For summary endpoints (e.g., E_{max}, E_{min}, minimum pupil diameter), a mixed-effects model for crossover studies was used; the fixed effects were treatment, period, treatment sequence, and first-order carryover and the predose measurement was included as the covariate. Participants were nested within treatment sequence as random effect. This analysis of covariance model was used to determine significant differences between the least squares means (SE) between each group.

Results

Participant Disposition and Demographics

The disposition of participants from screening through to the qualification and treatment phases is listed in Fig. 1. In total, 41 participants were randomized to the treatment phase, 40 participants received at least one dose of study medication and were included in the safety population, and 35 (87.5%) completed all 5 crossover periods and were included in the pharmacodynamic analysis. The majority of the enrolled participants were men (80%), with most participants being white (88.6%), followed by Hispanic (5.7%), Asian (2.9%), and other races (2.9%). The mean (SD) age was 32.4 (9.0) in the randomized population and 31.9 (8.2) years in participants who completed all 5 periods (range, 18 to 51 years). Mean (SD) BMI (24.7 [3.3] kg/m^2) was within the normal range.

Cognitive, Psychomotor, and Subjective Effects Testing

The effects observed on all DA measures were more pronounced with OC-CR 60 mg vs OM-ER 30 mg. OC-CR 60 mg produced greater impairment than OM-ER 30 mg for target accuracy (target hits; $P < 0.001$ [Fig. 2]; false alarms; $P = 0.03$) (Table 1), manual tracking (percentage over road; $P < 0.001$) (Fig. 3); RMS diagonal distance, ($P < 0.001$) (Table 1, Fig. 4), furthest distance, $P < 0.001$) (Table 1), and reaction time/hit latency ($P < 0.001$, Table 1, Fig. 5). Four of the 6 DA measures were also significantly more affected by the lower 30 mg dose of OC-CR compared to the 15 mg dose of OM-ER: hit latency ($P = 0.03$, Table 1), target hits ($P = 0.02$, Fig. 2), percentage over road ($P = 0.007$, Fig. 3), and RMS diagonal distance ($P = 0.04$, Table 1).

In comparison to placebo, OC-CR 60 mg was significantly different on all DA variables except false alarms

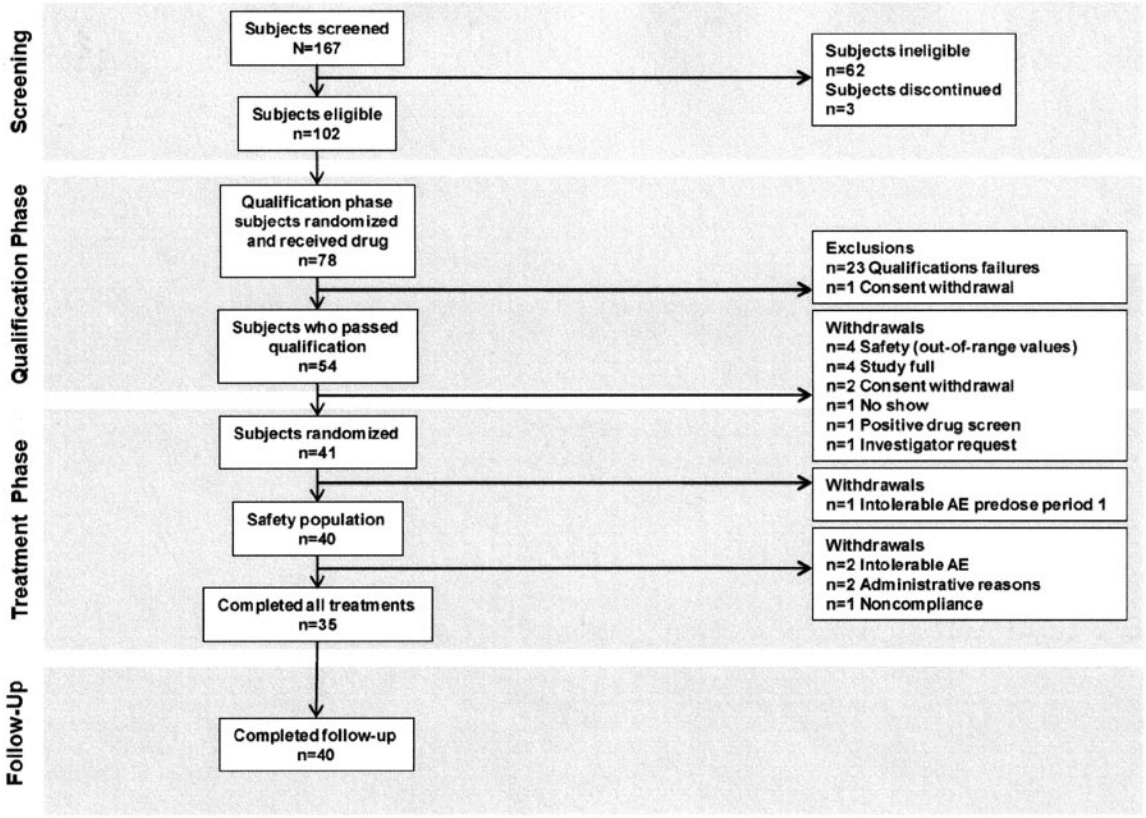

Fig. 1. *CONSORT diagram. AE=adverse event.*

(Figs. 2,3, Table 1), whereas OM-ER (15 mg, 30 mg) and OC-CR 30 mg were not different from placebo for false alarms (Table 1), farthest distance (Table 1) and target hits (Fig. 2). For RMS diagonal distance (Table 1) and percentage over road (Fig. 3), OM-ER doses were not significantly different from placebo. Both doses of OC-CR and OM-ER were significantly different from placebo for hit latency (Table 1).

Subjective effects were significantly more pronounced with OC-CR than with OM-ER for sedation (Table 1, Fig. 6), decreased stimulation (Table 1, Fig. 7), drowsiness (Table 1, Fig. 8), dizziness, relaxation, and dysphoria (Table 1), especially at the high doses (OC-CR 60 mg vs OM-ER 30 mg). At the low doses, OC-CR 30 mg produced more dizziness ($P < 0.001$ vs OM-ER 15 mg), relaxation ($P = 0.003$), dysphoria ($P < 0.001$), stimulation ($P = 0.01$), and sedation than OM-ER 15 mg ($P < 0.001$; Table 2).

Physiologic Effects

OC-CR provided the strongest pupillary response, with both doses producing significantly more miosis than either dose of OM-ER (Table 1). Miosis showed a similar pattern of response over time (albeit longer in duration), to those observed with the DA test and subjective measures for OC-CR, especially at the 60 mg dose.

Safety

The percentage of participants experiencing any AE during the study was higher for OC-CR 30 and 60 mg (87.5% and 97.5%, respectively) than for OM-ER 15 and 30 mg (59.5% and 73.7%). OM-ER was associated with a lower incidence of euphoric mood (OM-ER 15 mg, 24.3% and 30 mg, 52.6% vs OC-CR 30 mg, 67.5% and 60 mg, 92.5%), nausea (5.4% and 5.3% vs 15.0% and 45.0%, respectively), somnolence (21.6% and 26.3%

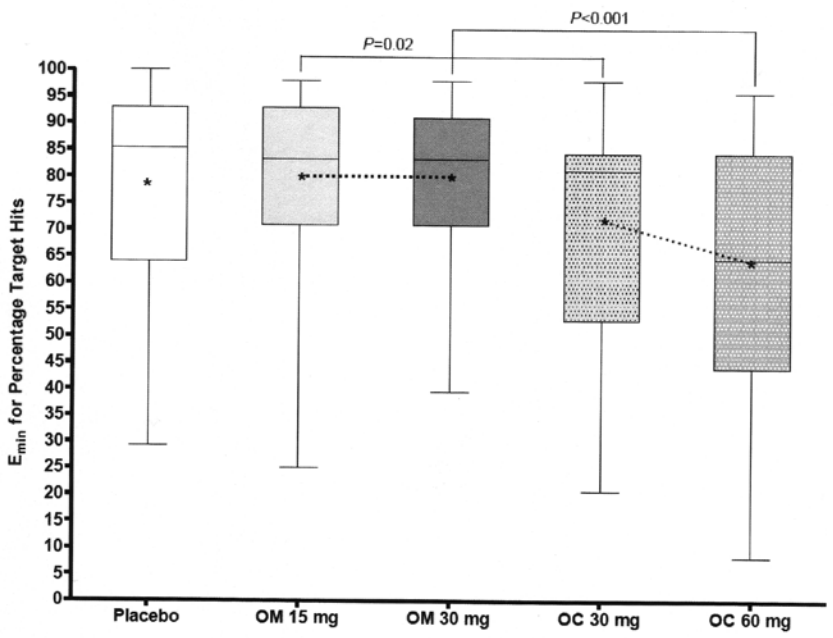

Fig. 2. ***Divided attention test results for percentage target hits.***
Box-plot data presented as mean (*) and 25th (box bottom), 50th (box midline), and 75th (box top) percentiles, and range (whiskers). The LS mean difference between groups was compared using a linear mixed model ANCOVA to generate the *P* values. The LS means may differ from the raw means owing to adjustment for missing observations (unbalanced design) and are appropriately adjusted for the other effects in the ANCOVA model. ANCOVA=analysis of covariance; E_{max}=maximum effect; E_{min}=minimum effect; LS=least squares; OC=oxycodone controlled release; OM=oxymorphone extended release.

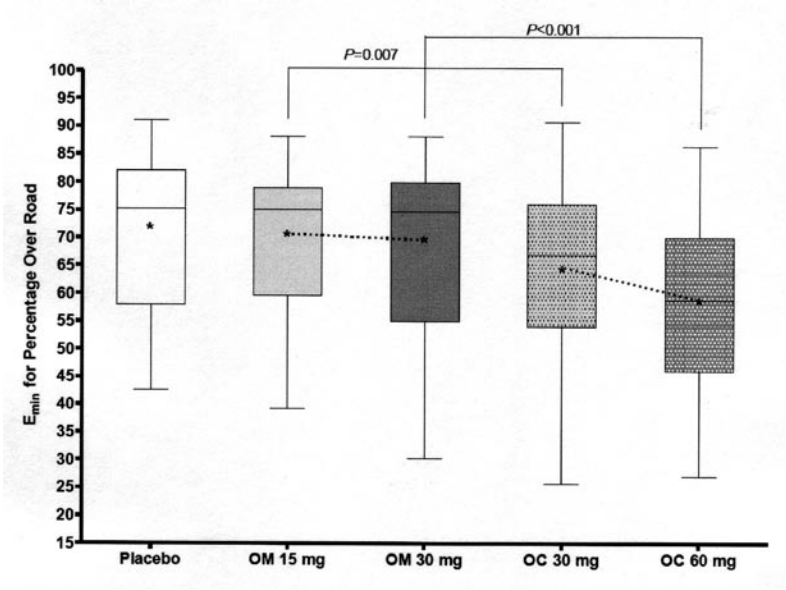

Fig. 3. ***Divided attention test results for percentage target hits, percentage over road.***
Box-plot data presented as mean (*) and 25th (box bottom), 50th (box midline), and 75th (box top) percentiles, and range (whiskers). The LS mean difference between groups was compared using a linear mixed model ANCOVA to generate the *P* values. The LS means may differ from the raw means owing to adjustment for missing observations (unbalanced design) and are appropriately adjusted for the other effects in the ANCOVA model. ANCOVA=analysis of covariance; E_{max}=maximum effect; E_{min}=minimum effect; LS=least squares; OC=oxycodone controlled release; OM=oxymorphone extended release.

Table 1. *Summary of Cognitive, Psychomotor, Subjective, and Physiologic (Pupillary) Effects of Oxymorphone ER and Oxycodone CR*

Testing *P*rocedure, LS Mean (SE)	Low Equianalgesic Doses			High Equianalgesic Doses			*P*lacebo vs Active Treatments *P* Values
	Oxymorphone ER 15 mg	Oxycodone CR 30 mg	*P* Value*	Oxymorphone ER 30 mg	Oxycodone CR 60 mg	*P* Value*	
Divided attention test							
Hit latency, E_{max}	571.2 (13.4)	588.1 (13.4)	0.03	572.4 (13.4)	604.3 (13.4)	<0.001	*P*=0.03 for oxymorphone 15 mg *P*=0.02 for oxymorphone 30 mg *P*<0.001 for oxycodone doses
RMS diagonal distance, E_{max}	39.5 (4.0)	47.8 (4.0)	0.04	42.1 (4.0)	57.3 (4.0)	<0.001	*P*=NS for oxymorphone doses *P*=0.04 for oxycodone 30 mg *P*<0.001 for oxycodone 60 mg
False alarms, E_{max}	5.3 (0.7)	6.0 (0.7)	NS	5.1 (0.7)	6.2 (0.7)	0.03	*P*=NS for all groups
Farthest distance, E_{max}	176.0 (11.3)	191.0 (11.4)	NS	185.4 (11.3)	227.6 (11.4)	<0.001	*P*=NS for oxymorphone 15 mg, oxymorphone 30 mg, oxycodone 30 mg *P*<0.001 for oxycodone 60 mg
ARCI scales							
Sedation (ARCI-*P*CAG), E_{max}	6.1 (0.4)	8.2 (0.4)	<0.001	7.4 (0.4)	9.4 (0.4)	<0.001	*P*=NS for oxymorphone 15 mg *P*<0.001 for oxymorphone 30 mg and both oxycodone doses
Stimulation (ARCI-BG), E_{min} (decreased stimulation)	3.6 (0.2)	2.9 (0.2)	0.01	3.4 (0.2)	2.2 (0.2)	<0.001	*P*=0.04 for oxymorphone 15 mg *P*=0.004 for oxymorphone 30 mg *P*<0.001 for oxycodone doses
Dysphoria (ARCI-LSD), E_{max}	4.4 (0.3)	5.5 (0.3)	<0.001	4.7 (0.3)	6.7 (0.3)	<0.001	*P*=NS for oxymorphone 15 mg *P*=0.008 for oxymorphone 30 mg *P*<0.001 for oxycodone doses
VAS							
Alertness/ Drowsiness, E_{min}†	35.8 (2.8)	23.9 (2.8)	<0.001	28.0 (2.8)	14.3 (2.8)	<0.001	*P*=NS for oxymorphone 15 mg *P*<0.001 for oxymorphone 30 mg and both oxycodone doses
Dizziness, E_{max}	15.4 (5.1)	35.8 (5.2)	<0.001	20.5 (5.2)	52.7 (5.2)	<0.001	*P*=NS for oxymorphone doses *P*<0.001 for oxycodone doses
Agitation/Relax-ation, E_{min}†	28.9 (2.8)	20.3 (2.8)	0.003	23.9 (2.8)	14.4 (2.8)	0.001	*P*=0.005 for oxymorphone 15 mg *P*<0.001 for oxymorphone 30 mg and oxycodone doses
*P*hysiologic measure							
*P*upillometry, PC_{min}	4.4 (0.1)	3.3 (0.1)	<0.001	3.7 (0.1)	2.8 (0.1)	<0.001	*P*<0.001 for all groups

ARCI=Addiction Research Center Inventory; ARCI-BG=ARCI Benzedrine Group; ARCI-LSD=ARCI Lysergic Acid Diethylamide; ARCI-PCAG=ARCI Pentobarbital-Chlorpromazine-Alcohol Group; CR=controlled release; ER=extended release; Emax=maximum effect; Emin=minimum effect; LS=least squares; NS=not significant; PCmin=minimum pupil diameter.
**P* value for comparison between equianalgesic doses (oxymorphone 15 mg vs oxycodone 30 mg; oxymorphone 30 mg vs oxycodone 60 mg).
†Bipolar VAS with 50 being the neutral point. Below 50 indicates increasing drowsiness/relaxation.

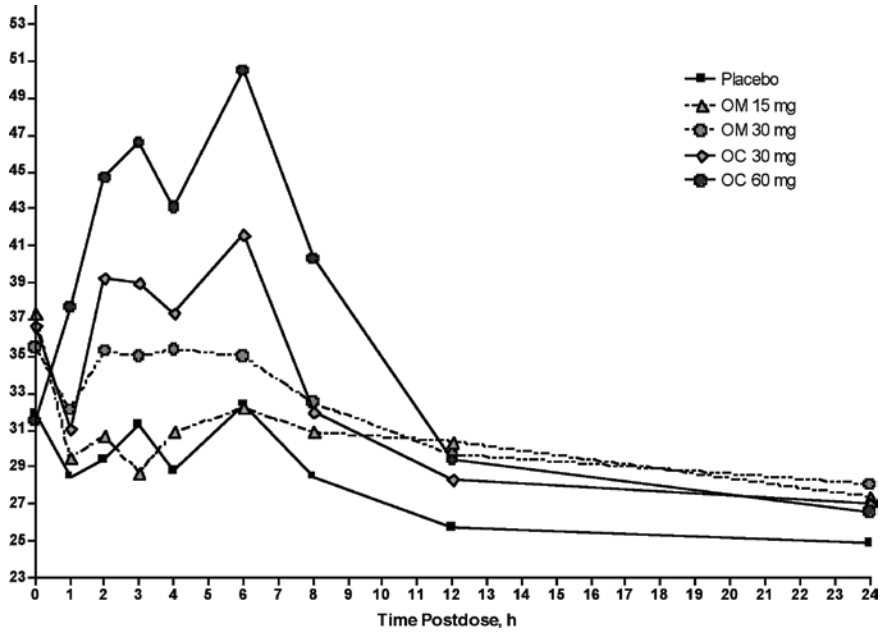

Fig. 4. ***Divided attention test results for percentage target hits time course of root mean square diagonal distance.***
Box-plot data presented as mean (*) and 25th (box bottom), 50th (box midline), and 75th (box top) percentiles, and range (whiskers). The LS mean difference between groups was compared using a linear mixed model ANCOVA to generate the *P* values. The LS means may differ from the raw means owing to adjustment for missing observations (unbalanced design) and are appropriately adjusted for the other effects in the ANCOVA model. ANCOVA=analysis of covariance; E_{max}=maximum effect; E_{min}=minimum effect; LS=least squares; OC=oxycodone controlled release; OM=oxymorphone extended release.

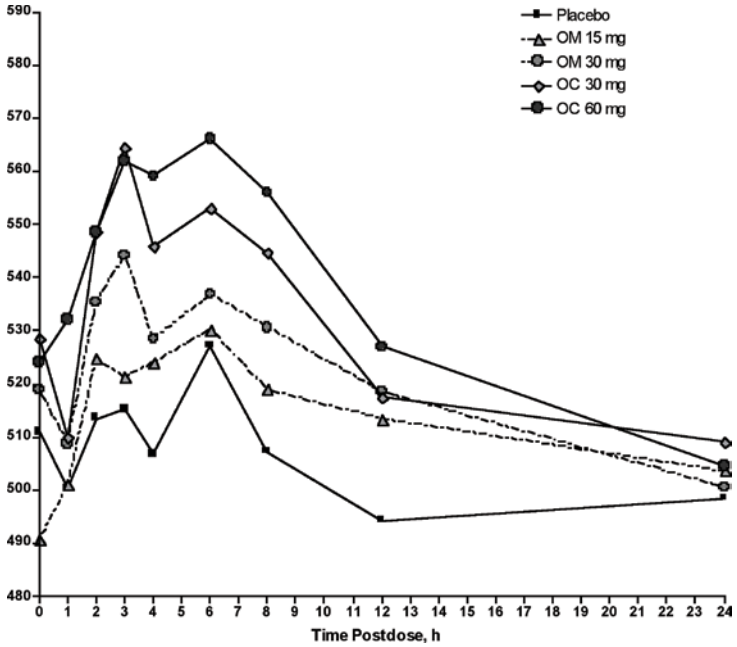

Fig. 5. ***Divided attention test results for percentage target hits time course of hit latency.***
Box-plot data presented as mean (*) and 25th (box bottom), 50th (box midline), and 75th (box top) percentiles, and range (whiskers). The LS mean difference between groups was compared using a linear mixed model ANCOVA to generate the *P* values. The LS means may differ from the raw means owing to adjustment for missing observations (unbalanced design) and are appropriately adjusted for the other effects in the ANCOVA model. ANCOVA=analysis of covariance; E_{max}=maximum effect; E_{min}=minimum effect; LS=least squares; OC=oxycodone controlled release; OM=oxymorphone extended release.

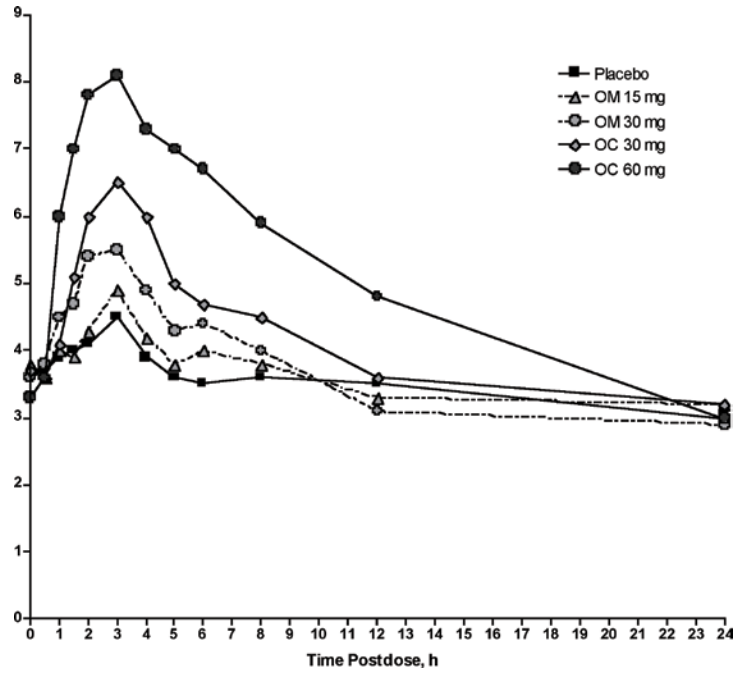

Fig. 6. *Time course results for sedation (ARCI-PCAG) (A).*
*Bipolar VAS; values below 50 indicate increasing drowsiness with lower scores. A/D-VAS=Alertness/Drowsiness Visual Analog Scale; ARCI=Addiction Research Center Inventory; ARCI-BG=ARCI Benzedrine Group; ARCI-PCAG=ARCI Pentobarbital-Chlorpromazine-Alcohol Group; Emax=maximum effect; Emin=minimum effect; OC=oxycodone controlled release; OM=oxymorphone extended release.

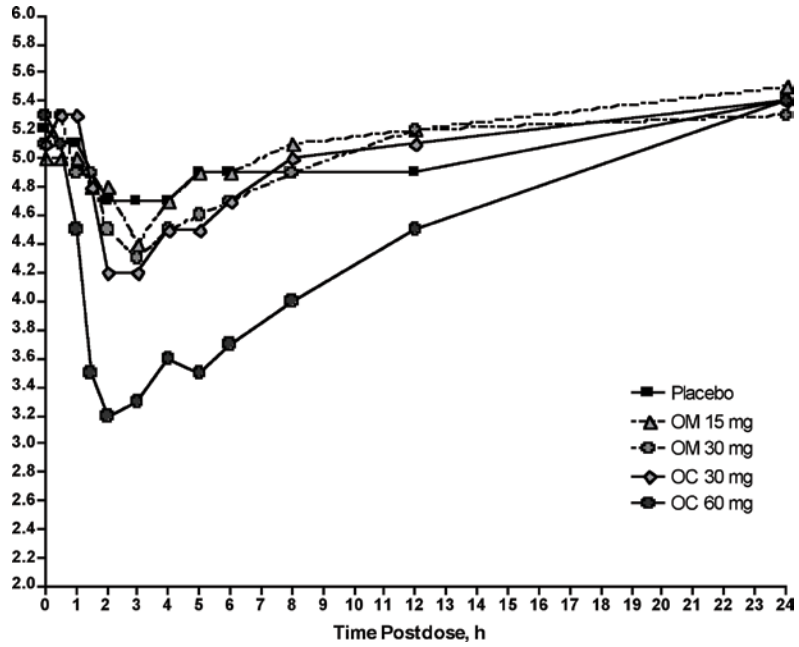

Fig. 7. *Time course results for stimulation (ARCI- BG).*
*Bipolar VAS; values below 50 indicate increasing drowsiness with lower scores. A/D-VAS=Alertness/Drowsiness Visual Analog Scale; ARCI=Addiction Research Center Inventory; ARCI-BG=ARCI Benzedrine Group; ARCI-PCAG=ARCI Pentobarbital-Chlorpromazine-Alcohol Group; Emax=maximum effect; Emin=minimum effect; OC=oxycodone controlled release; OM=oxymorphone extended release.

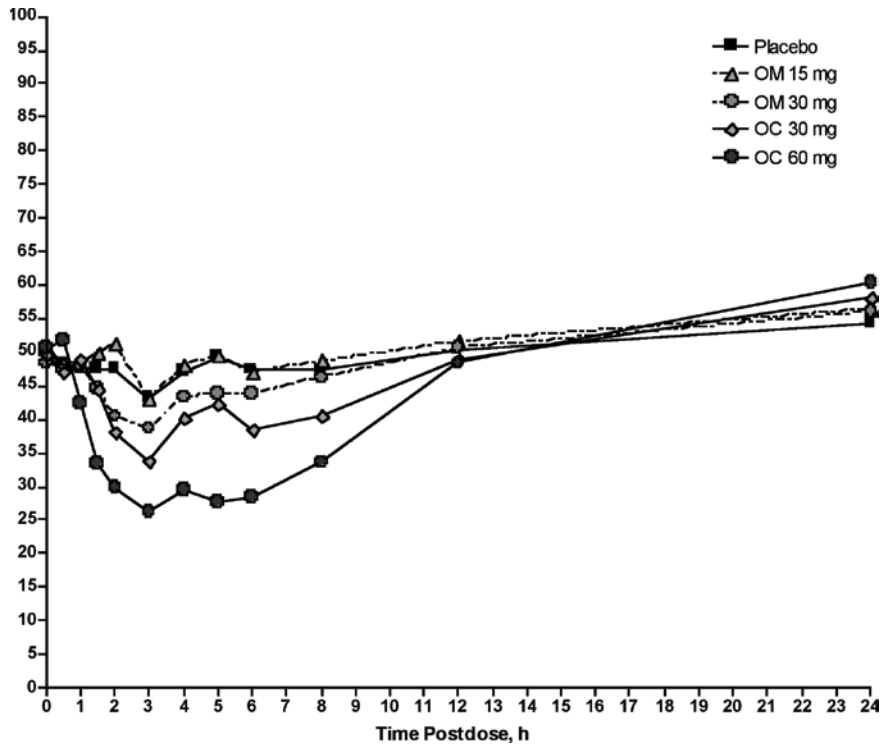

Fig. 8. *Time course results for alertness/drowsiness (A/D-VAS)* .*
*Bipolar VAS; values below 50 indicate increasing drowsiness with lower scores. A/D-VAS=Alertness/Drowsiness Visual Analog Scale; ARCI=Addiction Research Center Inventory; ARCI-BG=ARCI Benzedrine Group; ARCI-PCAG=ARCI Pentobarbital-Chlorpromazine-Alcohol Group; Emax=maximum effect; Emin=minimum effect; OC=oxycodone controlled release; OM=oxymorphone extended release.

vs 30.0% and 32.5%), vomiting (0% and 0% vs 2.5% and 22.5%), dizziness (10.8% and 5.3% vs 17.5% and 20.0%), pruritus (0% and 2.6% vs 17.5% and 20.0%), nasal discomfort (2.7% and 0% vs 10.0% and 20.0%), and fatigue (0% and 2.6% vs 12.5% and 10.0%). No serious AEs occurred.

Discussion

This exploratory study showed poorer cognitive and psychomotor performance and increased sedation, dizziness, and drowsiness with single intact oral doses of OC-CR, especially at the 60-mg dose, in comparison with single intact equianalgesic oral doses of OM-ER. Drowsiness (A/D-VAS), sedation (ARCI-PCAG), decreases in attention/stimulation (ARCI-BG, Emin), dysphoria (ARCI-LSD), and dizziness paralleled the intensity of cognitive and psychomotor impairment shown in the DA test. Thus, these subjective effects may have been related to the poor performance of participants receiving OC-CR. A Dutch study provides supportive data, albeit with lower doses of oxycodone (5 and 10 mg) than used in the current study. In the Dutch study (11), during an actual on-the-road driving test, participants reported experiencing significantly increased mental effort and reduced alertness in a dose-dependent manner with oxycodone. These findings are consistent with prescriber and patient anecdotal reports of greater sedation and cognitive impairment with equianalgesic doses of OC-CR versus OM-ER. However, data from the current study cannot be extrapolated to higher doses of OM-ER or OC-CR, which would likely produce more cognitive and psychomotor effects plus greater sedation. In contrast, it is interesting to note that a randomized controlled trial by Raja and colleagues (20) determined that morphine CR (mean dose = 91 mg) and methadone (mean dose = 15 mg) had no significant effect on cognitive functioning, whereas the tricyclic antidepressants nortriptyline (mean dose = 89 mg) and desipramine (mean dose = 63 mg) significantly worsened performance on the nondominant-hand grooved pegboard

and symbol substitution tests. As Raja et al (20) was a long-term dosing study in which doses were titrated up, the development of tolerance may have diminished cognitive effects once steady-state was achieved. However, these findings may warrant using additional cognitive/psychomotor measures, such as the pegboard and symbol substitution tests, to evaluate additional opioid drugs (eg, OM-ER; OC-CR) at various doses, although these tests may not be as sensitive as the DA test.

The opioid conversion table in the OM-ER prescribing information is based on the literature (17), and is consistent with recent clinical trials for OM-ER, in which the primary and supportive secondary endpoints assessed analgesia. For pain relief, a 2:1 conversion of OC-CR to OM-ER produces similar analgesia and tolerability (21,22). In the current study in nondependent recreational drug users, nonanalgesic measures such as miosis, sedation, and cognitive impairment were worse with OC-CR versus OM-ER when administered using a 2:1 ratio (i.e., equianalgesic doses). The difference in potency observed between analgesic trials of OM-ER and OC-CR and studies of subjective or psychomotor effects has been reported for other opioid comparisons; other researchers have shown that morphine produces less sedation and psychomotor impairment than equianalgesic doses of hydromorphone (23) and oxycodone (7), and speculate that dose equivalency for analgesia may be different from dose equivalency for subjective and cognitive/motor effects. Another study by Zacny and Gutierrez (8) found that oxycodone/acetaminophen produced more profound and persistent effects on psychomotor performance than a supposedly equianalgesic dose of hydrocodone/acetaminophen. Finally, Walsh and colleagues (24) reported that hydromorphone was only modestly more potent than hydrocodone and oxycodone with regard to subjective and psychomotor effects, noting that relative potency estimates may differ for subjective effects versus analgesic effects. These studies support the data from the current trial, suggesting that sedative and cognitive effects may differ between opioids even when administered according to opioid conversion tables.

One strength of this study was that the doses of OC-CR and OM-ER administered were in the mid-range of the doses used to maintain adequate analgesia in patients with both noncancer (22) and cancer pain (21). Nonetheless, there are important limitations of the current study. Foremost, the study only assessed single doses of intact oral tablets. Multiple sequential doses may be associated with different effects due to higher steady-state concentrations and the impact of tolerance. The impact of tampering with the products, other routes of administration, multiple sequential doses over consecutive days, or the use of larger single doses on the cognitive and sedative effects of both OM-ER and OC-CR cannot necessarily be extrapolated from these results. Second, the population comprised relatively young healthy volunteers (range, 18–51 years) without pain or comorbidities that might affect drug clearance. In comparison, pain patients often come from an older demographic and often have multiple comorbidities. The study also minimized the potential for drug interactions, so these data should not be generalized to clinical practice in which many patients, especially the elderly, receive many different medications, including central nervous system (CNS) medications, which could affect both cognitive abilities and sedation.

The potential implications of this study are manifold. In a parallel analysis from the current study, participants receiving OC-CR (15 and 30 mg) reported greater "drug liking" than with OM-ER (30 and 60 mg) (25). The latter observation is significant in view of previous research showing a substantial increase in OC-CR abuse when monitored over a 5-year period (2000–2004), with abusers using significantly higher doses per day in comparison with other oxycodone products and other opioids (26). Because of its newness to the market, necessary surveillance of OM abuse has not yet occurred, and the potential impact of the observed differences in subjective and cognitive effects on drug abuse rates is as yet undetermined. In the current study, OC-CR produced greater sedative effects and cognitive impairment than OM-ER when using mid-range doses for pain therapy. This may be associated with a higher incidence of accidents or falls; for example, research suggests that fatal car accidents are more common in opioid users (10), and decreased cognitive abilities and increased sedation could be among the reasons for the high accident rate. Further, it is important to note that although this study assessed young, healthy subjects, psychomotor impairment associated with opioid use is an ongoing concern in elderly patients at risk for fall-related injury (27,28). Finally, a 2009 report from Germany modeling managed care costs found that oxycodone has one of the highest costs per patient because of falls and fractures (12). In the elderly, falls and fractures substantially increase health care costs, and the authors recommended that physicians should try to avoid prescribing medications that could precipitate a fall.

Conclusions

In this exploratory study, single intact oral doses of 30 and 60 mg OC-CR produced significantly greater cognitive and psychomotor impairment plus more sedation, drowsiness, dizziness, and dysphoria than single intact equianalgesic oral doses of 15 and 30-mg OM-ER.

Acknowledgments

The authors would like to express their gratitude to Halima Thompson and Elizabeth Szymanski for managing and coordinating the study. Furthermore, the authors would like to acknowledge Kristine W. Schuler, MS, and Robert Gatley, MD, of Complete Healthcare Communications, Inc. (Chadds Ford, PA, USA), who provided medical writing and editorial support, which was funded by Endo Pharmaceuticals Inc. The authors were responsible for study design; management of the study; collection of data; statistical analyses; interpretation of the data; and the preparation, review, and final approval of the manuscript before submission. All coauthors contributed scientifically to the manuscript, but the first author exercised editorial control with final responsibility for content decisions and conclusions.

References

1. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2004; 100:1573-1581.
2. Chang VT, Hwang SS, Kasimis B. Longitudinal documentation of cancer pain management outcomes: A pilot study at a VA medical center. *J Pain Symptom Manage* 2002; 24:494-505.
3. Braden JB, Fan MY, Edlund MJ, Martin BC, DeVries A, Sullivan MD. Trends in use of opioids by noncancer pain type 2000-2005 among Arkansas Medicaid and HealthCore enrollees: Results from the TROUP study. *J Pain* 2008; 9:1026-1035.
4. Chou R, Fanciullo GJ, Fine PG, Adler JA, Ballantyne JC, Davies P, Donovan MI, Fishbain DA, Foley KM, Fudin J, Gilson AM, Kelter A, Mauskop A, O'Connor PG, Passik SD, Pasternak GW, Portenoy RK, Rich BA, Roberts RG, Todd KH, Miaskowski C. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. *J Pain* 2009; 10:113-130.
5. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008; 11: S63-S88.
6. McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, Lau J, Carr D. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain* 2003; 4:231-256.
7. Zacny JP, Gutierrez S. Characterizing the subjective, psychomotor, and physiological effects of oral oxycodone in non-drug-abusing volunteers. *Psychopharmacology (Berl)* 2003; 170:242-254.
8. Zacny JP, Gutierrez S. Subjective, psychomotor, and physiological effects profile of hydrocodone/acetaminophen and oxycodone/acetaminophen combination products. *Pain Med* 2008; 9:433-443.
9. Majdzadeh R, Feiz-Zadeh A, Rajabpour Z, Motevalian A, Hosseini M, Abdollahi M, Ghadirian P. Opium consumption and the risk of traffic injuries in regular users: A case-crossover study in an emergency department. *Traffic Inj Prev* 2009; 10:325-329.
10. Dubois S, Bedard M, Weaver B. The association between opioid analgesics and unsafe driving actions preceding fatal crashes. *Accid Anal Prev* 2010; 42:30-37.
11. Verster JC, Veldhuijzen DS, Volkerts ER. Effects of an opioid (oxycodone/paracetamol) and an NSAID (bromfenac) on driving ability, memory functioning, psychomotor performance, pupil size, and mood. *Clin J Pain* 2006; 22:499-504.
12. Hass B, Lungershausen J, Hertel N, Poulsen Nautrup B, Kotowa W, Liedgens H. Cost-effectiveness of strong opioids focussing on the long-term effects of opioid-related fractures: A model approach. *Eur J Health Econ* 2009; 10:309-321.
13. McColl S, Sellers EM. Research design strategies to evaluate the impact of formulations on abuse liability. *Drug Alcohol Depend* 2006; 83:S52-S62.
14. Katz N, Rauck R, Ahdieh H, Ma T, Gerritsen van der Hoop R, Kerwin R, Podolsky G. 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.
15. 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.
16. Rauck RL, Bookbinder SA, Bunker TR, Alftine CD, Ghalie R, Negro-Vilar A, de Jong E, Gershon S. The ACTION study: A randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin) for the treatment of chronic, moderate to severe low back pain. *J Opioid Manag* 2006; 2:155-166.
17. OPANA® ER (oxymorphone hydrochloride extended-release tablets). Full Prescribing Information, Chadds Ford, PA, Endo Pharmaceuticals Inc.; 2008.
18. Zacny JP, Lichtor SA. Within-subject comparison of the psychopharmacological profiles of oral oxycodone and oral morphine in non-drug-abusing volunteers. *Psychopharmacology (Berl)* 2008; 196:105-116.
19. Haertzen CA. Development of scales based on patterns of drug effects, using the addiction Research Center Inventory (ARCI). *Psychol Rep* 1966; 18:163-194.

20. Raja SN, Haythornthwaite JA, Pappagallo M, Clark MR, Travison TG, Sabeen S, Royall RM, Max MB. Opioids versus antidepressants in postherpetic neuralgia: A randomized, placebo-controlled trial. *Neurology* 2002; 59:1015-1021.
21. 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.
22. 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.
23. Hill JL, Zacny JP. Comparing the subjective, psychomotor, and physiological effects of intravenous hydromorphone and morphine in healthy volunteers. *Psychopharmacology (Berl)* 2000; 152:31-39.
24. Walsh SL, Nuzzo PA, Lofwall MR, Holtman JR, Jr. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. *Drug Alcohol Depend* 2008; 98:191-202.
25. Sellers E, Schoedel KA, McMorn S, Zerbe K, Chakraborty B, Potts SL. Oral intact extended-release oxymorphone is associated with less liking and lower positive subjective effects than equianalgesic doses of oral intact controlled-release oxycodone in healthy nondependent recreational opioid users. *J Pain* 2010; 11:S21.
26. Sproule B, Brands B, Li S, Catz-Biro L. Changing patterns in opioid addiction: Characterizing users of oxycodone and other opioids. *Can Fam Physician* 2009; 55:68-69, 69 e61-65.
27. Saunders KW, Dunn KM, Merrill JO, Sullivan M, Weisner C, Braden JB, Psaty BM, Von Korff M. Relationship of opioid use and dosage levels to fractures in older chronic pain patients. *J Gen Intern Med* 2010; 25:310-315.
28. Hanlon JT, Boudreau RM, Roumani YF, Newman AB, Ruby CM, Wright RM, Hilmer SN, Shorr RI, Bauer DC, Simonsick EM, Studenski SA. Number and dosage of central nervous system medications on recurrent falls in community elders: The Health, Aging and Body Composition study. *J Gerontol A Biol Sci Med Sci* 2009; 64:492-498.