## Title

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# Analgesic Effects of Hydromorphone versus Buprenorphine in Buprenorphine-Maintained Individuals

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## Abstract

**Background:** Managing acute pain in buprenorphine-maintained individuals in emergency or perioperative settings is a significant challenge. This study compared analgesic and abuse liability effects of adjunct hydromorphone and buprenorphine using quantitative sensory testing, a model of acute clinical pain, in persons maintained on 12–16 mg sublingual buprenorphine/naloxone.

**Methods:** Participants (N=13) were enrolled in a randomized within-subject double blind, placebo controlled three-session experiment. Each session used a cumulative dosing design with four intravenous (IV) injections (4mg+4mg+8mg+16mg hydromorphone or 4mg+4mg+8mg +16mg buprenorphine); quantitative sensory testing and abuse liability assessments were measured at baseline and after each injection. The primary analgesia outcome was change from baseline cold pressor testing; secondary outcomes included thermal and pressure pain testing, as well as subjective drug effects and adverse events.

**Results:** A significant two-way interaction between study drug condition and dose was exhibited in cold pressor threshold ($F_{10,110}$ =2.14, p=0.027) and tolerance ($F_{10,110}$ =2.69, p=0.006). Compared to placebo, participants displayed increased cold pressor threshold from baseline following cumulative doses of 32mg of IV hydromorphone (M±SD) (10±14sec, p=0.035) and 32mg buprenorphine (3±5sec, p=0.0.39), and in cold pressor tolerance following cumulative doses of 16mg (18±24sec, p=0.018) and 32mg (48±73sec, p=0.041) IV hydromorphone; cold pressor tolerance scores were not significant for 16mg (1±15, p=0.619) or 32mg (7±16, p=0.066) buprenorphine. Hydromorphone and buprenorphine compared to placebo showed greater ratings on subjective measures of *High*, any *Drug Effects*, *Good Effects*, and drug *Liking*. Adverse events were more frequent during the hydromorphone compared to buprenorphine and placebo conditions for nausea, pruritus, sedation, and vomiting.

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**Conclusion:** In this acute clinical pain model, high doses of IV hydromorphone (16–32mg) were most effective in achieving analgesia, but also displayed higher abuse liability and more frequent adverse events. Cold pressor testing was the most consistent measure of opioid-related analgesia.

## Summary Statement:

In buprenorphine maintained patients, doses of ≥16mg of hydromorphone may be necessary to treat acute pain, and adjunct buprenorphine may be effective to a lesser extent. However, high doses of hydromorphone confer increased risk of abuse liability.

### Keywords

Buprenorphine; analgesia; opioid; acute pain; hydromorphone; opioid use disorder

## Introduction

An increasing number of people are prescribed buprenorphine as a treatment for opioid use disorder, . Buprenorphine is effective at reducing the risk of overdose death and reducing craving for illicit opioids, , yet there are several clinical challenges in buprenorphine treatment including the management of acute pain. Acute moderate to severe pain is quite common in persons on opioid replacement therapy, , and given that the prevalence of opioid use disorder in older Americans is projected to rise in the coming years (and these individuals are more likely to undergo surgeries) , there is a need to develop medication strategies for acute analgesia in buprenorphine-maintained individuals. The same factors that make buprenorphine an excellent opioid use disorder treatment– for instance it is a partial agonist with high affinity and slow dissociation from the μ opioid receptor , – can be barriers to effective acute pain management in perioperative and/or emergency situations . In fact, experts in surgery , anesthesia , and emergency medicine have called for more research in this area.

Researchers have examined pharmacologic characteristics of buprenorphine in persons with opioid use disorder. For example, higher dose buprenorphine can prevent opioid withdrawal and dampen hydromorphone effects for up to 72 hours, . One study showed under double-blind conditions, that hydromorphone subjective drug effects (e.g. drug “liking” and “high”) were attenuated up to 98 hours after buprenorphine dosing . Additional parenteral buprenorphine (up to 16 mg) has been shown to produce euphoria in individuals maintained on 8 mg daily buprenorphine but this self-reported high was not as great as with hydromorphone (up to 18 mg) . Synthesizing these studies, maintenance buprenorphine does produce a long lasting and dose-dependent blockade of hydromorphone euphorogenic effects; but this blockade is incomplete and can be overcome. It is unclear if these results would translate to acute analgesia.

Quantitative sensory testing is a validated experimental model of acute pain, and has been used in the development of novel analgesic agents. Quantitative sensory testing includes standardized acute exposures to hot or cold temperatures as well as pressure algometry applied to the skin, and correlates with acute opioid pain relief achieved during clinical treatment in the emergency room and post-operatively. However, quantitative sensory testing has rarely been used to examine analgesic response in patients with opioid use disorder, .

The current study utilized a double-blind, placebo-controlled human laboratory design to compare the analgesic effects of intravenous (IV) hydromorphone and IV buprenorphine on quantitative sensory testing in buprenorphine-maintained patients. Given the controversy surrounding whether or not to stop buprenorphine prior to surgery, we decided to standardize the time since maintenance dose and focus only on analgesic response to increasing doses of opioids. We hypothesized that hydromorphone, a full μ-opioid agonist, would provide superior analgesia compared to buprenorphine given prior work on abuse liability, and that both hydromorphone and buprenorphine would provide superior analgesia compared to placebo. Moreover, we postulated that hydromorphone would elicit greater abuse liability, and that an association would emerge regarding abuse liability and analgesia for both IV hydromorphone and IV buprenorphine.

## Methods

### Study Design

This study utilized a double blind, placebo-controlled within-subjects design and was conducted on a supervised residential research unit. Participants were maintained on 12 or 16mg SL buprenorphine/naloxone (doses within the recommended range for maintenance) throughout the study. The order of the three experimental sessions (hydromorphone, buprenorphine, or placebo) was randomized by an unblinded study pharmacist, and sessions occurred at least seven days apart to allow for a drug washout period as well as to reduce likelihood of illicit drug relapse. Each residential session began 17 hours after maintenance dose - baseline measures occurred at 9:00 AM and first IV drug administration at 10:00 AM - to control for both the effect of circadian rhythms as well as time since maintenance dose. Participants had observed dosing of SL buprenorphine/naloxone by a study nurse the night before each session; each participant's treatment provider was contacted and the Maryland Prescription Drug Monitoring Program was also reviewed to confirm ongoing maintenance dose. Participants were also monitored overnight after sessions to ensure resolution of opioid agonist effects. Buprenorphine/naloxone dose was held on session day to reduce risk of opioid toxicity.

### Participants

Medically stable participants (n=13) that were maintained on buprenorphine/naloxone (12 or 16mg) for opioid use disorder completed three residential experimental sessions, which each lasted 40 hours. This study was registered on clinicaltrials.gov (NCT01642030). Specimens, records, and data were obtained at the Johns Hopkins Bayview Medical Center, and the Johns Hopkins Institutional Review Board approved this study.

Inclusion criteria for the study were as follows: (1) age 18–60; (2) opioid dependence according to the Mini International Neuropsychiatric Interview for DSM-IV (MINI) ; (3) urine toxicology negative for drugs of abuse but positive for opioid maintenance agent (only at session admission); (4) stable buprenorphine dose (12–16 mg) for the past 30 days; (5)

absence of acute/chronic pain as determined by medical history and physical examination and score of 0 on pain visual analog scale (VAS) at the start of experimental sessions; (6) able and willing to perform/tolerate pain procedures. Exclusion criteria for the study were: (1) current alcohol dependence; (2) medical or psychiatric condition known to influence quantitative sensory testing (i.e., HIV, peripheral neuropathy, schizophrenia, untreated current episode of Major Depressive Disorder, and Raynaud's syndrome); (3) current use of prescribed or over the counter analgesic agents; (4) previous allergic reaction to hydromorphone or buprenorphine; (5) women who were pregnant, lactating or planning to get pregnant during the course of the study.

## Study Drugs

Hydromorphone was purchased from McKesson Corporation (San Francisco, CA) through the inpatient pharmacy at Johns Hopkins Bayview Medical Center (Baltimore, MD). Buprenorphine/naloxone SL filmstrips (maintenance dosing) as well as buprenorphine powder for IV drug preparation was supplied by Indivior (Richmond, VA). Both study drugs were stored in locked cabinets at room temperature in the Behavioral Pharmacology Research Unit Pharmacy (Baltimore, MD). Hydromorphone, buprenorphine, or placebo was prepared on the morning of experimental sessions by BPRU pharmacy staff and study investigators were blind to the drug being given. The study physician administered study drugs via slow IV push over a 5-minute period.

## Experimental Sessions

Each of three blinded experimental sessions included quantitative sensory testing and abuse liability assessments completed at baseline and at 4 time points corresponding to expected peak dose effects of IV hydromorphone and buprenorphine, as well as at 2 additional time points after the last dose to measure waning analgesic response (total 7 time points). This study used a cumulative dose design, commonly used in abuse liability studies[-] to mimic clinical practice in treatment of acute pain in the emergency department and post-operatively. Hydromorphone total dose was 32mg IV (4+4+8+16 mg individual doses given 90 minutes apart) and buprenorphine total dose was also 32mg IV (4+4+8+16 mg individual doses given 90 minutes apart).

Prior to each session, a nurse inserted an IV catheter in the non-pain-testing arm. At 9:00 AM, participants underwent baseline quantitative sensory testing and abuse liability testing (this battery lasted approximately 30–45 minutes). At 10:00 AM, 11:30 AM, 1:00 PM, and 2:30 PM, a physician administered either hydromorphone, buprenorphine, or placebo via slow IV push over 5 minutes. Placebo administration was utilized to control for expectation bias and the known placebo analgesic effect of an IV drug administration related to release of endogenous opioids. Quantitative sensory and abuse liability testing began 15 minutes post-injection during each of the three sessions (when active drugs reach peak effect)[,] . The battery of testing was also repeated at 4 PM and 5:30 PM. There were 7 sessions (out of a total of 39), which started a mean (SD) of 30.9 (13.0) minutes later due to weather, physician availability, or other unforeseen circumstance; however, the timing of each study medication dose was kept 90 minutes apart.

## Physiological measures

Physiological measures included vital signs (pulse, blood pressure, and respiration rate) percent oxygen saturation, and pupil diameter. Vital signs and percent oxygen saturation were measured by trained medical staff at baseline and every minute during the 5 minutes of each study drug administration as well as the 5 minutes after drug administration to ensure safety of the participant. Between injections and until end of study session, vital signs and percent oxygen saturation were measured every 15 minutes. Pupil diameter was assessed by research staff with a digital pupilometer (Neuroptics, Inc.) in constant room lighting at baseline and at each time point. Measurements were not dark-adapted.

## Quantitative Sensory Testing

Trained research staff, following standardized protocol developed prior to study initiation, measured all quantitative sensory testing outcomes. Prior to performing quantitative sensory testing with study participants, research staff were required to show high agreement with the lead study investigator (DAT).

**Cold pressor test:** The participant placed their hand up to the wrist in a circulating water bath (Versa Cool, Thermo Fisher Scientific, Waltham, MA) maintained at approximately 4°C (up to 5 minutes). The amount of time in seconds between the first contact with cold water and the first instance of self-reported pain was defined as the *threshold.* The time a participant's hand remained underwater before pain was unbearable was defined as *tolerance.* The cold pressor test is specifically validated to evaluate the analgesic effects of opioids, and was the primary outcome in this study.

**Pressure pain:** An electronic algometer (Somedic; Horby, Sweden) with a 1cm$^2$ hard rubber probe was used to assess responses to noxious mechanical pressure on the trapezius and thumb[,] . Pressure was gradually increased at a constant rate (30kPA/sec). Pressure pain *threshold* was defined as the pressure (kPA) at which the participant reported pain, and the average threshold across two trials was calculated.

**Thermal pain:** Contact heat stimuli (at non-tissue damaging temperatures) was delivered using a peltier-element-based stimulator on the dorsal forearm of the arm without the IV (Medoc PATHWAY Model CHEPS, Ramat Yishai, Israel). The thermode's temperature gradually increases 0.5$^{o}$C/sec from a pre-set baseline (31$^{o}$C) until no longer tolerated (max 51 $^{o}$C). The thermal pain *threshold* was defined as the temperature ($^{o}$C) at which the participant first reported pain, and thermal pain *tolerance* was defined as the temperature at which the pain became unbearable. Threshold and tolerance scores were averaged across two trials for each time point.

## Abuse Liability Assessments

**Visual analog scales (VAS):** Single item questions that assessed subjective drug effects were entered into a computer by the participant positioning an arrow along a 100-mm line marked at either end with "none" (0) and "extremely" (100). Questions included: (1) How high are you?; (2) Do you feel any drug effects?; (3) Does the drug have any good effects?; (4) Does the drug have any bad effects?; (5) Do you like the drug?; and (6) Does this drug make you feel sick? The Food and Drug Administration recognize the peak effects of “Liking” as the primary outcome in abuse liability research.

**Money vs. Drug Questionnaire:** Participants were asked to indicate on a sliding scale a monetary value above which they would prefer money and below which they would prefer the drug they received during the experimental session, . This question was asked once at the end of the session and again on the following day.

**Next Day Questionnaire.—**On the day after the experimental session, participants were asked to reflect on their overall session experience and answer a series of questions on the study drug effects, including (1) Rate the overall strength of the drug effect you experienced yesterday; (2) How well did you like the drug you received yesterday?; (3) Did you feel any good effects from the drug yesterday?; (4) Did you feel any bad effects from the drug you received yesterday?; and (5) Rate the degree to which you would like to take again yesterday’s drug. Participants were also asked to estimate the amount of money the drug would be worth on the street, .

### Statistical Analysis

An a priori power analysis was based upon prior work examining euphorogenic effects of parenteral buprenorphine and hydromorphone versus placebo in buprenorphine maintained individuals, as no similar work has examined opioid analgesia in this population. Using the statistical analysis plan described below, the power analysis estimated 80% power to detect session effect sizes of 0.23 or greater with a sample size of 30. For each quantitative sensory testing, physiological, and abuse liability outcome, a two-way repeated measures ANOVA with a Bonferroni adjustment for main effects was utilized to measure within subject differences between experimental conditions (hydromorphone, buprenorphine, and placebo) across time points; given a significant interaction between experimental condition and time, a one-way repeated measures ANOVA with a Bonferroni posthoc adjustment was utilized by each time point. All quantitative sensory testing data were adjusted to change from baseline scores. Raw data for peak quantitative sensory testing analgesia, peak minimum session physiological data, and peak abuse liability assessments, were also analyzed via one-way repeated measures ANOVA with Bonferroni adjustment. Fisher’s exact tests were used to determine differences between sessions regarding adverse events. Missing data were excluded case wise and not interpolated; alpha levels for significant findings were set at $p<.05$ and analyses were conducted using SPSS version 24.0.

## Results

Participants were recruited between 2013–2017 from Baltimore-area buprenorphine providers. Sixty-seven persons presented for an in-person screening and 33 (49%) qualified to be in the study (Figure 1). Of those who qualified, 17 were randomized and received at least one dose of study medication. Four participants did not complete all three sessions. Their information was included in the analysis of adverse events (safety) but not in the analysis of QST and abuse liability outcomes. Of these four, one person was withdrawn due to inability to obtain venous access for the 3rd session; one person was withdrawn as they stopped their buprenorphine program after the first session, and two others were lost to follow-up.

Participants who completed the study (N=13) had a mean (SD) age of 43 years (11), a mean (SD) body mass index of 27 (4), were primarily male (69%) and African American (69%). Participants had been on buprenorphine maintenance for a mean (SD) of 8 (11) months. Lastly, the majority of study completers (77%) were current smokers.

### Analgesia outcomes (quantitative sensory testing)

The pre-specified primary quantitative sensory testing outcome was cold pressor tolerance, as this has shown the greatest ability to predict opioid analgesia. Participants displayed a significant two-way interaction in cold pressor threshold ($F_{10,110} = 2.14$, p=0.027) and tolerance ($F_{10,110} = 2.69$, p=0.006), which was attributed to increased cold pressor threshold and tolerance during the hydromorphone compared to the placebo condition, and increased cold pressor threshold in the buprenorphine compared to placebo condition (Figure 2).

There were no significant differences regarding change from baseline scores in pressure pain threshold ($F_{10,110} = 1.06$, p=0.399), thermal pain threshold ($F_{10,110} = 0.90$, p=0.534), or thermal pain tolerance ($F_{10, 110} = 1.68$, p=0.095) (Figure 3). Within session baseline and peak outcomes from each task are listed in Table 1.

## Physiological Outcomes

Participants displayed a significant two-way interaction in percent oxygen saturation ($F_{10,110} = 3.44$, p=0.001), with reduced percent oxygen saturation after 16mg cumulative dose of buprenorphine, and after 16mg and 32mg cumulative doses of hydromorphone, relative to placebo (Figure 4). There were no significant two-way interactions in heart rate or blood pressure across time points. Differences in session minimum blood pressure can be found in Table 1. Participants displayed a significant two-way interaction in change from baseline pupil diameter ($F_{10,110} = 4.99$, $p<0.001$). As expected, participants displayed a larger decrease in pupil diameter (miosis) in the hydromorphone condition relative to buprenorphine or placebo, and in the buprenorphine condition relative to placebo (Figure 4); although the mean pupil size was not pinpoint, demonstrating the ongoing blocking effect of maintenance buprenorphine.

## Abuse Liability Outcomes

There were no significant two-way interactions among the abuse liability assessments across time points. There were significant differences in peak effects (following 32mg of either hydromorphone or buprenorphine) for *High, Drug Effect, Good Effect,* and *Liking,* but not for *Bad Effects* or *Sick* (see Table 2 for details). One day after sessions, participants endorsed different levels of *desire to take drug again* in the hydromorphone (mean ± standard deviation) 61±34, buprenorphine 46±37, and placebo 21±35 sessions ($F_{2,11}$=5.85, p=0.021); pairwise comparisons revealed that desire to take drug again was greater in hydromorphone (p=0.011) and buprenorphine (p=0.010) conditions compared to placebo. Participants also endorsed different levels of *street value ($)* in the hydromorphone

30.4±24.6, buprenorphine 25.2±26.5, and placebo 5.8±7.0 sessions ($F_{2,11}$=5.30, p=0.031); pairwise comparisons revealed that *street value* was greater in hydromorphone (p=0.009) and buprenorphine (p=0.03) conditions compared to placebo. Finally, participants endorsed different levels of *willingness to pay* for the drug in the hydromorphone 15.4±14.6, buprenorphine 16.7±17.3, and placebo 5.0 ±6.5 sessions ($F_{2,11}$=7.19, p=0.012); pairwise comparisons revealed that willingness to pay was greater in hydromorphone (p=0.005) and buprenorphine (p=0.037) conditions compared to placebo.

### Adverse Events

Despite the high doses of opioids given in this study, there were no serious adverse events and the adverse events that were reported are common among individuals utilizing opioids for pain (e.g. nausea, somnolence, and dry mouth). Although rescue medication (naloxone) was available, it was never used. There were adverse events reported within each condition. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) . In the hydromorphone condition, the most common adverse events were nausea (61.5%) and somnolence (53.8%) (Table 3). In the buprenorphine condition, the most common adverse events were somnolence (53.8%) and dry mouth (30.8%). In the placebo condition, the most common adverse events were fatigue (15.4%) and somnolence (15.5%). A full list of adverse events can be found in Table 3. Although these results suggest that patients on buprenorphine may tolerate larger opioid doses safely during the treatment of acute pain, the participant population was relatively healthy with few co-occurring diseases and few, if any, concomitant medications

## Discussion

### Major Findings: Analgesia versus Abuse Liability

This study reports on the analgesic properties of cumulative doses of IV hydromorphone and buprenorphine for individuals maintained on buprenorphine/naloxone. The results suggest that ≥16mg of hydromorphone are necessary to provide analgesia during experimental pain testing; doses at or above the cumulative dose of 16mg were sufficient to increase cold pressor threshold and tolerance compared to placebo (Figure 2). In clinical situations, high doses of supplemental opioids for this population may be required for pain relief. Our results also suggest that additional IV buprenorphine may be useful in clinical pain management. However, the peak effects of hydromorphone also resulted in increases on abuse liability indices, most notably increased *Drug Effects, High, Good Effects, and Liking* (Table 2). Moreover, participants in the hydromorphone and buprenorphine conditions endorsed other indices of abuse liability following the session, including greater desire to take the drug again, street value of the drug, and willingness to pay for the drug. The balance between analgesia and abuse liability is particularly important in this population with opioid use disorder, and patients should be informed prior to use if possible that the opioid medication could trigger relapse. In this study, additional IV buprenorphine showed significant analgesic effects on cold pressor threshold (although not as robust as hydromorphone), suggesting that buprenorphine could be used as an option where the risks of full μ opioid agonists outweigh the potential analgesic benefits. On the other hand, while not statistically significant, a cumulative dose of 32mg hydromorphone provided marginally increased cold pressor threshold and tolerance compared to 32mg buprenorphine, which may be clinically significant (Figure 2).

The similarity in analgesic results between hydromorphone and buprenorphine was quite surprising, as each dose of buprenorphine was predicted to result in up to four times greater analgesia as hydromorphone given standard opioid conversion tables. These conversion tables are often developed from studies in opioid naïve individuals, and may not account for receptor efficacy in full versus partial agonist opioids. This study provides further evidence that these conversion tables should be used with caution in buprenorphine maintained individuals. In addition, analgesia and subjective effects lasted for much longer than predicted, with most patients reporting some degree of ongoing subjective drug effect 3 hours after last study medication administration. In addition, significant analgesia was still present 3 hours after last hydromorphone injection as indicated by increase in baseline cold pressor tolerance (Figure 2). Although buprenorphine has a greater inter-individual variability in elimination half-life, no lingering analgesia was seen in any modality 3 hours after last buprenorphine injection.

## Clinical versus Experimental Considerations

There were no serious adverse events, and the reported adverse events are common among individuals utilizing opioids for pain (e.g., nausea, somnolence, dry mouth) . It is noteworthy that participants tended to experience more adverse events in the hydromorphone condition (Table 3). In addition, there were significant decreases in minimum systolic and diastolic blood pressure in the buprenorphine versus placebo condition, and decreased diastolic blood pressure in the buprenorphine versus hydromorphone condition. Previous studies have shown that opioid tolerance leads to dampened neuro-hormonal signaling that can result in insensitivity to high doses of full μ opioid agonists, . Furthermore, 16mg and 32mg of hydromorphone or buprenorphine did result in significant decreases in oxygen saturation compared to placebo (Figure 4), a vital sign that should be closely monitored when administering high doses of opioid agonists. Although unknown, it is likely that as the length of time since buprenorphine dose increases beyond 17 hours, the analgesic benefits as well as the risks of IV hydromorphone would increase. Future studies could examine the time since buprenorphine dose and the response to IV opioids using similar rigorous methods, to assess whether clinical recommendations to stop buprenorphine prior to elective surgery might result in greater analgesic control with less opioid medication.

From an experimental standpoint, the finding that cold pressor testing was the most sensitive measure in discerning the analgesic effects of hydromorphone and buprenorphine is important for future studies in persons maintained on buprenorphine (Figure 2/Table 1). Cold pressor testing has been used across studies to model opioid analgesia, as it has shown sensitivity to a wide variety of opioids and is reliable over multiple testing sessions, . In addition, cold pressor testing has previously been utilized in buprenorphine maintenance to examine hyperalgesia. In the current study, other measures of pain testing were not significant regarding change from baseline scores (Figure 3), although raw peak scores from thermal pain tolerance were significantly higher in the hydromorphone compared to buprenorphine condition (Table 1). Cold pressor testing has been widely used to model acute musculoskeletal pain, . Musculoskeletal pain is commonly reported in accidental injury, and can often lead to chronic pain conditions. The cold pressor test has been shown to be more sensitive in discerning analgesic effects than heat or electrical stimulation in a study comparing two doses of transdermal fentanyl (a full μ opioid receptor agonist) and transdermal buprenorphine compared to placebo. Cold pressor testing has also been reliable in measuring pain in healthy persons as well as those with chronic pain ; this study extends the utility of the cold pressor task to individuals maintained on buprenorphine.

Although there is no consensus within the medical field regarding treatment of acute pain for individuals maintained on buprenorphine, recent guidelines have been suggested in the perioperative period. These guidelines address two main issues, whether to stop buprenorphine prior to surgery and how to optimize additional opioids to improve pain control while limiting risk for respiratory depression. This study did not address the first issue but does provide controlled evidence that doses up to 32 mg IV hydromorphone or IV buprenorphine may be given safely without respiratory depression in select buprenorphine maintained individuals. This finding is specific to persons maintained on 12–16mg sublingual buprenorphine/naloxone for opioid use disorder, who are approximately 17 hours removed from their last dose and in the absence of concomitant medications that may cause further respiratory depression or other negative effects. Determining the dose effects of adjunct opioids on acute pain is an important step in devising treatment strategies for buprenorphine maintained individuals. Future randomized controlled trials should examine the analgesia requirements, surgical outcomes and relapse risk associated with either stopping/reducing buprenorphine prior to elective surgery or continuing maintenance dose.

## Limitations

This study has several limitations. The low number of participants and absence of chronic pain patients in this study limits the generalizability of the results. Previous controlled studies in buprenorphine maintained patients have also utilized small sample sizes and found positive results, and the current study found positive results via the cold pressor task despite recruiting a smaller sample size than suggested by our *a priori* power analysis. In addition, morphine-equivalent doses of hydromorphone and buprenorphine were not used; instead, normally prescribed doses were used, which have more direct clinical implications (comparative effectiveness) but limit the ability to determine comparative efficacy. It is challenging to provide morphine-equivalent doses when comparing a full μ-opioid agonist vs. partial agonist. Commonly used instruments indicate that the relative analgesic ratio for acute IV hydromorphone and IV buprenorphine doses in non-tolerant individuals is 4:1, however, the 1:1 dosing in this study shows results in the opposite direction. Future studies could look at both comparable opioids (including additional sublingual buprenorphine) and non-opioid pharmacotherapies to provide analgesia in this population, such as ketamine, cannabinoid receptor agonists, or anti-inflammatory medications. This study examined treatment of acute experimental pain, not clinical pain. This approach was chosen to enhance control of possible influences of analgesic outcomes and to isolate the study medication dose response curve. Quantitative sensory testing has been shown to closely mimic acute clinical pain and its responsiveness to opioid administration, although future studies should examine optimal pain treatment in clinical settings. Lastly, the timing of buprenorphine/naloxone maintenance dose was held constant in this study. It is probable that the results would have been different if the maintenance dose had been given much closer to experimental sessions or if we waited longer than 17 hours. However, trough levels were utilized to balance risk of respiratory depression with safety of withholding buprenorphine treatment in a stable patient.

## Conclusion

This study provides crucial, controlled experimental evidence concerning pharmacological strategies for acute analgesia in persons maintained on buprenorphine. We report that doses of ≥16mg of hydromorphone were necessary to provide analgesia in this population, and that additional buprenorphine may also be effective. However, high doses of hydromorphone conferred increased risk of abuse liability. The current study demonstrates that high doses of opioids may be necessary to treat acute pain in buprenorphine maintained individuals, however, it is important to note that clinical acumen is necessary to determine safety on a case-by-case basis.

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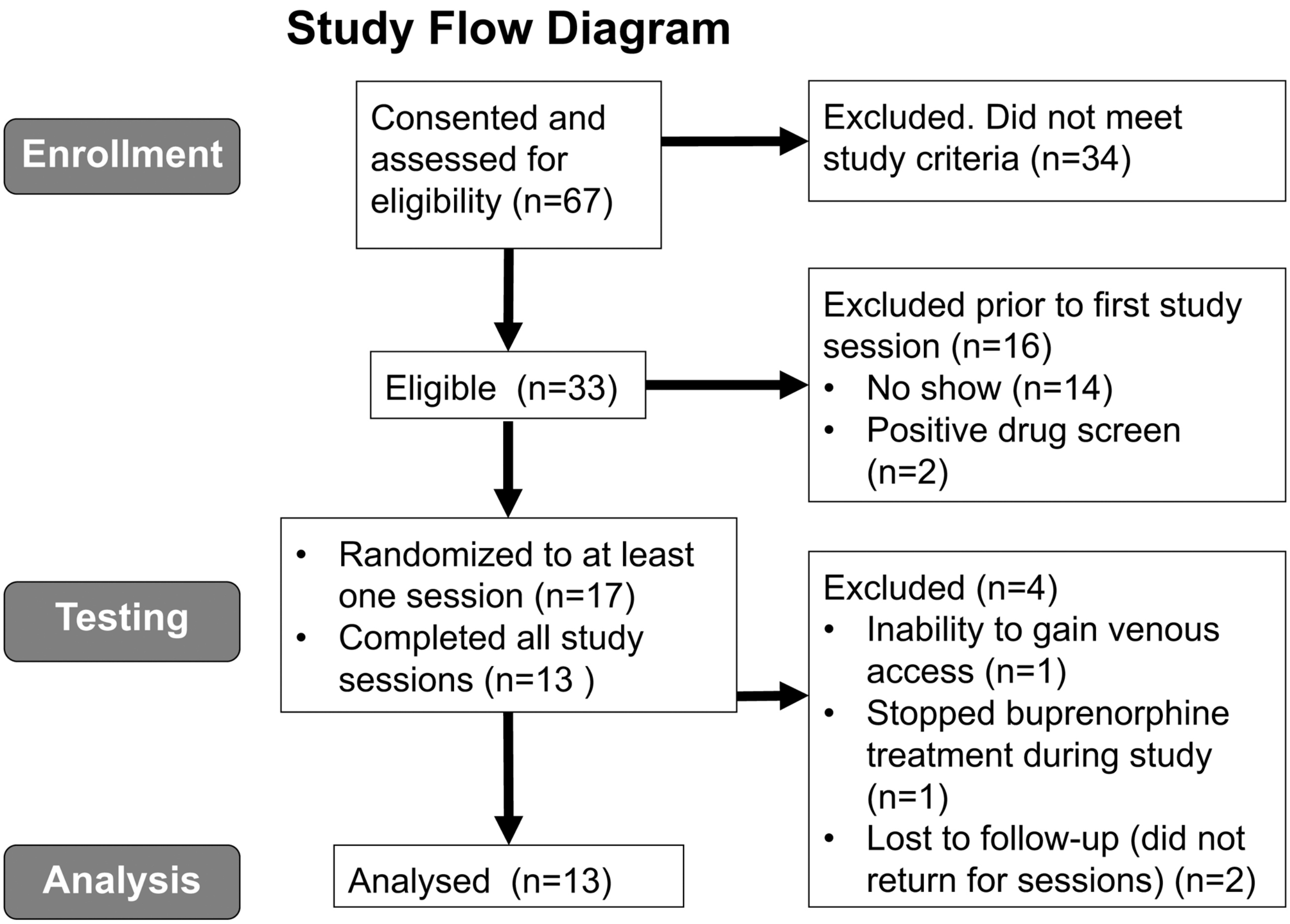

**Figure 1:**

Flow chart of study enrollment, including individuals that were excluded during screening, prior to first study session, and after first study session.

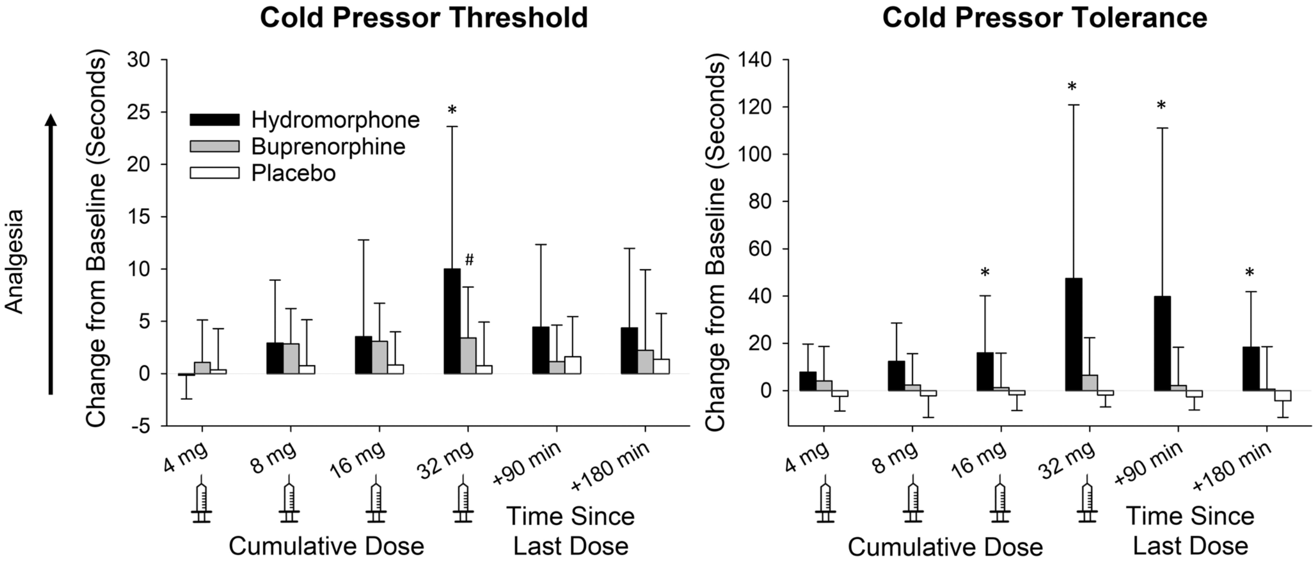

**Figure 2:**

Change from baseline and subsequent mean values for cold pressor testing, which was performed 15 minutes after each injection (4+4+8+16 mg individual doses given 90 minutes apart, corresponding to cumulative doses of 4mg, 8mg, 16mg, and 32mg respectively), as well as 90 and 180 minutes following final drug administration. Repeated-measures ANOVA with Bonferroni correction was used to examine pairwise comparisons at each time point. Bars represent sample means and error bars represent standard deviations. Hydromorphone vs Placebo *=p<0.05; **=p<.01; ***=p<.001. Buprenorphine vs Placebo #=p<.05.

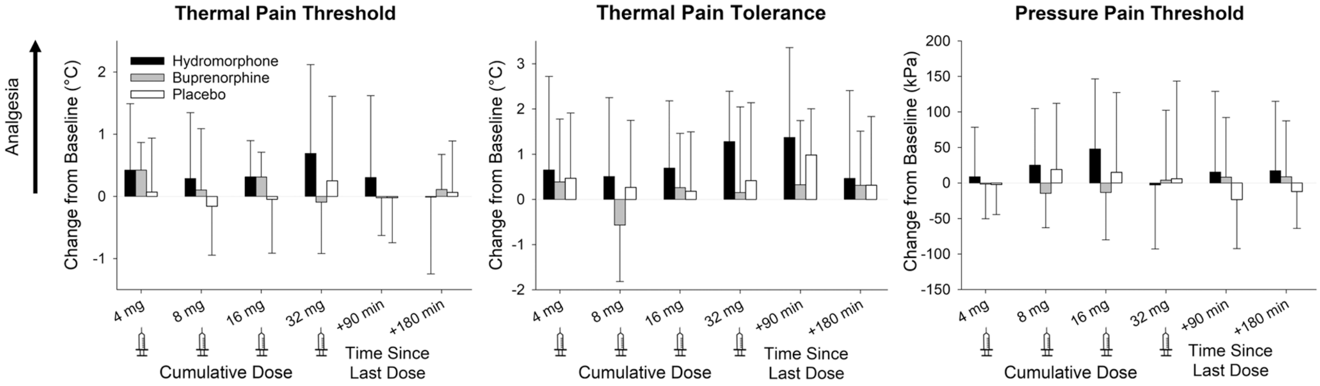

**Figure 3:**

Change from baseline and subsequent mean values for thermal pain and pressure pain, was performed 15 minutes after each injection (4+4+8+16 mg individual doses given 90 minutes apart, corresponding to cumulative doses of 4mg, 8mg, 16mg, and 32mg respectively), as well as 90 and 180 minutes following final drug administration. Repeated-measures ANOVA with Bonferroni correction was used to examine pairwise comparisons at each time point. Bars represent sample means and error bars represent standard deviations. No significant differences were found in these pain testing modalities.

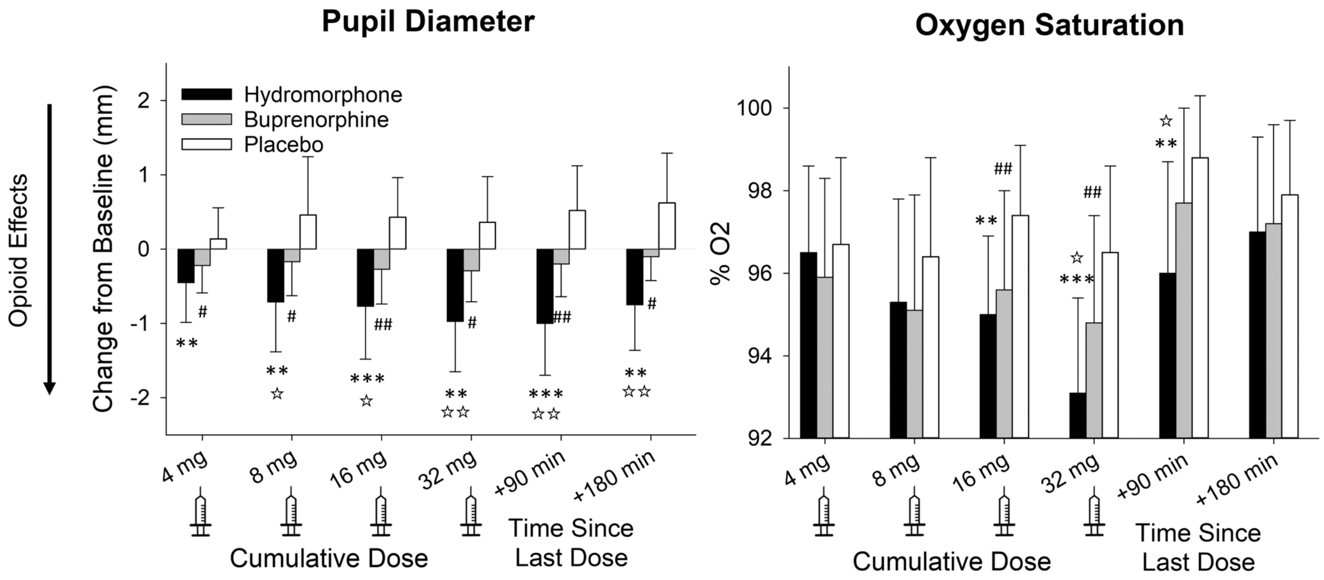

**Figure 4:**

Change from baseline pupil diameter and minimum values for percent oxygen saturation for the 10 minutes surrounding each injection (4+4+8+16 mg individual doses given 90 minutes apart, corresponding to cumulative doses of 4mg, 8mg, 16mg, and 32mg respectively), as well as 90 and 180 minutes following final drug administration. Repeated-measures ANOVA with Bonferroni correction was used to examine pairwise comparisons at each time point. Bars represent sample means and error bars represent standard deviations. Hydromorphone vs Placebo *=p<0.05; **=p<.01; ***=p<.001. Buprenorphine vs Placebo #=p<.05; ##=p<.01. Hydromorphone vs Buprenorphine ☆=p<0.05; ☆☆=p<0.01. Millimeter (mm); percent oxygen saturation (% O2).

## Table 1.

Baseline and Peak Values for Quantitative Sensory Testing and Physiological Measures.

| | Placebo | Buprenorphine | Hydromorphone | F (p value) |
|---|---|---|---|---|
| **Quantitative Sensory Testing** | | | | |
| **Cold Pressor Threshold (Seconds)** | | | | |
| Baseline M ± SD | 11 ± 4 | 13 ± 6 | 12 ± 5 | |
| Peak M ± SD | 12 ± 6 | **16 ± 8**[a] | **22 ± 18**[a] | **4.27 (0.027)** |
| **Cold Pressor Tolerance (Seconds)** | | | | |
| Baseline M ± SD | 33 ± 16 | 35 ± 21 | 30 ± 12 | |
| Peak M ± SD | 32 ± 18 | **42 ± 28**[a] | **79 ± 82**[a] | **4.53 (0.023)** |
| **Thermal Pain Threshold (°C)** | | | | |
| Baseline M ± SD | 42.6 ± 2.7 | 43.2 ± 3.0 | 42.3 ± 3.3 | |
| Peak M ± SD | 43.3 ± 3.1 | 43.4 ± 3.2 | 43.4 ± 3.1 | 0.01 (0.994) |
| **Thermal Pain Tolerance (°C)** | | | | |
| Baseline M ± SD | 46.9 ± 2.2 | 47.1 ± 2.2 | 47.2 ± 2.2 | |
| Peak M ± SD | 47.1 ± 2.2 | 47.0 ± 2.3 | **47.9 ± 2.1**[b] | **4.33 (0.026)** |
| **Pressure Pain Threshold (kPa)** | | | | |
| Baseline M ± SD | 378 ± 110 | 365 ± 143 | 400 ± 133 | |
| Peak M ± SD | 390 ± 158 | 369 ± 158 | 411 ± 116 | 0.62 (0.550) |
| **Physiological Measures** | | | | |
| **Heart Rate** Minimum M ± SD | 54 ± 9 | 55 ± 12 | 55 ± 9 | 0.35 (0.707) |
| **Systolic** Minimum M ± SD | 97 ± 10 | **90 ± 8**[a] | 99 ± 8 | **7.83 (0.004)** |
| **Diastolic** Minimum M ± SD | 59 ± 5 | **52 ± 6**[a] | **58 ± 7**[b] | **10.87 (0.001)** |

Baseline and peak values for quantitative sensory testing. Baseline values were collected approximately 60 minutes before drug administration and peak values were taken after placebo or a cumulative dose of 32mg buprenorphine or hydromorphone. Minimum values for physiological measures represent the lowest measurement during the entire session. Repeated-measures ANOVA with Bonferroni correction shown for comparison between placebo, buprenorphine, and hydromorphone. Mean (M); standard deviation (SD); kilopascal (kPa); visual analogue scale (VAS). Significant differences in **bold**. Difference from placebo

[a] = p<.05

[aa] = p<.01; difference from buprenorphine

[b] = p<.05

[bb] = p<.01.

## Table 2.

Abuse Liability Measures

| | Placebo | Buprenorphine | Hydromorphone | F (p value) |
|---|---|---|---|---|
| **High (VAS 0–100)** | | | | |
| Peak M ± SD | 15 ± 26 | **49 ± 30**[aa] | **65 ± 28**[aaab] | **18.03 (<0.001)** |
| **Drug Effect (VAS 0–100)** | | | | |
| Peak M ± SD | 15 ± 22 | **53 ± 32**[aa] | **75 ± 25**[aaab] | **20.73 (<0.001)** |
| **Good Effect (VAS 0–100)** | | | | |
| Peak M ± SD | 15 ± 22 | **53 ± 35**[aa] | **55 ± 34**[aa] | **13.76 (<0.001)** |
| **Liking (VAS 0–100)** | | | | |
| Peak M ± SD | 16 ± 22 | **50 ± 31**[aa] | **53 ± 37**[aa] | **13.78 (<0.001)** |
| **Bad Effect (VAS 0–100)** | | | | |
| Peak M ± SD | 6 ± 15 | 19 ± 18 | 24 ± 30 | 2.26 (0.128) |
| **Sick (VAS 0–100)** | | | | |
| Peak M ± SD | 5 ± 15 | 11 ± 18 | 20 ± 35 | 1.34 (0.283) |

Session peak values for abuse liability testing were taken after placebo or a cumulative dose of 32mg buprenorphine or 32mg hydromorphone. Repeated-measures ANOVA with Bonferroni correction shown for comparison between buprenorphine, hydromorphone, and placebo. visual analogue scale (VAS); Mean (M); standard error (SE). Significant differences in **bold.** Difference from placebo

[a] = p<.05

[aa] = p<.01

[aaa] = p<.001; difference from buprenorphine

[b] = p<.05.

## Table 3.

Adverse Events

| | Placebo n (%) | Buprenorphine n (%) | Hydromorphone n (%) |
|---|---|---|---|
| Nausea | 0 | 0 | **8 (61.5)**[aaa] |
| Pruritus | 0 | 1 (7.7) | **6 (46.2)**[aa] |
| Sedation | 0 | 3 (23.1) | **6 (46.2)**[a] |
| Vomiting | 0 | 0 | **5 (38.5)**[aa] |
| Somnolence | 2 (15.4) | 7 (53.8) | 7 (53.8) |
| Headache | 1 (7.7) | 3 (23.1) | 6 (46.2) |
| Dry Mouth | 1 (7.7) | 4 (30.8) | 2 (15.4) |
| Urinary Retention | 0 | 1 (7.7) | 2 (15.4) |
| Vision Blurred | 0 | 0 | 2 (15.4) |
| Dyspepsia | 1 (7.7) | 0 | 1 (7.7) |
| Abdominal Pain Upper | 0 | 1 (7.7) | 1 (7.7) |
| Constipation | 0 | 0 | 1 (7.7) |
| Fatigue | 2 (15.4) | 1 (7.7) | 1 (7.7) |
| Dizziness | 0 | 0 | 1 (7.7) |
| Infusion Site Pain | 0 | 2 (15.4) | 0 |
| Swelling | 0 | 1 (7.7) | 0 |
| Confusional State | 0 | 2 (15.4) | 0 |

Columns indicate the frequency counts and percent of participants reporting an adverse event in each study condition. Adverse events were coded according to terms in the Medical Dictionary for Regulatory Activities ("MedDRA"). Fisher's exact test used to identify differences between conditions. Significantly different findings in **bold.**

[a] $=p<0.05$

[aa] $=p<0.01$

[aaa] $=p<0.001$.