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Effects of short-term oxycodone maintenance on experimental pain responses in physically dependent opioid abusers

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Abstract

A common clinical problem with opioid analgesics is the loss of analgesic efficacy after repeated dosing; when this occurs, it is not clear what principles should guide providing effective analgesia among opioid-dependent individuals. This within-subject inpatient study aimed to determine if physically dependent opioid abusers (n=11) experience changes in oxycodone-induced analgesia during two oxycodone maintenance (30mg p.o./q.i.d.) phases: Initial Stabilization (Days 1–3) and after 6 weeks of Chronic Dosing. Six sessions (three each phase), measured Threshold, Tolerance & pain ratings for a Pressure Pain Test [PPT] and Cold Pressor Test [CPT]) after a single double-blind dose of oxycodone 30mg (Initial Stabilization) and 0, 30 & 60mg (Chronic Dosing) given in place of a scheduled maintenance dose. Physiologic and opioid agonist effects were assessed during Chronic Dosing sessions. There was no analgesic response to oxycodone 30mg. Oxycodone (60mg) produced a 25% increase in peak CPT Threshold compared to placebo, and significantly increased expired breath CO₂, miosis, and ratings of abuse liability measures. These data suggest that more than twice the acute oxycodone maintenance dose is needed to produce robust acute analgesia, though adverse effects (e.g. respiratory depression and abuse signals) may occur with lower doses.

Keywords

opioid; oxycodone; analgesia; tolerance

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1. Introduction

While opioids are effective analgesics for treatment of acute pain in normal populations, there is limited evidence for their efficacy in treating pain in persons who are physically dependent on opioids (whether they be chronic pain patients or persons with opioid use disorders who develop physical dependence). Relatively few studies have assessed opioid analgesic efficacy in either of these populations compared to healthy populations. In fact, no studies of long-term (>1 year) opioid efficacy in chronic pain have been conducted, as was highlighted in the recently released CDC guidelines for Chronic Opioid Prescribing⁵. Using healthy volunteers (instead of persons physically dependent on opioids) for laboratory examinations of opioid analgesia reduces confounds and allows investigators to make inferences more clearly about analgesic effects and pain mechanisms. The few studies reporting pain-related outcomes in persons dependent on opioids (typically methadone or buprenorphine-treated individuals) are important because they have demonstrated significant differences in pain and opioid analgesia between these persons and healthy controls^{6, 8, 7}.

Loss of analgesic potency with repeated opioid exposure is well-documented in the clinical literature and occurs irrespective of pain severity or opioid dose². The underlying cause for this may be related to tolerance and/or development of opioid-induced hyperalgesia, the latter being a phenomenon whereby repeated opioid exposure leads to increased pain sensitivity⁴. One commonly employed clinical approach for temporarily surmounting loss of analgesic efficacy is dose escalation. Unfortunately, while efficacy continues to diminish, opioid-related risks and harms are exacerbated by longer durations of exposure and higher doses^{15, 5}. In a population-based evaluation of patients who were eligible for publicly funded prescription drug coverage and received opioid prescriptions for non-malignant pain in Canada, Gomes and colleagues¹⁵ found dose-related increases in overdose deaths (as determined by coroner reports), with persons receiving intermediate (50–99 morphine milligram equivalents [MME]) and high (> 200 MME) daily doses of opioids at nearly 2- and 3-fold greater risk of opioid-related death compared to persons receiving low daily opioid doses (<20 MME).

There are many types of pain (e.g. visceral, musculo-skeletal, neuropathic, etc.) and experimental pain models have been developed to study these types of pain (for a review of human pain models and the underlying pharmacology, see²⁵). Importantly, both the specific pain assay used as well as the type of opioid administered can affect pain sensitivity measurements^{24, 20}. The experimental pain models used in the current study probe two different pain modalities: mechanical stimulation via Pressure Pain Test (PPT) and thermal stimulation via Cold Pressor Test (CPT). The PPT has been used to assess analgesic efficacy of drugs such as ibuprofen, ketamine, tramadol, and codeine²⁹. The CPT has been used frequently for hyperalgesic testing in populations dependent on opioids^{8, 7}, and it is sensitive to opioid analgesia with morphine²⁸, oxycodone¹⁶, fentanyl²¹, and tramadol^{12, 26}.

The specific aims of this study were threefold: 1) to assess if there is evidence of rapid changes in algesic responding during initial stabilization onto oral oxycodone maintenance (30 mg/q.i.d), 2) to evaluate analgesic, abuse-related, and physiologic responses to 0, 30 and 60mg of oral oxycodone following approximately 6 weeks of maintenance, and 3) to

determine whether changes in analgesic responding to 30mg oxycodone occurred between Initial Stabilization (Days 1–3) and Chronic Dosing (Week 6).

2. Methods

2.1 Volunteers

Healthy persons ages 18–50 with current opioid physical dependence (confirmed by physician interview, self-report of opioid withdrawal, observed urine drug tests positive for an opioid, and self-reported use of short-acting opioids on 21 days in the 30 days preceding study entry) were recruited to participate. A modified timeline-follow back (TLFB) and the Addiction Severity Index (ASI)²³ assessed substance use behaviors. Volunteers were recruited through local newspaper and magazine advertisements, word-of-mouth, and fliers posted in public areas. Good general health was determined by history and physical examination, blood and urine laboratory testing, psychiatric interview, and electrocardiogram. Exclusion criteria included: physiological drug dependence requiring medical management other than opioids (i.e., benzodiazepines or alcohol), currently pregnant or breastfeeding, BMI > 30, seeking substance abuse treatment, taking daily prescription medications, ongoing medical (e.g. diabetes) or psychiatric (e.g. major depression) problems, or intolerance to the pain testing procedures.

The study was approved by the University of Kentucky (UK) Institutional Review Board, was conducted in accordance with the Declaration of Helsinki, and volunteers gave written informed consent prior to participating. A Certificate of Confidentiality was obtained from the National Institute on Drug Abuse. Volunteers were paid \$40 per day that they resided in the hospital, and upon completion of the entire study, they earned an additional \$40 per study day.

2.2 Study Setting

Volunteers resided on the UK residential research unit for approximately 6.5 weeks. Daily urine drug tests for unauthorized illicit drug use (cocaine, THC, amphetamine, methamphetamine, methadone, opiates, phencyclidine, barbiturates, benzodiazepines, and oxycodone), and weekly pregnancy tests were conducted. Breath alcohol was confirmed to be 0.00 prior to each experimental session. A caffeine-free diet of three standard meals daily and snacks available between meals was provided. Smoking was permitted at any time except for 30 min before and during sessions. Medications (e.g., acetaminophen, magnesium, and ibuprofen) for common ailments were available as needed, but were restricted after midnight preceding session and until session completion.

2.3 Drugs

This study was conducted under an investigator-initiated Investigational New Drug Application from the Food and Drug Administration (#69,214). All study medications were stored and prepared by the UK Investigational Pharmacy. Oxycodone hydrochloride tablets (30mg; Mallinckrodt, Hazelwood, MO) were over-encapsulated and loose-filled with lactose monohydrate powder (Medisca Pharmaceuticals, Plattsburgh, NY) for daily maintenance and experimental session dosing; placebo was identical capsules filled with lactose.

2.4 Study design and procedures

These data were collected as part of a larger within-subject, double-blind, placebo-controlled, randomized study evaluating abuse liability of intranasal buprenorphine²³. The present report focuses on two additional phases of the study not previously reported: the Initial Stabilization Phase (during the first full 3 days of oxycodone maintenance after admission and before onset of the primary [i.e. buprenorphine abuse liability] study procedures) and the Chronic Dosing Phase (after ~6 weeks of oxycodone maintenance and after completion of the primary study procedures). Volunteers completed the last test session of the primary study three days before the first Chronic Dosing Phase session, an interval chosen to preclude pharmacological carryover. Session measures and timing are displayed in Table 1.

2.4.1 Oxycodone Maintenance Procedure—On admission day (Day 0), volunteers began oral oxycodone maintenance, receiving 30mg four times/day (8 AM, 12PM, 6PM, 10PM); this continued throughout the inpatient stay (~6.5 weeks). Volunteers were purposefully maintained on a short-acting opioid (i.e., oral oxycodone) in order to allow for testing of acute opioid responses during test sessions without interference of the maintenance drug. The majority of volunteers (n=10) were admitted as inpatients the afternoon of Day 0 with the first session occurring the following day (1PM); thus, they received four or five oxycodone doses (mean = 4.5) before the first session. One volunteer was admitted immediately before a holiday; therefore, his Day 1 session was delayed by 5 days, and he received 20 maintenance doses prior to his first session. A sensitivity analysis determined that the statistical results were not significantly altered by inclusion of his data ($p>.05$). Volunteers completed the Subjective Opiate Withdrawal Scale¹⁷ (SOWS) daily upon waking (~7AM) and at 10AM to assess the efficacy of the maintenance procedure in preventing withdrawal. The SOWS consists of 16 symptoms rated on a 5-point scale of intensity as follows: 0=not at all, 1=a little, 2=moderately, 3=quite a bit, 4=extremely. The total score is a sum of item ratings and ranges from 0 to 64.

2.4.2 Oxycodone Initial Stabilization Phase Sessions—Sessions took place on the UK inpatient unit in a quiet room and were supervised by a trained research assistant. During the Initial Stabilization Phase (Days 1, 2 & 3), two pain tasks (details below) were administered 1 and 2 hours after the volunteers' normally scheduled 12PM maintenance dose. Immediately after each pain test, volunteers responded to two visual analog scales (VAS) 1) "How unpleasant was the pain you just experienced?" and 2) "How intense was the pain you just experienced?" scored from 0 (not at all) to 100 (extremely).

Cold pressor test (CPT) — Two water coolers (one containing room-temperature water [$37.0\pm0.1^{\circ}\text{C}$] and one containing ice water [$2.0\pm0.1^{\circ}\text{C}$]) were used; the latter employed an aquarium pump to maintain consistent water temperature. The volunteer submerged their non-dominant arm above their elbow into the room-temperature water with fingers spread apart and were instructed not to touch the sides or bottom of the cooler. After 2 min, the volunteer immediately transferred their arm to the ice water. The volunteer verbally reported when they first felt pain (i.e., Threshold) and kept their arm submerged until they could no longer tolerate the pain (i.e., Tolerance)- at which point they immediately removed their arm

from the ice bath. Threshold and Tolerance were quantified in seconds. For safety reasons, volunteers were never allowed to leave their arm submerged in the ice bath for more than 5 min.

Pressure pain test (PPT) — Using a hand-held pressure algometer (Medoc U.S.A. Durham, NC), mechanical pressure was applied with a rubber probe to the thenar eminence of the volunteer's dominant hand. Pressure was applied with slowly increasing force (parameters guided by a computer program). The volunteer pressed a button when they first felt pain (Threshold) and again when the pain became intolerable (Tolerance). The upper safety limit for pressure was set at 1500 kilopascals (kPa). The PPT was administered twice at each time point (with an inter-trial interval of 5 min) —for a total of four times in each Initial Stabilization Phase session and eight times in each Chronic Dosing Phase session. Results of the two trials for each timepoint were averaged, and the average was used for analysis.

2.4.3 Oxycodone Chronic Dosing Phase Sessions—During the final week of the study and after ~6 weeks of daily oxycodone maintenance, three additional sessions were conducted at least 48 h apart to assess analgesic response to a single dose of oral oxycodone [0, 30 or 60mg]. Volunteers received their 8AM maintenance dose, and sessions began at 11:30AM. The double-blind, randomized oxycodone dose (0, 30, or 60mg) was substituted for the 12PM standard maintenance dose (i.e., 30mg oxycodone), and volunteers completed the same pain tasks done during the Initial Stabilization Phase. Scheduled maintenance dosing (30mg oxycodone q.i.d.) resumed between sessions.

Pain tests (described above) were administered 20 min before and 1, 2 & 3 h after test session drug administration. Subjective effects measurements included VAS, street value estimation, and a subject-rated opioid agonist adjective checklist¹⁴. Observers used a 12-item opioid agonist scale and the Objective Opioid Withdrawal Scale (OOWS)¹⁷. The VAS were “Do you feel any DRUG EFFECT?” “How HIGH are you?” “Does the drug have any GOOD...BAD effects?” How much do you LIKE the drug?” “How much do you DESIRE OPIATES right now?” and “How severe is your OPIATE WITHDRAWAL?”. Volunteers placed an arrow along a 100mm line anchored at 0 (not at all) and 100 (extremely). Street value was ascertained by asking “What is the street value of the dose you just received?”. Adjective checklists (subject and observer-rated) were scored on a Likert scale (0 not at all —4 extremely), and the Objective Opioid Withdrawal Scale (OOWS) was scored from 0 to 13. Pupil diameter and end tidal CO₂ (EtCO₂) were measured throughout these sessions.

2.5 Data analysis

Raw data from the pain tests were evaluated for outliers using the Boxplot Outlier Labeling Rule^{19, 18} and results determined one volunteer consistently reported above the upper limit criteria on the CPT. Thus, data from 10 volunteers (6 male) are presented for the CPT; while data from 11 are presented for all other outcomes. Data were analyzed using repeated measures linear models for time course as well as peak effects. For Initial Stabilization Phase sessions, time course analyses used a 2-factor model (maintenance day [3 levels: Day 1, Day 2 & Day 3] × time [2 levels: 1 & 2 h post drug administration) to assess CPT and PPT outcomes. Peak scores were then analyzed in a 1-factor (maintenance day) model, and

Tukey HSD post hoc tests were performed to explore significant main effects of maintenance day. For pain outcomes collected during Chronic Dosing Phase sessions, time course analyses used a 2-factor model (dose [3 levels: 0, 30 & 60mg oxycodone] $\times$ time [4 levels: -20 min, 1, 2 & 3 h post drug administration], with 1-factor (dose) model analyses of peak scores. For outcome measures listed in Table 3, both time course and peak analyses were conducted. Tukey HSD post-hoc tests were performed to evaluate significant main effects of dose. To evaluate effects of maintenance duration on algescic responding, a 2-factor analysis (session day [4 levels: Initial Stabilization Phase Sessions on Days 1, 2 & 3 and Chronic Dosing Phase 30mg oxycodone Session Day] $\times$ time [2 levels: 1 & 2 h post dose]) was conducted. In these 4 sessions, oxycodone 30mg was administered at 12PM with pain testing at 1PM and 2PM and, thus, are comparable testing conditions. Peak algescic data calculated from equivalent timepoints (1 and 2 h post dose) were then analyzed in a 1-factor (session day) model, and Tukey HSD post hoc tests were performed to further investigate significant main effects. All statistics were completed using Proc Mixed in SAS 9.3 (Cary, NC) with significance level at $p < .05$.

3. Results

3.1 Volunteers

Sixty-two volunteers screened for the study; twenty were admitted to the inpatient unit. Nine were discharged early for the following reasons: could not tolerate spontaneous withdrawal during first week ($n=1$), personal reasons ($n=2$), unable to understand or follow directions ($n=4$), and violating study protocol ($n=2$). Eleven Caucasians (7 male) completed the study. Demographic and drug (recent and lifetime) use data are shown in Table 2. All demographic and drug use variables (Table 2) were compared between completers and non-completers with t-tests. No significant differences were found, $p > .05$, with the exception that there was more lifetime amphetamine use in non-completers ($n=3$) compared to completers ($n=0$). The volunteers' urine drug screen at admission could test positive for short-acting opioids and THC only.

3.2 Assessments during Initial Stabilization Phase: Withdrawal and algescic testing results

Withdrawal—SOWS scores were stable and low (maximum score is 64) across Days 1–3 (3.3 [0.8] on Day 1; 3.3 [1.1] on Day 2; and 3.6 [1.0] on Day 3).

Algescic Testing—Time course analysis of the Pressure Pain Test (PPT) and Cold Pressor Test (CPT) showed that neither Threshold or Tolerance nor the pain VAS ratings of “Intense” and “Unpleasant” changed as a function of maintenance days 1–3. Examination of peak scores for the PPT and CPT also revealed no significant differences in Threshold and Tolerance outcomes across these three days; however, peak ratings of “Intense” and “Unpleasant” for the PPT significantly increased across the first three days of stabilization testing as seen in Table 3.

3.3. Assessments after Chronic Dosing: Algesic testing, subject-and observer-rated opioid agonist effects, and physiological monitoring results

Algesic Testing—After approximately six weeks (between 38 and 44 days) of maintenance (i.e., 30mg oxycodone q.i.d), time course analyses revealed no oxycodone dose effects for the PPT; however, significant time effects were seen for Tolerance and both pain VAS outcomes (Figure 1). Specifically, PPT Tolerance decreased over repeated testing within session and VAS ratings of “Intense” and “Unpleasant” increased over repeated testing within session, particularly at the 2 and 3 h time points. There were no significant effects of dose or time for any CPT outcome measure.

When analyzed as peak scores, there were no effects for any PPT outcome measure; however, there was a significant peak dose effect for CPT Threshold ($F[2,18]=4.2$, $p=0.03$) in that peak CPT Threshold times were ~ 25% higher after 60mg oxycodone (10.1 [± 1.5] sec) compared to placebo (8.0 [± 1.3] sec, $p=.027$). Peak CPT Tolerance times were more than 10sec longer for oxycodone 60mg compared to oxycodone 30mg and placebo. This was not statistically significant due to a large error term caused by one individual reporting peak Tolerance times 3 standard deviations above the rest of the group. Peak CPT Pain VAS ratings were not significant.

Subject-and observer-rated opioid effects—Figure 2 displays time course analysis results for the VAS item “How much do you LIKE the drug?”, street value estimations, and pupil diameter. There were significant dose effects ($F[2,20]$) for VAS items “Any Drug Effect” (3.8) and “High” (3.5) and significant dose $\times$ time interactions ($F[22,220]$) for “Any Drug Effect” (2.2), “Good Effects” (2.0), and “High” (2.1), $p<.05$ for all, with time course profiles similar to that of “Like” (i.e. greater scores for the 60mg dose). Dose effects emerged for the agonist scale of the observer-rated adjective checklist ($F[2,20]=7.1$, $p=.005$), but not the agonist scale of the subject-rated adjective checklist ($p>.05$). Peak analyses for these measures (see Table 4) all showed significant dose effects except for “Bad Effects” and “Desire Opiates”.

Physiological outcomes—Time course analyses revealed that oxycodone produced miosis (Figure 2), but did not alter EtCO₂. Trough pupil diameter and peak EtCO₂ analyses revealed an effect of dose for both, with significant HSD post hoc differences for both 30 and 60mg oxycodone compared to placebo (Table 4).

3.4 Comparison of withdrawal and algesia: Initial Stabilization Phase Days 1, 2 & 3 and Chronic Dosing Phase 30mg oxycodone Session

Analysis of SOWS scores collected before each of the six sessions (three in stabilization and three in Week 6) showed no significant differences across these sessions ($p=.096$). Pain outcomes were compared across the Initial Stabilization Phase Days 1, 2 & 3 test sessions and the Chronic Dosing Phase 30mg oxycodone test session. Time course analyses revealed no differences between Initial Stabilization Phase test sessions and the Chronic Dosing Phase test session on PPT Threshold or Tolerance outcomes, but there were significant effects of test session for volunteers’ ratings of PPT “Intense” ($F[3, 29]=4.0$, $p=.017$) [data not shown]. There were no significant main effects or interactions for any CPT outcome

measure. Peak data for the four comparable sessions are displayed in Table 3. Peak analyses $F[3, 29]$ showed no significant effects of test session for PPT Threshold or Tolerance outcomes $p>.05$. Both PPT pain VAS outcomes showed a significant main effect of test session (“Intense”: 7.5, $p=.001$; “Unpleasant”: 3.0, $p=.047$), with volunteers rating the PPT as significantly more intense on the Initial Stabilization Phase Day 3 test session compared to the Chronic Dosing Phase 30mg oxycodone test session, HSD $p=.001$.

Peak analyses of CPT outcomes revealed a significant effect for Tolerance only ($F[3, 27]=5.0$, $p=.007$) with volunteers removing their arms from the cold water significantly more quickly on the Chronic Dosing Phase 30mg oxycodone test session compared to the Initial Stabilization Phase Day 3 test session, HSD $p=.009$ (Table 3).

4. Discussion

Treating pain in individuals with OUD and physical dependence is a challenge for physicians because little research has been conducted to determine what treatments may be most effective in this population. This study is the first to examine experimental pain responses in individuals with OUD and physical dependence maintained on short-acting opioids, and it provides evidence that oxycodone may produce euphoric and physiological effects without conferring analgesia in physically dependent opioid users. These data also suggest that modest increases in opioid dosage do not significantly increase analgesia in this population and that an acute dose of greater than 50% of the total daily dose would be necessary to achieve robust analgesia.

Both the Pressure Pain Test and Cold Pressor Test reliably produced pain during initial stabilization onto oxycodone maintenance and after ~6 weeks of maintenance. After ~6 weeks of maintenance, little analgesia was observed after dosing with 60mg oxycodone (twice the 30mg maintenance dose), as measured by Threshold, Tolerance and pain VAS (Intense, Unpleasant) indices. The only statistically significant analgesic response was a modest 2sec increase in peak CPT Tolerance after 60mg oxycodone compared to placebo. The failure of 30mg oxycodone to produce detectable analgesia was not unexpected as volunteers were maintained on 30q.i.d. What is noteworthy is that a more robust analgesic effect was not observed after 60mg oxycodone (i.e. half the total daily dose and a fairly high acute analgesic dose). While it may seem like an acute opioid dose of 50% the total daily dose should produce more robust signals of analgesia (this dose is at the upper end of dosing recommendations for breakthrough pain in patients maintained on opioids)¹⁷, it is unknown whether oxycodone or other opioid-induced analgesia is a linear dose-related function in physically dependent opioid users. One possibility is that a floor effect must be surmounted, but once passed, oxycodone will produce a somewhat linear analgesic dose-response curve. As this study did not administer doses higher than 60mg, further studies need to be conducted to test this hypothesis. Opioid tolerance or hyperalgesia may have blunted the response to oxycodone at doses within the therapeutic range. Importantly, while oxycodone failed to produce substantive analgesia in these experimental pain models, both 30 and 60mg oxycodone doses produced other typical *mu* opioid effects, such as miosis and increased ratings on abuse liability measures. Repeated testing effects were seen for the PPT, both across Initial Stabilization Phase test sessions and within each Chronic Dosing Phase test

session; an effect not observed for the CPT. The only difference in pain response to oxycodone 30mg between Initial Stabilization (i.e., Day 3 specifically) and the Chronic Dosing Phase was with CPT Tolerance and PPT VAS “Intense” whereby both outcomes were lower after chronic dosing, although the repeated testing effect for the PPT confounds these results.

CPT Threshold and Tolerance have been previously reported to be sensitive to the analgesic effects of oxycodone in both non-opioid users^{16, 11, 27} and opioid users without physical dependence¹. The magnitude of effects previously reported exceed what was observed in the current study (increase of CPT Threshold by 25%). In non-opioid using volunteers, there is a clear dose-response relationship between oral oxycodone and changes in CPT outcomes—. 2mg/kg (~14mg) increased peak Tolerance by 38% (Threshold not reported)²⁷; .3mg/kg (~20mg) increased Threshold by 64% and Tolerance by 50%¹¹; and .5mg/kg (~35mg) increased peak Threshold by 130% and peak Tolerance by 122%¹⁶. In one study of sporadic opioid users without physical dependence, peak CPT Threshold and Tolerance were sensitive to 40mg oxycodone administration (66% increase in Threshold, 72% increase in Tolerance), but not to 10 or 20mg¹. In contrast, the observed 25% decrease in CPT Threshold after 60mg oxycodone in the current study is an ~40% smaller effect than was observed after 20mg in healthy volunteers.

To our knowledge, no studies have examined experimental pain responses in individuals maintained on short-acting opioids, but our results can be contextualized within the literature describing pain responses in individuals maintained on long-acting opioids (methadone and buprenorphine). The reported range of CPT Threshold and Tolerance scores in methadone maintained individuals varies widely: Threshold scores are between 7sec⁹ and 12sec⁷, and Tolerance scores are between 13sec⁷ and 59sec⁶. Even less is known about buprenorphine-maintained individuals’ CPT responses, but the range of CPT Tolerance scores reported in the literature (i.e., 17.7sec for those on 16–24mg/day⁷ to 61.7sec for those on an average of 8.9mg/day⁶) are higher than what was seen in the current study. The wide range of responses is likely due to methodological differences between studies (e.g. daily maintenance dose, weeks since last dose change, and whether CPT was assessed at putative peak or trough concentration). Nevertheless, it appears that the CPT responses observed in the current study are within the range of those observed in studies of individuals maintained on long-acting opioids.

The increase in PPT VAS ratings from Day 1 to Day 3 and the decrease in PPT Tolerance—with related increases in PPT VAS ratings during each individual Chronic Dosing Phase session—are potentially indicative of a repeated-testing effect. The PPT was always applied to the same area (the thenar eminence) and may have resulted in soreness that affected successive trials. Volunteers anecdotally reported soreness the morning after sessions, although baseline pain measures were not collected to assess this systematically. While the pressure algometer is commonly used by physical therapists to assess pressure changes in pain threshold of specific muscle areas before and after therapy^{30, 22, 13}, and has been used successfully to test analgesia in non-patient settings²⁹, it may have less validity in specific research settings³¹. This could be due to the frequency of testing: when used clinically, pressure is applied to the target region before and after a course of therapy (which may last

weeks or months). The current study administered the PPT twice at each time point—four times in each Initial Stabilization session and eight times in each Chronic Dosing Phase session; the increased frequency of testing during Chronic Dosing Phase sessions may account for the decrease in PPT Tolerance during the Chronic Dosing Phase that was not observed during Initial Stabilization.

The increase in PPT pain VAS ratings and decrease in peak CPT Tolerance from Day 3 to Week 6 could be explained by either hyperalgesia and/or tolerance—processes mediated by mu-opioid receptor changes in response to repeated activation (i.e. downregulation, desensitization, and altered signaling. For a review of mechanisms underlying opioid tolerance, see³¹). A decrease in CPT Tolerance across time in opioid-dependent persons has been previously characterized as hyperalgesia¹⁰ and the results of the current study are consistent with that theory. Baseline (i.e. drug-free) analgesia was not measured because the volunteers were opioid dependent; therefore, the ideal control condition (i.e., testing the same individuals in a drug-free state before development of opioid physical dependence) for hyperalgesia was not possible. Volunteers were presumably opioid tolerant prior to entering the study as all were physically dependent and had been using opioids for an average of ~8 years.

The pain tests used in this study were chosen because they activate different pain mechanisms (thermal and pressure) and would capture a range of pain responses; therefore, differences observed in pain responses to the CPT and PPT were expected. It is commonly reported that algesic responses vary between pain modalities²⁰. It is possible that the PPT is a pain modality unaffected by opiate tolerance. It has been suggested that the CPT is particularly sensitive to opiate effects⁷, and the results here support that conclusion.

Despite the lack of robust analgesia reported by volunteers, subject-rated effects, observer-rated effects, and physiological effects were significantly altered after active dose compared to placebo. Subject-rated increases on abuse-related effects were observed after both 30 and 60mg oxycodone (Figure 2), but achieved statistical significance only with 60mg. These results indicate that, in this population, there is a pharmacological disconnect between the relative potency of oxycodone to produce analgesia versus psychoactive effects related to its abuse liability. This finding also has important clinical implications because it demonstrates that a dose of 30–60mg oxycodone, a dose that produces analgesia in non-dependent individuals, is ineffective in those maintained on 30mg/q.i.d. Physicians may be hesitant to prescribe supra-therapeutic doses to patients with physical dependence on opioids due to fear of reinforcing and/or producing addiction and/or drug-seeking behavior because of the clear dose-related non-analgesic effects these medications produce (e.g., euphoria, sedation). Moreover, patients' requests for higher doses due to the lack of analgesic efficacy may be incorrectly interpreted as drug-seeking behavior, particularly if they have observable physiologic effects (e.g. miosis) or endorse other opioid agonist signs or symptoms as was evident in this study (see Table 4). Concerns about respiratory depression and unintentional overdose may also prevent physicians from prescribing supra-therapeutic opioid doses. While end tidal CO₂ significantly increased after 30 and 60mg oxycodone compared to placebo, values remained within the normal range (35–45 mmHg); suggesting that

volunteers were tolerant to this effect. Nevertheless, it is unknown if respiratory depression would be clinically significant at doses necessary to achieve analgesia in this population.

This study has important limitations to consider. The small sample size and significant attrition rate limited the statistical power of the study. Future studies should further characterize how age, sex, and other factors may influence baseline pain responses in this population. There is also a need for research describing how opioid-induced changes in experimental pain threshold and tolerance translate to clinically meaningful changes in acute and/or chronic pain outcomes among patients maintained on daily short-acting opioid analgesics. The CPT is the most commonly used experimental pain assessment used in opioid-dependent persons and can model some aspects of clinical pain³; nevertheless, it is unknown how opioid-induced changes in experimental pain threshold and tolerance may reflect analgesia to clinical pain.

In summary, the current study demonstrated that, in physically dependent opioid users maintained on 30mg/q.i.d. oxycodone, acute oxycodone 30mg provided no analgesic benefit over placebo and 60mg produced a modest signal of analgesia on one experimental pain model. Importantly, despite the absence of a strong analgesic signal, other opioid-related pharmacodynamic effects were evident, including subjective ratings of measures related to abuse potential. Given the high rates of chronic opioid analgesic prescribing, chronic pain and OUD, determining effective analgesic strategies for treating pain among persons maintained on short- and long-acting opioids (for pain, for OUD, and/or the combination) should be a research priority. Clinicians are urged to consider differential tolerance development to the euphoric, physiological, and analgesic effects of opioids when evaluating treatment needs of pain patients with OUD.

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References

1. Babalonis S, Lofwall MR, Nuzzo PA, Walsh SL. Pharmacodynamic effects of oral oxymorphone: abuse liability, analgesic profile and direct physiologic effects in humans. *Addict Biol.* 2016; 21:146–158. [PubMed: 25130052]
2. Ballantyne JC, Shin NS. Efficacy of opioids for chronic pain: a review of the evidence. *Clin J Pain.* 2008; 24:469–478. [PubMed: 18574357]
3. Chen AC, Dworkin SF, Haug J, Gehrig J. Human pain responsivity in a tonic pain model: psychological determinants. *Pain.* 1989; 37:143–160. [PubMed: 2664663]

4. Chen L, Sein M, Vo T, Amhmed S, Zhang Y, Hilaire KS, Houghton M, Mao J. Clinical interpretation of opioid tolerance versus opioid-induced hyperalgesia. *J Opioid Manag.* 2014; 10:383–393. [PubMed: 25531956]
5. 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.* 10:113–130.e122.
6. Compton P, Charuvastra VC, Ling W. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. *Drug Alcohol Depend.* 2001; 63:139–146. [PubMed: 11376918]
7. Compton P, Canamar CP, Hillhouse M, Ling W. Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. *J Pain.* 2012; 13:401–409. [PubMed: 22424799]
8. Compton PA, Ling W, Torrington MA. Lack of effect of chronic dextromethorphan on experimental pain tolerance in methadone-maintained patients. *Addict Biol.* 2008; 13:393–402. [PubMed: 18507735]
9. Doherty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W. Hyperalgesic responses in methadone maintenance patients. *Pain.* 2001; 90:91–96. [PubMed: 11166974]
10. Dumas EO, Pollack GM. Opioid Tolerance Development: A Pharmacokinetic/Pharmacodynamic Perspective. *The AAPS Journal.* 2008; 10:537–551. [PubMed: 18989788]
11. Eisenberg E, Midbari A, Haddad M, Pud D. Predicting the analgesic effect to oxycodone by 'static' and 'dynamic' quantitative sensory testing in healthy subjects. *Pain.* 2010; 151:104–109. [PubMed: 20621419]
12. Enggaard TP, Poulsen L, Arendt-Nielsen L, Brosen K, Ossig J, Sindrup SH. The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to CYP2D6. *Anesth Analg.* 2006; 102:146–150. [PubMed: 16368820]
13. Farasyn AD, Meeusen R, Nijs J. Validity of cross-friction algometry procedure in referred muscle pain syndromes: preliminary results of a new referred pain provocation technique with the aid of a Fischer pressure algometer in patients with nonspecific low back pain. *Clin J Pain.* 2008; 24:456–462. [PubMed: 18496311]
14. Fraser HF, Van Horn GD, Martin WR, Wolbach AB, Isbell H. Methods for evaluating addiction liability. (A) "Attitude" of opiate addicts toward opiate-like drugs (B) a short-term "direct" addiction test. *J Pharmacol Exp Ther.* 1961; 133:371–387. [PubMed: 13701509]
15. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-related mortality in patients with nonmalignant pain. *Arch Intern Med.* 2011; 171:686–691. [PubMed: 21482846]
16. Grach M, Massalha W, Pud D, Adler R, Eisenberg E. Can coadministration of oxycodone and morphine produce analgesic synergy in humans? An experimental cold pain study. *Br J Clin Pharmacol.* 2004; 58:235–242. [PubMed: 15327582]
17. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse.* 1987; 13:293–308. [PubMed: 3687892]
18. Hoaglin DC, Iglewicz B. Fine-Tuning Some Resistant Rules for Outlier Labeling.
19. Hoaglin DC, Iglewicz B, Tukey JW. Performance of Some Resistant Rules for Outlier Labeling.
20. Kindler LL, Sibille KT, Glover TL, Staud R, Riley JL 3rd, Fillingim RB. Drug response profiles to experimental pain are opioid and pain modality specific. *J Pain.* 2011; 12:340–351. [PubMed: 21146469]
21. Koltzenburg M, Pokorny R, Gasser UE, Richarz U. Differential sensitivity of three experimental pain models in detecting the analgesic effects of transdermal fentanyl and buprenorphine. *Pain.* 2006; 126:165–174. [PubMed: 16901645]
22. May S, Littlewood C, Bishop A. Reliability of procedures used in the physical examination of non-specific low back pain: a systematic review. *Aust J Physiother.* 2006; 52:91–102. [PubMed: 16764546]
23. McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The Fifth Edition of the Addiction Severity Index. *J Subst Abuse Treat.* 1992; 9:199–213. [PubMed: 1334156]

24. Olesen AE, Staahl C, Arendt-Nielsen L, Drewes AM. Different effects of morphine and oxycodone in experimentally evoked hyperalgesia: a human translational study. *Br J Clin Pharmacol*. 2010; 70:189–200. [PubMed: 20653672]
25. Olesen AE, Andresen T, Staahl C, Drewes AM. Human experimental pain models for assessing the therapeutic efficacy of analgesic drugs. *Pharmacol Rev*. 2012; 64:722–779. [PubMed: 22722894]
26. Poulsen L, Arendt-Nielsen L, Brosen K, Sindrup SH. The hypoalgesic effect of tramadol in relation to CYP2D6. *Clin Pharmacol Ther*. 1996; 60:636–644. [PubMed: 8988065]
27. Samer CF, Daali Y, Wagner M, Hopfgartner G, Eap CB, Rebsamen MC, Rossier MF, Hochstrasser D, Dayer P, Desmeules JA. Genetic polymorphisms and drug interactions modulating CYP2D6 and CYP3A activities have a major effect on oxycodone analgesic efficacy and safety. *Br J Pharmacol*. 2010; 160:919–930. [PubMed: 20590588]
28. Schulte H, Graven-Nielsen T, Sollevi A, Jansson Y, Arendt-Nielsen L, Segerdahl M. Pharmacological modulation of experimental phasic and tonic muscle pain by morphine, alfentanil and ketamine in healthy volunteers. *Acta Anaesthesiol Scand*. 2003; 47:1020–1030. [PubMed: 12904196]
29. Staahl C, Drewes AM. Experimental human pain models: a review of standardised methods for preclinical testing of analgesics. *Basic Clin Pharmacol Toxicol*. 2004; 95:97–111. [PubMed: 15447733]
30. Vanderweeen L, Oostendorp RA, Vaes P, Duquet W. Pressure algometry in manual therapy. *Man Ther*. 1996; 1:258–265. [PubMed: 11440515]
31. Validity of an electronic pressure algometer. *International Journal of Osteopathic Medicine*. 2007; 10:24–28.

Perspective

To understand sensitivity to opioid analgesia in opioid dependent individuals, this article describes experimental pain, subjective and physiological responses during stabilization onto, and after six weeks of, oxycodone maintenance. Oxycodone produced euphoric effects and miosis with limited evidence of analgesia.

Highlights

- Persons with opioid dependence underwent pain testing during oxycodone maintenance.
- Analgesic testing occurred at stabilization and 6 weeks later.
- Oxycodone produced euphoric effects and miosis without robust analgesia.
- Clinicians should consider differential tolerance when treating pain and OUD.

Figure 1.

Behavioral (top row) and pain VAS (bottom row) for Pressure Pain Test (left) and Cold Pressor Test (right) after six weeks of oxycodone maintenance, before (i.e. -20) and after (1, 2 & 3 hours) drug administration (0, 30, and 60mg oxycodone). Data are means with unidirectional standard error bars. Two-factor linear models (dose, time) showed a significant main effect of time for Pressure Pain Test Tolerance, ($F[3,30] = 3.5, p=.027$), with Tolerance decreasing as session progressed. There were also time effects for the two pain VAS measures for the Pressure Pain Test, “Intense”: $F = 3.1, p=.042$ and “Unpleasant”: $F = 3.0, p=.048$, with both increasing as session progressed. There were no significant effects of dose or time for the Cold Pressor Test (right half of figure).

Figure 2.

Subjective and physiological outcomes collected before (i.e. -20) and after (1, 2 & 3 hours) drug administration (0, 30, and 60mg oxycodone). Data are means with unidirectional standard error bars. Two-factor linear models (dose, time) showed significant dose $\times$ time interactions for all measures (“Like”: $F[22,220] = 1.7$, $p=.034$; street value $F[20,200] = 2.1$, $p=.007$; and pupil diameter: $F[22,220] = 2.1$, $p=.003$). Main effects of dose for “Like” and street value trended toward significance $p=.082$ and $p=.065$, respectively and were significant for pupil diameter ($F[2,20] = 10.2$, $p=.001$). There was a significant effect of time for all outcomes (“Like”: $F[11,110] = 10.4$, $p<.0001$; street value $F[10,100] = 10.2$, $p<.0001$; and pupil diameter $F[11,110] = 4.3$, $p<.0001$).

Table 1**Session Timing and Outcome Measures**

	Initial Stabilization Phase	Chronic Dosing Phase
Total number of sessions	3 (1/day on consecutive days)	3 (1/day at least 48 h apart)
Time of sessions	12:30–2:30 PM	11:30–3:30 PM
Time of drug administration	12:00 PM	12:00 PM
Double-blind test dose administered (oxycodone mg, p.o.)	30	0, 30, 60 (randomized order)
Time of experimental pain testing (relative to drug administration)	1 & 2 h	–20 min, 1, 2 & 3 h
<i>Session Outcomes</i>		
Experimental pain	PPT/CPT Threshold, Tolerance, and Pain VAS	PPT, CPT Threshold, Tolerance, and Pain VAS
Abuse liability	None	Adjective Rating Scale (subject-and observer-rated), Drug Effect VAS
Physiologic	None	Pupil diameter, EtCO ₂
Number of times PPT administered per timepoint (total times administered per session)	2 (4)	2 (8)
Number of times CPT administered per timepoint (total times administered per session)	1 (2)	1 (4)

Volunteers were maintained on oral oxycodone 30 mg/qid (8 AM and 12, 6, 10 PM) throughout the study. On session days, the 12:00 maintenance dose was substituted with the test dose indicated above. SOWS was collected at 9:00 prior to each session day. PPT indicates Pressure Pain Test. CPT indicates Cold Pressor Test.

Table 2

Participant Demographics and Substance Use Characteristics *

	mean (s.e.m.)
Age (years)	28.4 (1.5)
Females (n = 4)	
Education (years)	11.7 (0.4)
Weight (kg)	65.2 (2.7)
Number of cigarettes smoked per day (n = 10)	16.1 (2.1)
Number of days in the last 30 use of:	
Any opioids	27.7 (1.0)
Short-acting prescription opioids	18.7 (3.3)
Heroin (n = 5)	23.6 (4.1)
Cocaine (n = 1)	1.0 (0.0)
Benzodiazepines (n = 8)	1.4 (0.2)
Marijuana (n = 6)	10.0 (4.4)
Alcohol (n = 5)	4.2 (2.7)
Lifetime years of regular (at least once per week) use of:	
Short-acting prescription opioids	8.1 (1.4)
Heroin (n = 5)	3.0 (0.5)
Cocaine (n = 5)	2.6 (0.3)
Benzodiazepines (n = 7)	3.3 (0.7)
Marijuana (n = 9)	7.9 (1.6)
Alcohol (n = 9)	4.5 (1.3)

*
n = 11 unless otherwise noted.

Table 3

Peak Maximum Threshold, Tolerance, and Subjective Pain VAS Ratings

	Initial Stabilization Phase			Chronic Dosing Phase
	Day 1	Day 2	Day 3	30mg Session
Pressure Pain Test:				
Threshold (kPa)	624.1 (81.5)	606.1 (83.0)	622.2 (69.9)	598.9 (88.9)
Tolerance (kPa)	1000.8 (113.1)	946.5 (93.0)	955.0 (100.2)	866.8 (105.3)
VAS "Intense"	41.5 (6.2)	48.4 (6.5)	50.5 (6.6)	33.8 (6.2)*
VAS "Unpleasant"	45.0 (7.4)	50.4 (7.2)	52.0 (6.8)	39.6 (6.4)
Cold Pressor Test:				
Threshold (sec)	8.9 (1.2)	10.0 (1.8)	10.6 (1.9)	9.0 (1.5)
Tolerance (sec)	20.9 (3.0)	23.3 (4.2)	23.8 (5.0)	19.2 (5.0)*
VAS "Intense"	66.3 (7.4)	67.4 (7.3)	66.7 (7.8)	58.6 (9.8)
VAS "Unpleasant"	73.0 (7.2)	72.9 (7.2)	70.9 (7.5)	66.4 (9.5)

Data are means (s.e.m). PPT n=11, CPT n=10. Peaks analysis proceeded in two steps. Peak values were first compared across Initial Stabilization Phase Sessions on Days 1, 2 & 3 only. Bolded values indicate significant Tukey post hoc compared to Initial Stabilization Phase test session on Day 1 ($p<.05$).

To assess changes in pain responding across both study phases, peak values were calculated from all comparable (30mg oxycodone administered 1 & 2 h before pain testing) test session days.

* indicates significant Tukey post hoc compared to the Initial Stabilization Phase test session on Day 3 ($p<.05$).

Table 4

Peak Measures for Analgesic and Non-Analgesic Opioid Effects During Chronic Dosing Phase

	Oral Oxycodone		
	0 mg	30 mg	60 mg
<i>Peak Maximum:</i>			
Pressure Pain Test			
Threshold (kPa)	532.4 (68.9)	600.2 (88.5)	639.9 (88.5)
Tolerance (kPa)	777.2 (68.9)	871.0 (104.6)	914.3 (103.3)
VAS How Intense?	45.2 (7.0)	38.2 (6.0)	41.4 (8.5)
VAS How Unpleasant?	47.7 (7.2)	44.5 (6.2)	46.0 (9.0)
Cold Pressor Test			
Threshold (sec)	8.0 (1.3)	9.4 (1.5)	10.1 (1.5)
Tolerance (sec)	15.9 (2.0)	19.5 (4.5)	29.6 (11.2)
VAS How Intense?	66.1 (8.9)	61.9 (9.8)	64.8 (9.7)
VAS How Unpleasant?	72.4 (9.2)	70.6 (9.6)	73.1 (10.2)
Drug Effect VAS			
Any Drug Effect	12.2 (6.0)	27.8 (7.4)	42.5 (7.2)
High	11.5 (6.3)	28.1 (7.7)	42.2 (7.3)
Like	13.1 (6.8)	28.0 (7.8)	41.3 (7.6)
Good	12.5 (6.2)	28.4 (7.7)	41.8 (7.5)
Street value (\$)	7.5 (4.1)	16.6 (5.3)	26.9 (6.4)
Subjective opioid adjectives			
Agonist scale total score	6.1 (1.3)	8.5 (1.6)	10.3 (1.8)
Observer opioid adjectives			
Agonist scale total score	5.0 (0.5)	7.0 (0.9)	10.5 (1.4) *
End tidal CO ₂ (mm Hg)	41.4 (1.4)	43.5 (1.2)	44.5 (1.3)
<i>Peak Minimum:</i>			
Pupil diameter (mm)	3.6 (0.3)	2.6 (0.1)	2.5 (0.1)
OOWS (total)	0.8 (0.2)	0.2 (0.1)	0.2 (0.1)

Data are means (s.e.m.). Peak CPT Tolerance and all non-analgesic outcomes had a significant main effect of dose ($p < .05$). Bolded values indicate a significant post hoc compared to placebo.

* indicates a significant post hoc compared to 30 mg oxycodone.