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Comparative Cognitive and Subjective Side Effects of Immediate Release Oxycodone in Healthy Middle Age and Older Adults

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Abstract

This study measured the objective and subjective neurocognitive effects of a single 10mg dose of immediate-release oxycodone in healthy, older (>65 years) and middle age (35 – 55 years) adults who were not suffering from chronic or significant daily pain. Seventy-one participants completed two separate study days and were blind to medication condition (placebo, 10 mg oxycodone). Plasma oxycodone concentration peaked between 60 and 90 min post dose ($p < 0.01$) and pupil size, an indication of physiological effects of the medication peaked at approximately 90 to 120 min post dose ($p < 0.01$). Significant declines in simple and sustained attention, working memory and verbal memory were observed at one hour post dose compared to baseline for both age groups with a trend toward return to baseline by five hours post dose. For almost all cognitive measures there were no medication by age interaction effects, which indicates that the two age groups exhibited a similar responses to the medication challenge. This study suggests that for healthy older adults who are not suffering from chronic pain, neurocognitive and pharmacodynamic changes in response to a 10 mg dose of immediate release oxycodone are similar to those observed for middle age adults.

Perspective—Study findings indicate that the metabolism, neurocognitive effects, and physical side effects of oral oxycodone are similar for healthy middle-age and older adults. Therefore, clinicians should not avoid prescribing oral opioids to older adults based on the belief that older adults are at higher risk for side effects than younger adults.

Keywords

opioid analgesic; oxycodone; older adults; cognition; side effects; pharmacokinetics; pharmacodynamics

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Introduction

Persistent musculoskeletal pain is a common problem in older adults, and is often associated with significant physical and psychosocial disability.^{2, 14, 19, 64} Estimates of the prevalence of persistent pain problems among community-dwelling older adults persons have ranged from 30–80%.^{9, 14, 27, 30, 50, 72} Opioids are becoming more accepted for the management of persistent pain that impairs function and quality of life.^{2, 3} Although the analgesic efficacy of opioids is well documented, many factors hinder their use. Actual or fear of side effects is one prominent reason that makes clinicians reluctant to prescribe, and patients reluctant to take opioids.^{9, 25, 46, 73}

Understanding the incidence, severity, and patterns of side effects will assist patients, providers, and caregivers in making decisions on the use of opioids. Neurocognitive side effects are a particular concern because even a minor decrement in functioning can have catastrophic consequences for frail older adults, including accidents, falls, impaired judgment, delirium and a loss of independence.^{58, 84} Thus, the American Geriatrics Society recommends that patients on opioid therapy be regularly monitored for cognitive effects.² Unfortunately, the empirical literature offers little guidance for clinicians and patients.

Several comprehensive reviews have examined the empirical literature of neurocognitive effects of opioids.^{24, 45, 86} Oral opioids (morphine 10–40 mg; codeine 60–120 mg) appear to have minimal effects on the neurocognitive function of young volunteers with chronic pain (21–35 years).^{32, 54, 79} Studies have also examined cognitive functioning in patients with persistent cancer pain. The evidence suggests measurable cognitive impairments during stable doses of opioids, but that pain and functional status may influence cognitive performance more than opioids.⁶⁶ In addition, recent studies have indicated that chemotherapeutic agents may also impact cognition, thus making it difficult to ascertain the relative contribution amongst many medications.^{43, 53} There have been very few studies examining cognitive effects of opioids in persistent nonmalignant pain patients, and even fewer studies in older adults. The goal of the present study was to examine the neurocognitive effects of a commonly used oral opioid—oxycodone in a sample of healthy older adults. We elected to conduct the study in healthy, and relatively pain free older adults to allow an unambiguous assessment of the neurocognitive effects of an oral opioid without the complications of pain and other disease variables. We hypothesized that the older adults would demonstrate greater decrements in cognition. We further hypothesized that increased severity of opioid side effects in older adults compared to middle age subjects may be associated with age-related variation in oxycodone pharmacokinetics. Accordingly, pharmacokinetics of oxycodone and its metabolites were characterized in the two age groups. A portion of these results were presented at the American Pain Society meeting, 2007, in Washington, D.C., USA.¹⁵

Methods

The study and all procedures were approved by the University of Washington Human Subjects Review Committee prior to the start of any recruitment and enrollment activities.

Subjects

Participants were community dwelling, healthy older (65 + years) and middle age (35–55 years) adults. Participants were recruited through print advertisement in the newspaper and posting flyers at senior centers, libraries, stores and medical facilities.

Inclusion criteria

≥ 65 years of age OR age 35–55; no recent or current pain of moderate or severe intensity, as defined by a score of <3 on a 0 to 10 scale, where 0 indicates “no pain” and 10 indicates “pain as bad as could be”; also, no pain-related disability, defined as a Grade 0 on the Graded Chronic Pain Scale.^{77, 78}

Exclusion criteria

Major co-morbidity that could significantly alter cognition, medical stability, or opioid metabolism, including current unstable angina or congestive heart failure, cerebral vascular accident or recurrent transient ischemic attacks (TIA) in the prior 6 months, active cancer requiring current treatment, severe liver disease, or possible or probable dementia or mild cognitive impairment; major active psychiatric illness, including a diagnosis of schizophrenia, schizoaffective disorder, bi-polar affective disorder, major depressive disorder, somatization disorder, persistent PTSD or generalized anxiety disorder or other anxiety disorder requiring regular medication; current substance abuse including alcohol (history or >2 drinks/day), and/or history of alcohol or recreational drug use in the past five years; new or increased dose (within last 6 months) of CNS-active medications that may alter neurocognitive and/or psychomotor function; MAO Inhibitors, neuroleptics, antidepressants anticonvulsants; new or increased dose (within prior 6 months) of medications that may alter oxycodone metabolism, namely fluoxetine, paroxetine, antifungals, macrolide antibiotics, steroids, rifampin; known hypersensitivity to oxycodone and other opioids, or use of any opioid medication in the last thirty days; cognitive impairment as defined by a score of 85 or less on the 3MSE; pregnancy; currently working in a hospital or other location where opioid or other narcotics are readily available, cold pressor test tolerance of 180 seconds or greater; and current smoking habit. An outline of recruitment procedures is presented in Figure 1.

Procedures

Participants were first given a general phone screening to determine basic eligibility. Phone screening questions included questions about eyesight, health exclusions (active cancer or mental illness, alcohol consumption, opioid sensitivity or allergies, medications), current pain assessment and age. If participants passed the phone screening, they were asked to come to the University of Washington General Clinical Research Center (GCRC) for an in person screening visit.

Visit 1 (Screen)—Participants underwent informed consent process followed by a physical exam and medical history and laboratory assessment from the study physician (JA). Pre-baseline visit began with a formal, written consenting process. A complete cognitive protocol, side effect measures and the cold pressor-test (described below) were administered. The purpose of a pre-baseline administration of the cognitive measures is to help reduce practice effects. Participants who met study criteria were asked to return to the GCRC for two more visits, approximately two weeks apart.

Visits 2-3—The study outline for visits two and three can be found in Table 1. In general, visits two and three were identical with the exception that subjects were randomized to receive either placebo or 10 mg oxycodone (Roxicodone™, Roxane Laboratories, Inc.) on the first visit and received the alternate on the second visit. The University of Washington Medical Center Investigative Drug Service prepared the medication and randomized the order and both subjects and experimenters were blind to the assignment. Subjects were asked to refrain from using the following medications at least 48 hours prior to each study day: herbal medications, sedative-hypnotics, antihistamines, and benzodiazepines. Participants arrived at the GCRC in the early morning. An intravenous (IV) line was placed in the arm of the non-dominant arm to

allow participants to use their dominant hand for cognitive testing. Assessment of cognitive function, opioid side effects, and response to experimentally induced pain occurred at baseline just prior to study medication administration, and again at 60 minutes (around the time of peak plasma oxycodone concentration) and at 300 minutes after study medication administration. Blood sampling and pupillometry accompanied each of these assessments as well as in-between times to afford time profiles over the 8-hour period. Details of assessment are as follows.

Assessments

Eligibility and Demographic Measures

Graded Chronic Pain Scale (GCPS). Pain at the screening visit was evaluated using the GCPS⁷⁸ which consists of characteristic pain intensity and pain disability subscales. To assess pain intensity, respondents rate the intensity of their current, worst, and average pain over the past week using a 0 to 10 scale where 0 is “no pain” and 10 is “pain as bad as could be.” The mean of these ratings is the *characteristic pain intensity* score. Characteristic pain intensity has shown adequate to good internal consistency in previous research (alpha coefficients 0.77–0.86)²⁰. Such composite pain ratings have been shown to be more reliable than single pain ratings, and are sensitive to change over the course of pain treatment³⁷ including use with older adults. 21, 22, 57, 68, 77 During study days, subjects completed the “current pain” item from the GCPS.

Modified Mini-Mental Status Examination (3MSE). The 3MSE is a modified version of the commonly used mental status examination. The 3MSE is a brief comprehensive screening test useful in screening out pre-existing cognitive difficulties and dementia in older adults. The 3MSE takes approximately 10 minutes to complete and includes measures of verbal memory, orientation and language.³⁸ The test has been shown to be sensitive to differentiating healthy older adults from those with dementia in community dwelling older adults.^{26, 38, 69}

Neurocognitive Tests

For all neurocognitive tests, participants were administered equivalent, alternate forms on each study visit and within each visit, except for screening measures which were administered only once and computerized tests for which the stimuli are always randomly presented. Version order was randomized among participants. Neurocognitive testing was administered by two research assistants trained in standard administration techniques by a Neuropsychologist (MMC). Research assistants were observed periodically throughout the study to ensure uniformity and consistency of administration.

Simple and Choice Reaction Time—Participants were administered simple reaction time (SRT), and choice reaction time (CRT) tasks on a Dell laptop computer with a 10 inch screen using Eprime® software (<http://www.pstnet.com/products/e-prime/>) and a serial response box with five buttons. For the simple reaction time task the word YES appeared on the screen with random and variable inter-trial delays (1 – 5 seconds) and participants were directed to press the ‘yes’ button as quickly as possible when they saw the YES appear on the screen. For the choice reaction time task, the words YES and NO appeared randomly on the screen and variable inter-trial delays (1 – 5 seconds) and participants were directed to press the ‘yes’ button as quickly as possible when they saw the YES appear on the screen and to press the ‘no’ button when the word NO appeared on the screen. An average for each inter-trial stimulus was calculated as well as an overall average.

Symbol Digit Modalities Test (SDMT)—The SDMT is a test of visual attention and concentration. Subjects are shown corresponding numbers and figures and they must complete a sheet with the appropriate corresponding symbol as quickly as possible. This test has been shown to be sensitive to changes in attention secondary to plasma opioid level manipulations

as well as in differentiating healthy controls from head injured patients^{61, 79}. The SDMT is resistant to practice effects^{34, 51} and demonstrates good test-retest reliability and comparability of alternate forms.⁷⁴

Alphabet and Number Sequencing—Participants were administered a task based on the Wechsler Memory Scale-III Letter Number Sequencing subtest.⁸³ Participants hear increasingly longer strings of numbers and letters and they must repeat the numbers in order followed by letters in alphabetical order. Total correct for all trials (one point each) is recorded. The task is a measure of working memory and sequencing. The test is valid in discriminating disorders with working memory deficits and has good test-retest reliability.⁸³ It is also sensitive to changes from medication³⁵ and has been shown to help discriminate chronic pain patients with structural brain abnormalities.¹³

Word List Test—Participants were administered a verbal list learning task based on the Rey Auditory Verbal Learning Test (RAVLT) and the Hopkins Verbal Learning Test (HVLT). Subjects were presented with a 15-item word list presented orally on three consecutive trials. The number of words recalled was recorded after each presentation of the list and again after a 20 minute delay. A yes/no recognition list immediately follows the delayed recall. An alternate form (new list) was used at each time point (baseline, 1 hour, 5 hours) and additional long-term recall for the baseline list was obtained at 1 and 5 hours. HVLT and RAVLT tests have demonstrated utility in detecting memory impairments in older adults and has been shown to be reliable in test re-test studies.^{1, 4, 5, 7, 10, 28, 49, 60, 63, 65, 75}

Sustained Attention Test—Subjects were given a test of selective attention and mental concentration that was based on the D2 Attention test and modified for equal, alternate forms.¹¹ The subject is shown a piece of paper with lines of individual letters (e.g. d & p) with dashes above and below the letters. The participant is instructed to cross out each occurrence of the letter d while scanning the page one line at a time. Total correct and both errors of omission (missing) and commission (incorrect letters) are recorded for 14 lines and the task lasts over four minutes. The d2 test has been shown to be internally consistent and a valid measure of visual scanning accuracy, speed and attention and in addition it is sensitive to medication effects and correlates with driving ability.^{6, 11}

Other Measures

Subjective Side Effects—Subjective responses to the intervention were measured using adaptations of two scales from Walker and Zacny, which have been used extensively to examine the subjective and objective side effects of opioids.^{8, 79–81, 86–93}

Opioid Adjective Checklist (OAC)—Participants were presented with a list of common side effects from opioid medications and asked to indicate on a scale of 0 (“not at all”) to 4 (“extremely”) and include effects such as “skin itchy,” “dry mouth,” and “turning of the stomach”. The OAC consists of 12 items derived from earlier scales of opioid side effects that were found to be sensitive to detecting common side effects.^{59, 70}

Opioid Cognitive Effects Checklist-Revised (OCEC-R)—The OCEC scale has 23 items evaluating the current experience of several cognitive effects of opioids, including, “confused,” “drunk,” “dizzy,” and “difficulty concentrating.” The checklist is sensitive to opioid medication and has been validated.⁷⁹ We used a revised OCEC which asked subjects to rate each item on a 0 – 10 ordinal scale rather than the original 0 – 100mm VAS. Ordinal scales are recommended for older adults to minimize failure rates for instrument completion.³³

Physiological Measures

Pupillometry—Pupil diameter of the left eye was assessed throughout the 8-hour study using an infrared pupillometer (Pupilsan 12A, Keeler Instruments) at controlled low ambient light condition. Following cognitive testing participants were allowed to adapt to the same ambient light conditions for 12 minutes prior to pupil measurement. Opioids suppress cortical centers that ordinarily inhibit the Edinger-Westphal nucleus of the oculomotor nerve, thereby causing pupil constriction, a well recognized physiological effect of opioids. Pupil size has been shown to be a valid surrogate marker of therapeutically relevant opioid effects.^{16, 23, 44} Three measurements of pupil size were obtained at each time point and the average of these was recorded.

Analgesia

Cold Pressor Test—The cold pressor test involves placing the hand in a bath of very icy cold water (1°C) followed by immersion in a warm water bath to extinguish the painful sensation. Participants were instructed to place their hand in the 37°C water bath for two minutes while they listened to instructions; immersion in the warm bath ensures consistency of hand temperature. Participants were instructed to place their hand in the cold water and indicate at which point they feel pain and then to remove their hand when they could ‘no longer stand it’. The cold pressor test has been shown to be sensitive to analgesic effects of opioids in a dose dependent manner⁷⁹ and is safe to use in older adults.^{55, 56, 82}

Pharmacokinetic Analysis

Plasma concentration of oxycodone and its oxidative metabolites (viz. noroxycodone, oxymorphone, noroxymorphone) were assayed by a previously reported sensitive liquid chromatography-mass spectrometry procedure.⁴⁴ Quality control samples were assayed along with each batch of samples. The inter-day coefficients of variation were consistently less than 10%.

Pharmacokinetics of oxycodone and its *N*-demethylated (noroxycodone), *O*-demethylated (oxymorphone), and *N,O*-didemethylated (noroxymorphone) metabolites in plasma were characterized by non-compartmental methods using the pharmacokinetic software WinNonlin 5.2 (Pharsight Corporation, Mountain View, CA). The following parameters were estimated for the parent drug—oxycodone: maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}), terminal elimination half-life (T_{1/2}), area under the plasma concentration-time curve from time zero to infinity (AUC), plasma clearance (Cl) with and without normalization by body weight, and mean residence time (MRT). For each of the metabolite, the estimated parameters included C_{max}, T_{max}, apparent terminal T_{1/2}, and AUC, along with the ratio of metabolite AUC to parent drug AUC, which serves as an index for the relative abundance of the metabolite in circulation.

Data Entry and Statistics

Data from screening and study visits were scored and entered into an Excel spreadsheet. Random data checks for accuracy were performed by another research assistant who did not enter the data. Neurocognitive and side effects data were analyzed using SPSS v.13.0 (SPSS Inc., Chicago, IL). Differences between subjects who completed all visits and those who did not were analyzed using t-tests and chi square analysis. Neuropsychological test scores were analyzed using mixed model, repeated measure ANOVA and MANOVAs with random effects. Randomization order and age group were between group factors and assessment time points as repeated factors and planned comparisons to baseline. Post-hoc comparisons were subjected to Bonferroni correction. Data were organized and analyzed with medication day followed by

placebo day, and this order is reflected in all figures. Demographic data was analyzed using summary statistics, T-tests and chi square between age groups.

Pharmacokinetic data for oxycodone and its metabolites were analyzed using the general linear model (GLM) procedure in SAS/STAT 9.2 (SAS Institute Inc., Cary, NC). Age, sex and weight, along with age-by-sex interaction, were specified as the independent variables for the regression model. Sex and age were entered as categorical variables, i.e., male or female and middle age (35–55 years) or older (≥ 65 years) group. Body weight in kg was entered as a continuous variable. The values of each pharmacokinetic parameter were log transformed to satisfy normality assumption.

Results

Seventy-three participants completed one visit and 71 participants completed all study visits. There were no significant age, education or gender differences between those that completed all visits versus those that dropped out after one visit. Demographic information is presented in Table 2. Statistical analyses were performed on participants completing both visits. As expected, there was a significant difference between the middle age and older adults for age ($p < .05$). However, there was no significant difference between these groups for education or gender. Five (15%) subjects in the older age group and three (9%) subjects in the middle age group experienced vomiting that occurred between 1.5 – 2 hours post dose. This was resolved with cold compresses on the forehead and ice chips and all subjects completed study procedures despite the vomiting. Additional subjective ratings of side effects are reported below. Results for individual ANOVA and MANOVAs are indicated below. For all outcomes there were no significant medication (randomization) order effects unless indicated. Significant between-group differences were evident for the two age groups for several of the neurocognitive measures. However, as these were expected to be different between groups, we have chosen not to highlight these findings in the results section below. Rather, we focused on medication-by-age interaction effects, i.e., oxycodone vs placebo differences that varied between the older and middle age groups.

Oxycodone Metabolite Pharmacokinetics

Figure 2 compares the mean plasma concentration-time profiles of oxycodone and its *N*-demethylated metabolite—noroxycodone, *O*-demethylated metabolite—oxymorphone, and *N,O*-didemethylated metabolite—noroxymorphone between older and middle-age subjects. Plasma concentrations of noroxycodone were comparable to those of parent oxycodone. In comparison, plasma oxymorphone and noroxymorphone were several-fold lower than oxycodone. In 11 of 71 subjects, plasma oxymorphone and noroxymorphone fell below measurable level before the last blood sampling at 8 hours post dose. Those cases were treated as missing data in summary and analysis of the pharmacokinetic parameters.

Mean plasma concentrations of oxycodone and all three of its oxidative metabolites following a single 10 mg dose of oxycodone did not differ significantly between older and middle-age adults. Pharmacokinetic parameters of oxycodone and its metabolites are presented in Table 3. For those cases where the plasma oxymorphone and noroxymorphone concentration-time data were insufficient to allow a reasonable estimation of the terminal $T_{1/2}$ and hence AUC extrapolation, their data were excluded from the analysis, i.e., treated as missing values. Except for noroxycodone C_{max} and oxymorphone T_{max} , none of the parameter estimates for oxycodone and its metabolites showed a significant difference between age or between sex, or a significant age-by-sex interaction. Both noroxycodone C_{max} and oxymorphone T_{max} showed a marginal significance in age effect. However, the magnitude of differences in the least-squares means is small and not clinically meaningful. Oral absorption and metabolism of oxycodone in older adults do not appear to differ compared to middle age adults.

Physiological Measures

Pupil diameter decreased significantly following oxycodone administration; peak effect occurred at 2 hours post dose in both middle age and older adult groups $F(19,48) = 14.8$, $p < 0.01$. There was a significant time-by-age group interaction $F(19,48) = 2.83$, $p < 0.01$ due to the slower return to baseline in the older adult group. Significant time-point comparisons to baseline are indicated in the legend for Figure 3.

There was evidence that oxycodone had an effect on response to cold pressor test as both older and middle age groups demonstrated a significant increase in their threshold or elapsed time prior to the sensation of pain as well as their tolerance of pain $F(10,56) = 4.10$, $p < 0.01$. There was no interaction effect suggesting that oxycodone's effects on experimental pain were similar for both middle age and older adults. The mean (standard deviation) time to threshold for middle age participants on the opioid day increased from 15 (8.2) seconds at baseline to 18 (9.1) seconds one hour after dose, and time to tolerance (can't stand the pain) increased from 35 (14.5) seconds at baseline to 62 (47.3) seconds one hour post dose. Mean time to threshold for older adult participants on the medication day increased from 15 (7.7) seconds at baseline to 18 (10.5) seconds one hour after dose, and time to tolerance and removal of arm from cold bath increased from 36 (23.6) seconds at baseline to 60 (45.6) seconds one hour post dose.

Neurocognitive Tests

Means and standard deviations for neurocognitive tests are presented in Table 4. On the verbal learning test for immediate recall there was a significant change in performance over time in the total number of correctly recalled words over three trials $F(5,62) = 14.8$, $p < 0.01$ for both age groups. This was due to a significant decline in performance at 1 hour and five hours post opioid dose compared to baseline $p < 0.01$. A similar pattern was noted for delayed recall, or recall of the list 30 minutes following the initial learning trials $F(5,62) = 34.5$, $p < 0.01$. In addition to recording performance on learning and recall, we also recorded the number of intrusion errors or words recalled that were not on the 'to be learned' list. It is not unusual for subjects to have intrusion errors, particularly when three separate word lists are presented throughout the day. For this outcome, an age-by-time interaction effect was observed $F(5,62) = 2.95$, $p < 0.05$, in addition to a change over time $F(5,62) = 8.66$, $p < 0.01$. This was due to a significant increase in the number of intrusion errors in the older adult group one hour post medication compared to baseline $p < 0.05$. As expected, there were increases in the number of errors over time on the placebo day. However, when the oxycodone data were analyzed separately the interaction effect remained significant $F(2,66) = 3.50$, $p < 0.05$, but the interaction effect for the placebo data was not significant.

A significant change in performance over time was evident for Digit Symbol a measure of sustained attention $F(5, 62) = 29.4$, $p < 0.01$ for both age groups. This was due to significantly lower scores or worse performance one hour and five hours post dose on the medication day compared to baseline for both groups ($p < 0.01$).

There was a significant change in performance on the D2 task a measure of sustained attention for both age groups $F(1,65) = 17.1$, $p < 0.01$. The older age group evidenced a worse performance one hour post dose than the baseline on the oxycodone day ($p < .01$). However, both middle age and older adults demonstrated an improving score over time on placebo day such that baseline and one hour assessments on the placebo day were significantly poorer (lower) compared to the last assessment (5 hour) on the placebo day ($p < .05$). Improving scores over the course of time on the placebo day may represent a practice effect whereby enhanced performance is due to repeated testing and increased efficiency. An analysis that included only the oxycodone data (baseline, 1 hour, 5 hours) found no interaction effect with randomization order or age. There was however, a significant time effect $F(2,65) = 10.06$, $p < 0.01$ for both

groups due to the decline at one and five hours post dose compared to baseline $p < 0.01$ for older adults and for one hour post dose compared to five hours post dose for the middle age group $p < 0.01$. An analysis that included each randomization group separately revealed no age interaction effects. Improvement over time on the placebo day was noted for several other tests, in each instance we ran an additional analysis of the medication day only to determine if randomization or order effects had any influence on those results and also with randomization group separated to determine if there was an interaction with age and these are noted below.

There was a significant change in reaction time over repeated assessments $F(10,57) = 6.50$, $p < 0.01$ with no significant interaction effect with age or randomization order. This was due to a significant increase in average reaction time (worse performance) one hour post dose compared to baseline for simple and choice reaction time tasks for both middle age and older adults ($p < 0.01$). There was a significant time-by-randomization order interaction effect $F(5,330) = 4.46$, $p < 0.01$ for simple reaction time but not choice reaction time. This was due to a practice effect for the simple reaction time task, such that participants who received placebo on the first day, gradually improved over time and their baseline on the medication day was lower (faster) than those who received medication on the first study day $p < 0.07$. However, both groups demonstrated a significant decline (slower) in reaction time at one hour post oxycodone compared to baseline as noted above and when separated by randomization order, there were no interaction effects for age.

A significant change in performance over time was found for Letter Number Sequencing task, a measure of working memory $F(5, 62) = 4.88$, $p < 0.01$ for both age groups. This was due to significantly lower scores, or worse performance, one hour and five hours post dose on the medication day compared to baseline for both groups ($p < 0.01$). Significant changes on the placebo day were also noted. An analysis of the medication day only revealed a significant change over time $F(2,66) = 6.12$, $p < 0.01$ due to a significant decline in performance for the young adults at one hour post dose compared to baseline $p < 0.01$, and a significant randomization order interaction effect $F(2,66) = 3.5$, $p < 0.05$. This was due to differences in the baseline performance of the two randomization groups. Subjects receiving placebo on the first day improved on the task over time such that their baseline on day two (i.e., day when they received oxycodone) was better (higher); therefore, the decline in performance at one hour post dose was more pronounced for these subjects than for those who were randomized to medication on day 1. However, there were no interaction effects for age regardless of randomization order.

Side Effect Measures

A significant omnibus change over time was evident for all OCEC adjective items $F(46,22) = 3.17$, $p < 0.01$ as well as for each individual item over time, and there was an omnibus time-by-age group interaction $F(46,22) = 1.98$, $p < 0.05$ for oxycodone data. Significant interaction effects between middle age and older adults included 'stimulated (energetic)' $F(2,134) = 7.78$, $p < 0.01$ in that older adults reported feeling significantly less energetic at 1 hour post medicine compared to the middle age group; middle age group reported greater feelings of being 'high' at one hour post medication $F(2,134) = 6.65$, $p < 0.01$; older adult group reported decreased feelings of 'elated' one hour post dose whereas middle age subjects reported an increase in elation $F(2,134) = 3.36$, $p < 0.05$; older adults reported greater increases in feeling 'dizzy' $F(2,134) = 4.43$, $p < 0.05$; older adults reported feeling less 'good' one hour post dose whereas middle age subjects remained constant $F(2,134) = 5.07$, $p < 0.01$; middle age group had increased pleasant thoughts and older adult group decreased at one hour post dose $F(2,134) = 7.16$, $p < 0.01$; middle age group decreased and older age group increased ratings of unpleasant thoughts at one hour post dose $F(2,134) = 3.48$, $p < 0.05$; middle age group increased and older age group decreased ratings of pleasant bodily sensation $F(2,134) = 4.65$, $p < 0.05$; For placebo

data, only middle age adults evidenced a change over time. In particular, middle age adults rated 'flushing' from OAC and hungry from OCEC as increased in severity at one hour post placebo compared to baseline. Table 5 presents the means and standard deviations of individual OAC items across study time points for oxycodone study day.

A significant omnibus change over time was evident for the Opioid Adjective checklist (OAC) $F(24,44) = 3.34, p < 0.01$. There were no significant time-by-age group interactions and change over time was significant only for the middle age group $F(24,44) = 2.76, p < 0.01$. Individual items that changed significantly over time included increased flushing $F(2,134) = 7.27, p < 0.01$; skin itching $F(2,134) = 3.31, p < 0.05$; numbness $F(2,134) = 14.5, p < 0.01$; dry mouth $F(2,134) = 23.5, p < 0.01$; drive $F(2,134) = 12.2, p < 0.01$; good mood $F(2,134) = 7.10, p < 0.01$; headache $F(2,134) = 8.55, p < 0.01$; nodding $F(2,134) = 12.68, p < 0.01$; vomiting $F(2,134) = 4.35, p < 0.05$.

Discussion

This study is one of the first to measure objective neurocognitive effects as well as subjective side effects of a specified dose (10 mg) of immediate-release oxycodone in healthy, older (>65 years) and middle age (35 – 55 years) adults. This study also documents that oxycodone pharmacokinetics following a single, low oral dose do not differ significantly between healthy older adults and middle age adults. The lack of a difference in oxycodone metabolism between the two age groups is supported by the absence of any significant differences in the pharmacokinetics of all three oxidative metabolites of oxycodone. Kokobun et al (2007)⁴² had previously reported an inverse correlation between clearance of intravenous or subcutaneous oxycodone and age in a group of Japanese cancer patients. On the other hand Villesen et al (2007)⁷⁶ reported, that the pharmacokinetics of intravenous oxycodone in a group of older adults patients (>70 years) undergoing hip surgery did not appear to differ remarkably from previous literature data gathered in younger subjects. Kaiko et al (1996)³⁹ also did not observe any significant difference in the AUC of a single 20 mg oral dose of controlled-release oxycodone between young (<45 years) and older (>65 years) subjects. They did observe a trend toward lower AUC of oxymorphone in older men and women compared to their younger counterparts. Moreover, there was a consistently higher oxymorphone AUC in men compared to women for both age groups. A recent study by Luikas et al. (2008)⁴⁷ in patients post-knee surgery found that, mean AUC of oxycodone in the 70–80 and 80–90 years age groups were 50–80% greater than the 20–40 years following single 10mg oral dose of oxycodone. Older adults (70–90 years) also had two-fold higher plasma oxycodone concentration compared to young adults twelve hours after the oxycodone test dose. We failed to observe any significant differences between our middle age and older adults. It appears there is a modest and gradual decline in oxycodone clearance with age, the effect is only evident when comparing older adults patients to relatively young adults. Any observed differences in opioid side effects between the middle age and older adults cannot be readily attributed to age related differences in oxycodone pharmacokinetics.

In the present study, we did not observe any differences between men and women in the pharmacokinetics of oxycodone or its metabolites, in particular oxymorphone. We also did not detect any age-by-sex interaction, i.e., a difference between age groups that is gender-dependent.

Neurocognitive effects and subjective side effects were similar in middle age and older adults such that both groups evidenced significant changes one hour post dose compared to baseline with some evidence of a trend toward return to baseline at five hours post dose. Similarities and difference between groups are discussed in more detail below.

Both middle age and older adults had increased difficulties with attention such as a simple reaction time task, and more demanding attention tasks such as the choice reaction time task, a sustained attention task and Digit Symbol at the time of peak drug effect (60 – 90 minutes post dose). Numerous studies have examined the effects of opioid medications on cognition in cancer samples and non-cancer samples (see ^{24, 66, 86} for reviews). Impairments in attention are commonly reported; however, not all studies support impairments in attention. Decrements in attention usually follow a dose escalation or from the addition of an immediate release opioid on top of a regular sustained release regimen (see for example ⁴⁰ and ¹²). Numerous other factors may also account for, or contribute to cognitive impairments in a cancer sample such as stage and severity of illness, other treatment medications or drug interactions, impaired hepatic metabolism, loss of sleep or fatigue making it difficult to single out opioid effects.

Studies in healthy, young or middle age patients suffering from chronic non-cancer pain generally find small or minimal decrements in attention, particularly once a stable medication regimen has been achieved. ^{17, 29, 36, 48, 62, 71} Although exceptions have been reported.⁶⁷ Very few of these studies have focused on older adults. In a study of opioid use in chronic non-cancer pain, Jamison et al. (2003) ³⁶ reported results for different age groups and found that the group aged 60 and older demonstrated an improvement on the Trail Making Test (a psychomotor sequencing test) and no significant change on the digit symbol substitution test (a measure of attention) following initiation of opioid therapy. More recently, assessment of older adults from a specialized pain clinic that included some, but not all participants taking opioids found no significant difference between those taking opioids and the rest of the sample, and overall the older adults were within the normal range on a brief screening test that included attention subtests. ⁸⁵ However, in a subsequent sample from the same clinic, a relationship between pain and difficulties with a mental switching task were found, suggesting that pain itself, may be detrimental to optimal cognitive functioning in older adults. ⁴¹

Although we found similar changes in both the middle age and older adults for measures of attention we did find one area in which there was a group-by-age interaction, i.e., a difference in response to oxycodone between the two age groups. Both groups evidenced difficulties in learning a list of words one and 5 hours post dose. However, the older adults evidenced more intrusion errors or interference from the previous lists. It is not unusual to find interference effects for serially presented word lists and in fact both the middle age and older adult groups evidenced increasing errors over time on both (placebo and medication) study days. However, the older adult group evidenced a sharper increase at one hour post oxycodone dose. This is most likely secondary to medication effects as the interaction effect was not observed on the placebo visit. Older adults typically evidence greater interference effects than younger adults and our results indicate this may be exacerbated during the peak medication period. ^{18, 31, 52}

Taken together, the results from the cognitive tests indicate that both middle age and older adults show declines in cognitive function with regard to attention and verbal memory during peak drug effects and that older adults may be more susceptible to verbal interference effects. Scores from the two groups were compared to normative data where available. Interestingly, despite declines in performance compared to baseline, neither group evidenced a magnitude of decline that could be characterized as within the impaired range for attention tasks. For verbal memory (delayed recall) the change from baseline for both the middle age and older adult groups were in the impaired range. This suggests that although changes from baseline may be evident, it is important to consider both the areas of cognition that may be affected as well as the impact on day to day functioning. Even though changes from baseline were observed in the present study, these may not have an impact on day to day functioning. This is important given that pain itself may have an adverse impact on cognition.

Both age groups reported experiencing marked side effects the severity of which were greatest at peak medication levels. Overall, the experience of side effects was similar between the two groups with minor exceptions. In addition to subjective changes, both groups demonstrated physiological evidence of medication effects as demonstrated by pupil diameter changes (see Figure 3). Pupil size for older adults was smaller at baseline and appeared to take slightly longer to return to baseline, which indicates a subtle age-related change in the pupillary response to oxycodone.

In summary, this study examined the cognitive and other side effects and pharmacokinetics of an immediate release, oral opioid medication in a sample of older and middle age adults. We did not observe any differences between older and middle age adults for oxycodone pharmacokinetics or its metabolites nor did we observe any gender differences. As expected, we did observe decrements in attention and verbal memory as well as changes in subjective ratings of side effects during peak drug effects (60 – 90 minutes post dose) and these effects were reasonably similar for both age groups. Our results and interpretation of findings are limited by our use of healthy, pain-free older adults as well as the use of experimental pain. Our study design included a placebo day which due to practice effects and other expectancies may have introduced some additional variability into the research design. Nonetheless, these results provide valuable information to clinicians who work with older adults taking an occasional dose of oxycodone on an as needed basis. Future work in this area should address a sample of older adults who are suffering from chronic, non-malignant pain and who are taking sustained release opioid formulations on a regular schedule to better control pain.

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Figure 1.
Study flow outline.

Figure 2.

Time course of mean and standard deviations of plasma concentrations of oxycodone and its metabolites noroxycodone, oxymorphone, noroxymorphone. Older adults are represented by dark circles and middle age group by open circles.

Figure 3.

Mean pupil size in millimeters for Middle age subjects (black squares) and older subjects (open circles) at each study time point indicated by minutes on the X axis starting with baseline (BL) and continuing for each assessment indicated in minutes post oxycodone (10mg). Middle age subjects evidenced a significant decrease in pupil size at 90, 120 and 180 minutes and older adults at the same time points as well as 240, 300 and 360 minutes post oxycodone dose. All changes were significant at the $p < 0.01$ level except for 240 and 360 timepoints for older adults ($p < 0.05$).

Table 1**Study Visit Procedures and Timeline**

Procedures	Timeline
Neurocognitive Tests	–85 minutes
Side Effects Questionnaire	–35 minutes
Cold Pressor Test	–30 minutes
Insert I.V. Catheter	–25 minutes
Attach oximetry finger clip	–15 minutes
Blood pressure, pupil size, blood draw	–10 minutes
Take Study Medication/Placebo Pill	0
Blood pressure, pupil size, blood draw – 0, 30, 60, 90 and 120 minutes after medication and every 60 minutes thereafter-	0,30,60,90,120,180,240,300,360,480 minutes
Neurocognitive Tests	60 minutes (1 hour)
Side Effects Questionnaire	65 minutes
Cold Pressor Test	70 minutes
Lunch	75 minutes
Neurocognitive Tests	300 minutes (5 hours)
Side Effects Questionnaire	350 minutes
Cold Pressor Test	355 minutes
Discharged	Total time 9–10 hours

Table 2

Study Demographic Information Mean (SD)

	Older	Middle Age	Total
N	36	35	71
Age (mean, s.d., range)	74.39 (6.2)	48.42 (5.3)	61.82 (14.1)
Education (years)	16.81 (2.6)	16.46 (2.9)	16.56 (2.7)
3MSE	96.92 (2.3)	98.06 (2.7)	97.48 (2.5)
Weight (lbs)	167.08 (37.4)	174.73 (35.8)	170.81 (36.5)
Body Mass Index	26.43 (4.4)	26.74 (3.8)	26.58 (4.1)
Gender	16 M 20 F	15 M 20 F	71

Table 3

Pharmacokinetic Parameters of Oxycodone and its Three Oxidative Metabolites

Parameters	Older	Middle Age
Oxycodone		
C _{max} , ng/ml	18.1 (5.3)	21.2 (9.1)
T _{max} , min	87.0 (39.1)	74.5 (39.0)
Elimination T _{1/2} , min	259 (85)	267 (80)
AUC, ng/ml-min	6556 (3263)	7061 (2320)
Cl, ml/min	1805 (747)	1586 (576)
Cl, ml/min/kg	23.7 (11.1)	22.4 (10.6)
Noroxycodone		
C _{max} , ng/ml	11.5 (4.7) ²	14.6 (6.8)
T _{max} , min	91.2 (42.1)	80.3 (41.2)
Apparent T _{1/2} , min	483 (284)	477 (222)
AUC, ng/ml-min	7762 (6057)	9088 (5416)
AUC _m /AUC _p ¹	0.805 (0.357)	0.937 (0.465)
Oxymorphone		
C _{max} , ng/ml	0.41 (0.22)	0.42 (0.23)
T _{max} , min	85.1 (39.5) ²	71.5 (47.1)
Apparent T _{1/2} , min	249 (101)	274 (129)
AUC, ng/ml-min	134 (62)	146 (62)
AUC _m /AUC _p ¹	0.023 (0.013)	0.022 (0.009)
Noroxymorphone		
C _{max} , ng/ml	2.39 (1.67)	2.63 (1.58)
T _{max} , min	122 (74)	117 (77)
Apparent T _{1/2} , min	373 (115)	420 (138)
AUC, ng/ml-min	1346 (780)	1762 (1056)
AUC _m /AUC _p ¹	0.266 (0.196)	0.276 (0.210)

¹ Ratio of area under the plasma concentration time curve between metabolite (AUC_m) and parent drug (AUC_p).

² Statistically significant difference between older and middle age adults ($p \leq .05$, GLM).

Table 4

Neurocognitive tests. Means and standard deviations.

	Middle Age adults			Older Adults		
	Baseline	1 hour.	5 hours.	Baseline	1 hour.	5 hours
Attention						
Simple Reaction Time	363.30 (99.7)	377.97 (92.3)	368.56 (78.0)	345.72 (45.5)	356.04 (60.2)	331.48 (35.6)
Choice Reaction Time	554.36 (109.2)	586.99 (120.9)	553.81 (88.9)	540.02 (67.4)	638.90 (138.5)	622.65 (161.1)
Symbol Digit	66.67 (16.1)	56.17 (12.9)	62.06 (13.7)	60.67 (13.4)	52.06 (11.1)	53.89 (13.7)
Sustained Attention Test	463.28 (96.9)	448.06 (109.9)	468.33 (106.1)	406.00 (96.0)	381.11 (108.2)	402.72 (106.0)
Working Memory						
Alphabet and Number Sequence	12.28 (2.7)	11.72 (3.1)	12.50 (2.9)	10.33 (3.4)	10.39 (3.5)	10.39 (2.8)
Memory						
Word List Test- delay	10.78 (3.0)	7.50 (3.9)	8.56 (4.0)	8.11 (2.5)	4.67 (3.4)	4.72 (2.9)
Word List- intrusions	0.11 (0.3)	0.33 (0.8)	0.44 (0.8)	0.33 (0.5)	1.94 (3.6)	0.50 (0.7)

Mean and standard deviation of Neurocognitive tests. Bold indicates a significant change from baseline ($p < 0.01$), with the exception of choice reaction time middle age adults at 5 hours which was significant at the $p < 0.05$ level. Simple and choice reaction time – milliseconds; Digit Symbol -number correct and maximum score of 132; D2- number correct and maximum score of 182; Numbers and Alphabet Sequencing- number correct and maximum score of 21; Word List Delay- total number of words recalled after a 20 minute delay and maximum score of 15; Word List Intrusions- number of errors or words recalled that were not on the list to be learned.

Table 5

Opioid Adjective Checklist (OAC)

	Middle Age			Older		
	Baseline	60 min.	300 min.	Baseline	60 min	300 min.
OAC						
Flushing	0.11 (0.40)	0.51 (1.01)	0.31 (0.63)	0.14 (0.54)	0.50 (0.91)	0.11 (0.31)
Skin itchy	0.14 (0.55)	0.51 (0.88)	0.23 (0.54)	0.11 (0.39)	0.16 (0.56)	0.16 (0.50)
Sweating	0.17 (0.56)	0.23 (0.77)	0.20 (0.47)	0.14 (0.54)	0.27 (0.74)	0.11 (0.40)
Turning of stomach	0.28 (0.62)	0.23 (0.54)	0.17 (0.56)	0.08 (0.36)	0.64 (1.26)	0.27 (0.74)
Numb	0.03 (0.17)	0.48 (0.81)	0.11 (0.40)	0.00 (0.00)	0.27 (0.65)	0.05 (0.23)
Dry mouth	0.37 (0.69)	1.28 (1.27)	1.22 (1.03)	0.25 (0.55)	1.11 (1.23)	0.75 (0.99)
Drive (motivated)	2.74 (0.78)	2.11 (1.43)	1.97 (1.31)	2.69 (0.95)	2.16 (1.20)	2.33 (0.86)
Carefree	2.25 (0.95)	2.37 (1.23)	2.25 (1.09)	2.41 (0.90)	2.14 (1.01)	1.89 (1.06)
Good mood	2.88 (0.67)	2.68 (1.15)	2.48 (1.19)	3.08 (0.87)	2.58 (1.10)	2.55 (0.96)
Headache	0.57 (1.09)	0.20 (0.47)	0.85 (1.11)	0.19 (0.46)	0.16 (0.37)	0.44 (0.80)
Nodding	0.68 (0.93)	1.37 (1.16)	0.94 (1.05)	0.47 (0.81)	1.16 (1.27)	0.64 (1.01)
vomiting	0.00 (0.00)	0.17 (0.70)	0.00 (0.00)	0.00 (0.00)	0.19 (0.62)	0.05 (0.23)

Mean and standard deviation of rating (0 – 4) for study day in which participants received 10mg oxycodone.