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Publication Date

2021-09-01

DOI

10.1016/j.drugalcdep.2021.108869

Peer reviewed

HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2022 October 13.

Published in final edited form as:

Drug Alcohol Depend. 2021 September 01; 226: 108869. doi:10.1016/j.drugalcdep.2021.108869.

Methadone maintenance patients lack analgesic response to a cumulative intravenous dose of 32 mg of hydromorphone

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Abstract

Objectives: Acute pain management in patients with opioid use disorder who are maintained on methadone presents unique challenges due to high levels of opioid tolerance in this population. This randomized controlled study assessed the analgesic and abuse liability effects of escalating doses of acute intravenous (IV) hydromorphone versus placebo utilizing a validated experimental pain paradigm, quantitative sensory testing (QST).

Methods: Individuals ($N = 8$) without chronic pain were maintained on 80-100 mg/day of oral methadone. Participants received four IV, escalating/incremental doses of hydromorphone over 270 minutes (32 mg total) or four placebo doses within a session test day. Test sessions were scheduled at least one week apart. QST and abuse liability measures were administered at baseline and after each injection.

Results: No significant differences between the hydromorphone and placebo control conditions on analgesic indices on any QST outcomes were detected. Similarly, no differences on safety or abuse liability indices were detected despite the high doses of hydromorphone utilized. Few adverse events were detected, and those reported were mild in severity.

Conclusions: The findings demonstrate that methadone-maintained individuals are highly insensitive to the analgesic effects of high-dose IV hydromorphone and may require very high doses of opioids, more efficacious opioids, or combined non-opioid analgesic strategies to achieve adequate analgesia.

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1.1 Introduction

The prevalence of opioid use disorders (OUD) has risen substantially in the United States over the past 20 years, with an increasing number of people receiving life-saving pharmacotherapies such as methadone and buprenorphine (Okie et al., 2010). Despite the enormous clinical benefit of medication-assisted treatment (MAT), providing adequate pain management remains a formidable challenge for this patient population due to high tolerance associated with the long-term use of methadone (Eyler et a., 2013). Mounting preclinical and clinical evidence has demonstrated that repeated exposure to opioids can catalyze a series of anti-analgesic processes and adverse outcomes including nociceptive sensitization (i.e., hyperalgesia), tolerance, and loss of opioid efficacy in many patients (Lee et al., 2011; Sjogren et al., 1994). Cellular alterations associated with these phenomena have been identified at several anatomical sites such as afferent neurons, descending pain modulatory pathways, and neurotransmission within the spinal cord (Gardell et al., 2006., King et al., 2005, Mao et al., 2002). It is quite common for opioid-tolerant individuals to need escalating opioid doses to maintain adequate analgesia (duPen et al., 2007). Clinicians are faced with significant obstacles as they navigate the intricacies of treating their patients' acute pain in outpatient, inpatient (e.g., perioperative and postoperative), and emergency settings (Ballantyne & Shin, 2008). Acute pain needs among opioid-tolerant patients are frequent, with approximately one-fifth to one-third of OUD patients who present for medical and dental procedures requiring acute pain management (Bedard et al., 2017; Dunn et al., 2018; Hilliard et al., 2018; Mudumbai et al., 2016).

Despite the high prevalence of these clinical needs for acute pain control, there are insufficient controlled study data to guide clinical decision-making (Murnion et al., 2020). Due to fears, concerns and misconceptions about drug seeking behavior, inexperience with higher doses of opioid medications, or stigma against patients with substance use disorders, patients with OUD often receive poor pain treatment, particularly in hospital settings (Alford et al., 2006). These practices may lead to inferior pain treatment outcomes. Patients with suboptimal pain control are at higher risk of leaving the hospital or emergency department against medical advice (Simon et al., 2020; Strike et al., 2020), consuming illicit substances while hospitalized, or acting out against medical providers (Summers et al., 2018; Voon et al., 2018). If already on MAT, inadequate pain treatment may also lead to treatment dropout and more catastrophic OUD treatment outcomes including overdose death (Hines et al., 2008).

There is evidence to suggest that among methadone-maintained patients, the treatment of acute pain may be a particularly intractable problem. Previous studies have indicated that it is challenging to achieve adequate analgesia even after administering high-dose formulations of opioid and non-opioid medications such as morphine, additional doses of methadone, and gabapentin (Athanasos et al., 2006; Doverty et al., 2001; Murnion et al., 2020). Hydromorphone is a full μ-opioid receptor agonist often used to treat moderate-to-severe pain and has been identified as a promising pharmacotherapeutic strategy for overcoming these barriers. In previous studies with non-opioid tolerant individuals, 1-2 mg of intravenous (IV) hydromorphone has been found to provide clinically significant pain relief (Chang et al., 2011, 2013). In a recently published report, the analgesic effects of IV

hydromorphone were assessed in a buprenorphine-maintained sample (Huhn et al., 2019). That study provided preliminary evidence that at least 16 mg of IV hydromorphone may be necessary in clinical pain management for individuals maintained on 12-16 mg/day sublingual buprenorphine/naloxone. However, the peak effects of hydromorphone also resulted in increases on abuse liability indices, most notably increased ratings of drug effects, high, good effects, and drug liking. Additionally, in another study condition from the same report, 32 mg IV buprenorphine provided analgesia on only some but not all experimental pain assessments, indicating that additional buprenorphine may not be able to provide significant acute pain relief in patients on buprenorphine maintenance (Huhn et al., 2019). It is unclear, however, how these findings generalize to a population on methadone maintenance.

The primary aim of this study was to assess the dose efficacy of hydromorphone compared to placebo to reduce acute pain responses in patients maintained on moderate-to-high doses of oral methadone (80–100 mg/day). The study employed quantitative sensory testing (QST), a validated experimental model of acute clinical pain. The study also sought to identify the duration of these analgesic effects if they were detected and to assess the concurrent abuse liability of the escalating doses of hydromorphone. It was hypothesized that hydromorphone would provide superior analgesia to placebo at all time points.

1.2 Material and Methods

The current study utilized a within-subject double-blind randomized controlled cumulative dose design. Individuals maintained on 80-100 mg/day of oral methadone without chronic pain were recruited to participate in two residential experimental medication sessions (i.e., hydromorphone or placebo) that were scheduled at least one week apart. Patients were admitted to a residential research unit and provided their usual daily oral dose of methadone on the evening prior to each study session, at approximately 5:00 pm (instead of receiving this dose from their methadone clinic). At approximately 9:00 am the next day, research staff administered baseline QST and physiological measures (“baseline”). At approximately 10:00 am, the study nurse inserted an IV catheter into the participant’s arm (the arm not used for pain testing), and the study physician administered the study medication via IV push over five minutes. Participants received four doses of the IV study medication (32 mg total of hydromorphone delivered in escalating doses [4+4+8+16 mg each] or placebo) at 90-minute intervals. Subsequent QST and abuse liability testing began 15 minutes after each of the four injections to approximate the time at which hydromorphone reached peak effect (Dunn et al., 2018). These measures were also administered at 90 and 180 minutes following the last (i.e., fourth) injection to evaluate the duration of analgesia, for a total of six timepoints following baseline. Participants were asked to spend the night following their sessions at the residential research unit for additional medical monitoring. No participants declined to spend the night. Participants’ methadone doses were not administered to them on the session days to avoid inducing opioid toxicity.

1.2.1 Participants

The study enrolled and randomized ($N = 9$) adults on methadone maintenance for the treatment of OUD (ages 18 - 60), and all nine participants completed full study procedures. However, one of these participants was removed from the analysis after the study team discovered that he had received twice the amount of methadone on the evening prior to his first study session (see details below in Results). Participants were required to have been on a stable dosage of methadone for at least 30 days prior to enrollment and were excluded if they met Diagnostic and Statistical Manual of Mental Disorders (*DSM-IV*) criteria for current alcohol dependence; produced a urine toxicology positive for illicit substances or negative for methadone; carried any medical/psychiatric conditions that could potentially impact their ability to complete QST measures (e.g., peripheral neuropathy, schizophrenia); reported acute/chronic pain as determined by medical history and physical examination at the start of experimental sessions; were currently using any analgesic medications; had reported experiencing any allergic reactions in the past to hydromorphone; and if they were female and pregnant, lactating, or intending to become pregnant during the study period. The Johns Hopkins Institutional Review Board approved the trial.

1.2.2 Study Drug Preparation

Hydromorphone was obtained from McKesson Corporation (USA) via the inpatient pharmacy at the Johns Hopkins Bayview Medical Center. Methadone was obtained from Mallinckrodt (USA). The study drugs were stored in a locked safe at room temperature in the investigational pharmacy of the Behavioral Pharmacology Research Unit (BPRU) at Johns Hopkins. Pharmacy staff prepared study medications the morning of each study session. The outcome assessor, patient and physician administering the medication were all blinded to the identity of the study drug.

1.2.3 Analgesia Measures

1.2.3.1 Quantitative Sensory Testing (QST).—QST is a well-validated experimental model of acute pain and has been used to inform the study of pain pathways and the development of novel analgesic agents including opioid agonists (Grosen et al., 2013; Staahl et al., 2009). QST involves recording participant responses to experimental stimuli of various intensities (Staahl et al., 2009). All study staff underwent specialized training before administering the QST and were only credentialed for testing after demonstrating a high degree of correspondence with the lead study investigator (DAT) during training sessions. The order of the QST modalities was the same at each time point but was randomized across participants to control for potential order effects.

1.2.3.2 Cold Pressor Test.—The cold pressor test (CPT; Vera Cool, Thermo Fisher Scientific, USA) served as the primary outcome in this trial as in many previous studies of opioid effects on acute pain response (Coe et al., 2017). This test has been widely employed as a model for nociceptive pain. Previous experiments with healthy volunteers have demonstrated that CPT carries a favorable safety profile and has demonstrated adequate and reliable sensitivity to acute opioid analgesia (Tompkins et al., 2014). The immersion in ice water is believed to muscles and descending nerve pathways stimulates

local vasoconstriction and relay negative feedback to the spinal cord Participants were asked to immerse their non-dominant hand (which was not connected to the IV) for up to five minutes in a circulating water bath (Vera Cool, Thermo Fisher Scientific) cooled to approximately 4°C. Participants were asked to report to research staff the moment at which they first detected pain (i.e., cold pain threshold) and the moment at which they could no longer tolerate the pain (i.e., cold pain tolerance), and removed their hands from the water bath at that point.

1.2.3.3 Pressure Pain.—Pressure algometry is one of the most frequently used methods for quantifying acute pain (Brennum et al., 1989; Stahl et al., 2009). Muscle pressure pain is believed to be mediated by deep tissue groups III and IV afferents (Chaves et al., 2007; Graven-Nielsen et al., 2004). In the present study, an examiner used an electronic algometer (Somedic, Sweden) with a 1-cm^2 rubber probe to apply pressure at a gradual but constant rate on participants' trapezius muscles (30 kiloPascals; kPa/s). Participants were asked to verbally report to the tester the moment at which they first detected pain (i.e., pressure pain threshold in kPa units). Participants completed two trials at each time point, and the average threshold was calculated across each of the two trials.

1.2.3.4 Thermal Pain.—Thermal pain QST provides an indirect measurement of sensory nociceptive pathways (Harding, 2007) and has demonstrated high reproducibility in previous studies (Heldestad et al., 2010). A Peltier element-based stimulator was used to deliver contact heat stimuli on the dorsal forearm (Pathway model CHEPS; Medoc, Israel). The thermode temperature was increased gradually and continuously in 0.5°C/s increments. The starting temperature was 31°C and was increased until the point at which the participant could no longer tolerate the sensation (stopping at a maximum of 51°C). Participants were asked to report to research staff the moment at which they first detected pain (i.e., thermal pain threshold) and the moment at which they could no longer tolerate the pain (i.e., thermal pain tolerance). Threshold and tolerance scores were each averaged across two trials for each time point.

1.2.3.5 Other Physiologic Measures.—Vital signs (pulse, blood pressure, and respiration rate), as well as percent oxygen saturation were assessed at baseline, at every minute during the five minutes of each study drug IV push, and then five minutes following drug administration (i.e., 10 minutes after the start of the IV push) to ensure participant safety. Vital signs and percent oxygen saturation was measured every 15 minutes during the intervals between each injection and until the end of each study session. A digital pupilometer (NeurOptics, Inc., USA) was used in a room with constant lighting to measure pupil diameter at baseline and during each QST time point.

1.2.4 Abuse Liability Measures

1.2.4.1 Visual Analog Scale (VAS).—Subjective drug effects were measured with single item questions to which participants responded on a computer by clicking their cursor on a 100-millimeter ruler with endpoints marked "none" (= 0) or "extremely" (= 100). The following questions were asked: 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?" These assessments were administered once at each QST time point.

1.2.4.2 Money versus Drug Questionnaire.—Participants were asked to rate on a sliding scale the monetary value at and above which they would prefer the money and below which they would prefer the drug they had just received (Tompkins et al., 2010). This measure was administered at the end of each study session and on the following day.

1.2.4.3 Next Day Questionnaire.—On the day following each study session participants were asked to respond to a series of 0-100 VAS questions about the overall effects of the study medication from the previous day. The questions included: 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 approximate the amount of money they believed the drug would be worth if purchased on the street.

1.2.4.4 Adverse Events (AEs).—Adverse events (AEs) were collected via spontaneous report and through direct questioning by medical staff after each study medication administration and during each nursing shift on each of the nights after session completion.

1.2.5 Analytic Plan

A two-factor mixed ANOVA for main effects was used to measure within-subject differences between experimental conditions (hydromorphone and placebo) across time points. If a significant interaction was detected between experimental condition and time, or a significant main effect of condition (hydromorphone or placebo), *post hoc* pairwise comparisons were planned for each time point. All QST data were adjusted to change from baseline scores. Raw data were analyzed for QST and abuse liability outcomes after the fourth injection (peak medication dosage), and minimum values of physiologic data during the entire session with paired *t*-tests. Frequency counts for each adverse event item were assessed with chi-square tests. Alpha levels were set to $P < .05$, and all analyses were run in SPSS version 25.0 (IBM Corporation, USA).

1.3 Results

1.3.1 Participants

For information on participant flow from screening to data analysis please see Figure 1. Participants included in data analyses ($n = 8$) were, on average, aged 43.5 (standard deviation [*SD*] = 9.7; range 31 - 58) and had a body mass index of 28.9 (*SD* = 4.1; range 24.4 – 36.8). Participants were primarily White (88%) and male (63%) and had been on methadone maintenance treatment for an average of 17.8 months (*SD* = 26.5; range 1 - 71). One participant who had been randomized was removed from the analysis after it was discovered that he had received twice the amount of methadone on the evening prior to his first study session. The participant had dosed at his normal clinic prior to taking a second

dose of study methadone and had misrepresented this fact during session check-in. There were no adverse outcomes from this double methadone dosing.

1.3.2 Analgesic Outcomes

Contrary to study hypotheses, there was no evidence that hydromorphone increased pain tolerance on the primary analgesia (QST) outcomes. Specifically, there were no significant condition-by-time interactions on any of the QST parameters (i.e., cold pressor, pressure pain, or thermal pain measures), suggesting that the hydromorphone (total 32 mg) and placebo conditions did not differ as a function of time (see Table 1 for F statistic values for the test of interactions). Similarly, there were no significant main effects of medication condition, suggesting that the hydromorphone condition did not differ from placebo with respect to analgesic effects on these measures (i.e., cold pressor threshold [$F_{(1, 14)} = 1.57$, $p = .231$]; cold pressor tolerance [$F_{(5, 70)} = 1.30$, $p = .273$]; thermal pain threshold [$F_{(1, 14)} = 1.73$, $p = .210$]; thermal pain tolerance [$F_{(5, 70)} = 1.55$ $p = .233$]; pressure pain threshold [$F_{(1, 14)} = 1.98$, $p = .175$]). Change from baseline data are presented graphically in Figure 2. Baseline and mean session values after peak medication dosage (32 mg of hydromorphone or placebo) for QST are presented in eTable 1 in the Supplementary materials.

1.3.3 Physiologic Outcomes

Contrary to study hypotheses, there were no significant condition-by-time interactions on an any physiological outcomes, suggesting that the hydromorphone (total 32 mg) and placebo conditions did not differ as a function of time (see Table 1 for F statistic values for the test of interactions). There were also no significant main effects of medication condition on any of these outcomes (i.e., percent of oxygen saturation [$F_{(1, 14)} = .007$, $p = .935$]; heart rate [$F_{(1, 14)} = .104$, $p = .752$]; systolic blood pressure [$F_{(1, 14)} = .007$, $p = .935$]; diastolic blood pressure [$F_{(1, 14)} = .006$, $p = .938$]; pupil diameter [$F_{(1, 14)} = 1.43$, $p = .251$]). Change from baseline pupil diameter data are presented graphically in Figure 3 as this value is typically most sensitive to μ-opioid receptor agonist effects (Tegeder et al., 2003). Paired sample *t*-tests of minimum session values revealed significant differences between the hydromorphone [mean (M) = 51.38, $SD = 5.29$] and placebo ($M = 54.63$, $SD = 7.65$) conditions on heart rate ($p = .032$). There were no significant differences in session minimum values on systolic or diastolic blood pressure. See eTable 1 in Supplementary materials for details.

1.3.4 Abuse Liability Outcomes

Also contrary to study hypotheses, there were no significant condition-by-time interactions or main effects of condition on any of the abuse liability measures (see Table 1 for F statistic values for the test of interactions). There were also no significant main effects of medication condition on any of these outcomes (i.e., *high* [$F_{(1, 14)} = 1.21$, $p = .290$]; *liking* [$F_{(1, 14)} = .172$, $p = .684$]; *drug effect* [$F_{(1, 14)} = 2.07$, $p = .173$]; *good effects* [$F_{(1, 14)} = 1.07$, $p = .318$]; *bad effects* [$F_{(1, 14)} = 0.74$, $p = .405$]); *sick* [$F_{(1, 14)} = .045$, $p = .836$]. Lastly, there were no significant differences between the hydromorphone and placebo conditions on ratings for the Next Day Questionnaire and Money versus Drug Questionnaire administered one day after medication sessions (see Table 2).

1.3.5 Adverse Events

Despite the high doses of hydromorphone administered to participants in this study (16-32 times the normal dose for opioid naïve individuals [Chang et al., 2011, 2013]), there were no reports of serious adverse events (SAEs). Table 3 depicts the frequencies of AEs that were coded as *probably* or *definitely related* to the study medications. All AEs reported were rated to be mild in severity. There were greater reports of AEs during the placebo session, with the most commonly reported AEs being headache and nausea. During the hydromorphone session there were single reports of nausea, infusion site pain, pruritis, headache and hives/rash. A handful of participants reported experiencing more than one AE or the same AE over multiple study visits (see Table 3 for details).

1.4 Discussion

This randomized placebo-controlled crossover study sought to assess the analgesic, physiological and subjective effects of IV hydromorphone in methadone-maintained participants. A well-validated experimental pain paradigm was used to examine the effects of cumulative doses of IV hydromorphone on primary measures of QST as well as various safety and abuse liability outcomes. Notably, there were no significant differences between the hydromorphone and placebo conditions in analgesia on any of the QST outcomes nor any differences on safety or abuse liability measures despite the high doses of hydromorphone used here. To the best of the study team's knowledge, this study is the first to assess the effects of hydromorphone in individuals on methadone maintenance treatment using an experimental pain model. These findings provide intriguing insights into the multidimensional acute pain profiles of methadone patients.

Despite the high dosages of opioids administered, it is notable that there were very few adverse events, including respiratory depression or sedation, and those reported were mild in severity. There were also no significant differences in subjective drug effects reported between the conditions, which contrasts with findings from previous studies that found significantly increased ratings of subjective effects after 10 mg of hydromorphone (Strain et al., 1995) and up to 18 mg hydromorphone (McCaul et al., 1983) in patients on lower daily oral methadone doses (i.e., 30 – 60 mg/day). These findings are suggestive of the relatively favorable safety profile associated with the administration of large doses of opioids to methadone-tolerant patients.

These data agree with findings from other experimental trials that have administered high doses of opioids and failed to achieve analgesia in clinical samples of methadone-maintained patients (Athanasos et al., 2006; Doverty et al., 2001; Murnion et al., 2020). In prior studies, compared to matched controls, methadone-maintained patients actually show higher sensitivity to experimental pain (i.e., lower threshold and tolerance), while showing lower sensitivity/responsiveness to opioid analgesic effects (Compton et al., 2000, 2001; Ho & Dole, 1979; Martin & Inglis, 1965). One of these studies detected a small antinociceptive effect on an electrical stimulation measure, but not cold pressor tests, following large doses of morphine; however, that effect was very modest and did not persist beyond the acute phase of the medication infusion (Doverty et al., 2001). This pattern of consistent null findings is illustrative of the challenges involved in overcoming

the opioid pharmacodynamic tolerance and opioid blockade produced by methadone at the μ-opioid receptor. Various mechanistic theories regarding opioid receptor desensitization and downregulation, and imbalances between pro-nociceptive and antinociceptive pathways (Martin et al., 2019), have been proposed to explain these phenomena (DuPen et al., 2007). Shifts in cholecystokinin-related descending modulatory pathways (Lovick, 2008) and N-methyl-D-aspartate (NMDA) receptors also appear to contribute to opioid tolerance and may partially explain these study findings (King et al., 2005; Mao et al., 2002).

Opioid tolerance associated with chronic use of methadone presents unique challenges for clinicians attempting to provide acute pain management. The findings of the present study suggest that methadone-maintained individuals might require even greater doses of opioids, possibly up to 20-30 times those needed among opioid-naive patients, or require medications with higher analgesic efficacy (e.g., remifentanil) to achieve adequate analgesic effects (Hay et al., 2008). The clinical management protocol for severe acute pain (e.g., in the emergency department) typically involves 1 or 2 mg of IV hydromorphone (Chang et al., 2011, 2013). In a previously published report, 16 mg of IV hydromorphone was sufficient to achieve analgesia in buprenorphine-maintained patients on some, but not all, QST metrics. Additionally, the peak effects of hydromorphone in that study resulted in increases on several abuse liability indices (Huhn et al., 2019). The differences in analgesia observed in the present study compared with the Huhn and colleagues (2019) study might be related to whether the maintenance medication is a full or partial opioid agonist. Maintenance on a partial agonist, such as buprenorphine, could potentially preserve some of the opioid agonist activity. This may render a portion available for activation by a full opioid agonist such as hydromorphone. Alternatively, with maintenance on a full agonist such as methadone, it is possible that there will be no unoccupied portion of receptors available for future activation. Strategies for addressing opioid-induced pain tolerance in methadone-maintained patients have been proposed including the use of opioid rotation (Webster & Fine, 2012), multimodal non-opioid analgesic agents including the NMDA antagonists ketamine and dexmedetomidine (Kohler et al., 2016; Kumar et al., 2017; Webster & Fine, 2012), and peripheral nerve blockades (Martin et al., 2019).

These findings should be interpreted in the context of several limitations. Due to unexpected depletion of study funds, the present study did not end up enrolling the full number of participants ($n = 15$) that were pre-specified in the *a priori* Monte Carlo simulation power analysis and which had approximated detection of small-to-moderate-sized effects. The resultant sample size included in the final analysis ($n = 8$) was likely insufficiently powered to detect significant effects. However, this sample size is not dissimilar from previous within-subject trials with analogous study designs that have included fewer than 10 total participants and discerned significant nociceptive changes in subjective and objective drug effects (McCaul et al., 1983; Strain et al., 1995). An additional limitation of this study is the use of fixed dosages of hydromorphone, which is a common practice in clinical settings, and that methadone blood levels were not controlled. Weight adjusted dosing was also not used; however, the absence of significant findings with 32 mg of hydromorphone indicates that adjusting for weight would not have yielded a significant difference between conditions. It is also possible that participant' responses to QST outcomes were affected by learning or anticipation effects, especially after the 4th injection of the study medication.

A more rigorous study design would involve separation of injections on different study session in randomized order. Lastly, the time since methadone dosing was fixed at 17 hours. It is possible that there would have been significant differences on analgesia outcomes if greater time had elapsed. However, this would have rendered participants at higher risk for experiencing withdrawal symptoms. Although the strategy of holding methadone dose has been previously recommended prior to elective surgeries to prevent harm and increase one's sensitivity to analgesia, this method is impractical to use with patients outside of a closely monitored setting due to high risk for relapse.

In conclusion, the study findings suggest that methadone-maintained individuals are highly insensitive to the analgesic effects of hydromorphone as indexed by various experimental metrics of pain tolerance and threshold. This study is the first to assess the preliminary efficacy of hydromorphone in methadone patients with a QST paradigm. There were no significant analgesic effects or any meaningful differences in subjective effects or physiologic responses between the active and control conditions, suggesting that methadone patients may require more efficacious opioid analgesics or non-opioid analgesic strategies to achieve optimal acute pain relief. Providing adequate pain management remains a formidable challenge for methadone-treated patients. There is a strong imperative to identify alternate analgesic approaches to optimize treatment outcomes for this high-risk and vulnerable clinical population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

We would like to thank the research participants for volunteering their time for this study. We would like to thank the entire nursing and administrative staff at the Johns Hopkins Bayview Clinical Research Unit where sessions were conducted. Additionally, we thank Jessica Harras and Jasmyne Jardot for their invaluable assistance with recruitment, data collection, and conducting study sessions.

References

Alford DP, Compton P, Samet JH, 2006. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann. Intern. Med 44, 127–134. 10.7326/0003-4819-144-2-200601170-00010

Athanasos P, Smith CS, White JM, Somogyi AA, Bochner F, Ling W, 2006. Methadone maintenance patients are cross-tolerant to the antinociceptive effects of very high plasma morphine concentrations. Pain 120, 267–275. 10.1016/j.pain.2005.11.005 [PubMed: 16427197]

Ballantyne JC, Shin NS, 2008. Efficacy of opioids for chronic pain. Clin. J. Pain 24, 469–478. 10.1097/AJP.0b013e31816b2f26 [PubMed: 18574357]

Bannister K, Dickenson AH, 2010. Opioid hyperalgesia. Curr. Opin. Support. Palliat. Care 4, 1–5. 10.1097/SPC.0b013e328335ddfe [PubMed: 20019618]

Brennum J, Kjeldsen M, Jensen K, Staehelin Jensen T, 1989. Measurements of human pressure-pain thresholds on fingers and toes. Pain 38, 211–217. 10.1016/0304-3959(89)90240-6 [PubMed: 2780075]

Brown EG, Wood L, Wood S, 1999. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 20, 109–117.10.2165/00002018-199920020-00002 [PubMed: 10082069]

Chang AK, Bijur PE, & Gallagher EJ 2011. Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration protocol to usual care in the management of adult emergency department patients with acute severe pain. Ann. Emerg. Med 58, 352–359. 10.1016/j.annemergmed.2011.03.003 [PubMed: 21507527]

Chang AK, Bijur PE, Lupow JB, & Gallagher EJ 2013. Randomized clinical trial of the 2 mg hydromorphone bolus protocol versus the "1+ 1" hydromorphone titration protocol in treatment of acute, severe pain in the first hour of emergency department presentation. Ann. Emerg. Med 62, 304–310. [PubMed: 23694801]

Chaves TC, Nagamine HM, de Sousa LM, de Oliveira AS, Grossi DB, 2017. Intra- and interrater agreement of pressure pain threshold for masticatory structures in children reporting orofacial pain related to temporomandibular disorders and symptom-free children. J. Orofac. Pain 21, 133–142.

Coe MA, Nuzzo PA, Lofwall M,R, Walsh SL, 2017. Effects of short-term oxycodone maintenance on experimental pain responses in physically dependent opioid abusers. J. Pain 18, 10.1016/j.jpain.2017.02.433

Compton P, Charuvastra VC, Kintaudi K, Ling W, 2000. Pain responses in methadone-maintained opioid abusers. J. Pain Symptom Manage 20, 237–245. 10.1016/S0885-3924(00)00191-3 [PubMed: 11027904]

Compton P, Charuvastra VC, Ling W, 2001. Pain intolerance in opioid-maintained former opiate addicts: effect of long-acting maintenance agent. Drug Alcohol Depend. 63, 139–146. 10.1016/S0376-8716(00)00200-3 [PubMed: 11376918]

Doverty M, White JM, Somogyi AA, Bochner F, Ali R, Ling W, 2001. Hyperalgesic responses in methadone maintenance patients. Pain 90, 91–96. 10.1016/S0304-3959(00)00391-2 [PubMed: 11166974]

Dunn LK, Yerra S, Fang S, Hanak MF, Leibowitz MK, Tsang S, Durieux ME, Nemergut EC, Naik BI, 2018. Incidence and risk factors for chronic postoperative opioid use after major spine surgery: a cross-sectional study with longitudinal outcome. Anesth. Analg 127, 247. 10.1213/ANE.0000000000003338 [PubMed: 29570151]

DuPen A, Shen D, Ersek M, 2007. Mechanisms of opioid-induced tolerance and hyperalgesia. Pain Manag. Nurs 8, 113–121. 10.1016/j.pmn.2007.02.004 [PubMed: 17723928]

Eyler ECH, 2013. Chronic and Acute Pain and Pain Management for Patients in Methadone Maintenance Treatment. Am. J. Addict 22, 75–83. 10.1111/j.1521-0391.2013.00308.x [PubMed: 23398230]

Gardell LR, King T, Ossipov MH, Rice KC, Lai J, Vanderah TW, Porreca F, 2006. Opioid receptor-mediated hyperalgesia and antinociceptive tolerance induced by sustained opiate delivery. Neurosci. Lett 396, 44–49. 10.1016/j.neulet.2005.11.009 [PubMed: 16343768]

Graven-Nielsen T, Mense S, Arendt-Nielsen L., 2004. Painful and non-painful pressure sensations from human skeletal muscle. Exp. Brain. Res 159, 273–83. [PubMed: 15480607]

Grosen K, Fischer IWD, Olesen AE, Drewes AM, 2013. Can quantitative sensory testing predict responses to analgesic treatment? Eur. J. Pain 17, 1267–1280. 10.1002/j.1532-2149.2013.00330.x [PubMed: 23658120]

Hay JL, White JM, Bochner F, Somogyi AA, 2008. Antinociceptive effects of high dose remifentanil in male methadone-maintained patients. Eur. J. Pain 12, 926–933. 10.1016/j.ejpain.2007.12.012 [PubMed: 18262451]

Hilliard PE, Waljee J, Moser S, Metz L, Mathis M, Goesling J, Cron D, Clauw DJ, Englesbe M, Abecasis G, Brummett CM, 2018. Prevalence of preoperative opioid use and characteristics associated with opioid use among patients presenting for surgery. JAMA Surg. 153, 929–937. 10.1001/jamasurg.2018.2102 [PubMed: 29998303]

Hines S, Theodorou S, Williamson A, Fong D, & Curry K (2008). Management of acute pain in methadone maintenance therapy in-patients. Drug Alcohol Rev. 27, 519–523. [PubMed: 18696299]

Ho A, Dole VP, 1979. Pain perception in drug-free and in methadone-maintained human ex-addicts. Exp. Biol. Med 162, 392–395. 10.3181/00379727-162-40689

Huhn AS, Strain EC, Bigelow GE, Smith MT, Edwards RR, Tompkins DA, 2019. Analgesic effects of hydromorphone versus buprenorphine in buprenorphine-maintained individuals. Anesthesiology 130, 131–141. 10.1097/ALN.0000000000002492 [PubMed: 30418214]

King T, Ossipov MH, Vanderah TW, Porreca F, Lai J, 2005. Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? Neurosignals 14, 194–205. 10.1159/000087658 [PubMed: 16215302]

Kohler M, Chiu F, Gelber KM, Webb CA, Weyker PD, 2016. Pain management in critically ill patients: a review of multimodal treatment options. Pain Manag. 6, 591–602. 10.2217/pmt-2016-0002 [PubMed: 27188977]

Kumar K, Kirksey MA, Duong S, Wu CL, 2017. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. Anesth. Analg 125, 1749–1760. 10.1213/ANE.0000000000002497 [PubMed: 29049119]

Lee C, Song YK, Lee JH, Ha SM, 2011. The effects of intraoperative adenosine infusion on acute opioid tolerance and opioid induced hyperalgesia induced by remifentanil in adult patients undergoing tonsillectomy. Korean J. Pain 24, 7–12. 10.3344/kjp.2011.24.1.7

Lovick TA, 2008. Pro-nociceptive action of cholecystokinin in the periaqueductal grey: a role in neuropathic and anxiety-induced hyperalgesic states. Neurosci. Biobehav. Rev 32, 852–862. 10.1016/j.neubiorev.2008.01.003 [PubMed: 18295886]

Mao J, Sung B, Ji RR, Lim G, 2002. Neuronal apoptosis associated with morphine tolerance: evidence for an opioid-induced neurotoxic mechanism. J. Neurosci 22, 7650–7661. 10.1523/jneurosci.22-17-07650.2002 [PubMed: 12196588]

Martin JE, Inglis J, 1965. Pain tolerance and narcotic addiction. Br. J. Soc. Clin. Psychol 4, 224–229. 10.1111/j.2044-8260.1965.tb00467.x [PubMed: 5872680]

McCaul ME, Stitzer ML, Bigelow GE, Liebson IA, 1983. Intravenous hydromorphone: effects in opiate-free and methadone-maintained subjects. (Eds.), Problems of Drug Dependence 1982. National Institute on Drug Abuse research monograph 43. Washington, DC: pp. 238.

Mudumbai SC, Oliva EM, Lewis ET, Trafton J, Posner D, Mariano ER, Stafford RS, Wagner T, Clark JD, 2016. Time-to-cessation of postoperative opioids: a population-level analysis of the Veterans Affairs Health Care System. Pain Med. 17, 1732–1743. 10.1093/pm/pnw015 [PubMed: 27084410]

Murnion BP, Rivas C, Demirkol A, Hayes V, Lintzeris N, Nielsen S, 2020. Acute experimental pain responses in methadone- and buprenorphine/naloxone-maintained patients administered additional opioid or gabapentin: a double-blind crossover pilot study. Pain Med. 21, 1188–1198. 10.1093/pm/pnz178 [PubMed: 31504868]

Okie S, 2010. A flood of opioids, a rising tide of deaths. N. Engl. J. Med 363, 1981–1985. [PubMed: 21083382]

Sjøgren P, Jensen NH, Jensen TS, 1994. Disappearance of morphine-induced hyperalgesia after discontinuing or substituting morphine with other opioid agonists. Pain 59, 313–316. 10.1016/0304-3959(94)90084-1 [PubMed: 7892029]

Staahl C, Olesen AE, Andresen T, Arendt-Nielsen L, Drewes AM, 2009. Assessing analgesic actions of opioids by experimental pain models in healthy volunteers—an updated review. Br. J. Clin. Pharmacol 68, 149–168. 10.1111/j.1365-2125.2009.03456.x [PubMed: 19694733]

Strain EC, Preston KL, Liebson IA, & Bigelow GE, 1995. Buprenorphine effects in methadone-maintained volunteers: effects at two hours after methadone. J. Pharmacol. Exp. Ther 272, 628–638. [PubMed: 7853176]

Summers S, Grau L, Massel D, Rosas S, Ong A, Hernandez VH, 2018. Opioid use disorders are associated with perioperative morbidity and mortality in the hip fracture population. J. Orthop. Trauma 32, 238–244. 10.1097/BOT.0000000000001118 [PubMed: 29356800]

Tegeder I, Meier S, Burian M, Schmidt H, Geisslinger G, Lotsch J, 2003. Peripheral opioid analgesia in experimental human pain models. Brain 126, 1092–1102. 10.1093/brain/awg115 [PubMed: 12690049]

Tompkins DA, Lanier RK, Harrison JA, Strain EC, & Bigelow GE, 2010. Human abuse liability assessment of oxycodone combined with ultra-low-dose naltrexone. Psychopharmacology 210, 471–480. [PubMed: 20386884]

Tompkins DA, Smith MT, Bigelow GE, Moaddel R, Venkata SV and Strain EC, 2014. The effect of repeated intramuscular alfentanil injections on experimental pain and abuse liability indices in healthy males. Clin. J. Pain 30, 1–18. [PubMed: 23446082]

Voon P, Greer AM, Amlani A, Newman C, Burmeister C, Buxton JA, 2018. Pain as a risk factor for substance use: a qualitative study of people who use drugs in British Columbia, Canada. Harm Reduct. J 15, 1–9. 10.1186/s12954-018-0241-y [PubMed: 29304871]

Webster LR, Fine PG, 2012. Review and critique of opioid rotation practices and associated risks of toxicity. Pain Med. 10.1111/j.1526-4637.2012.01357.x

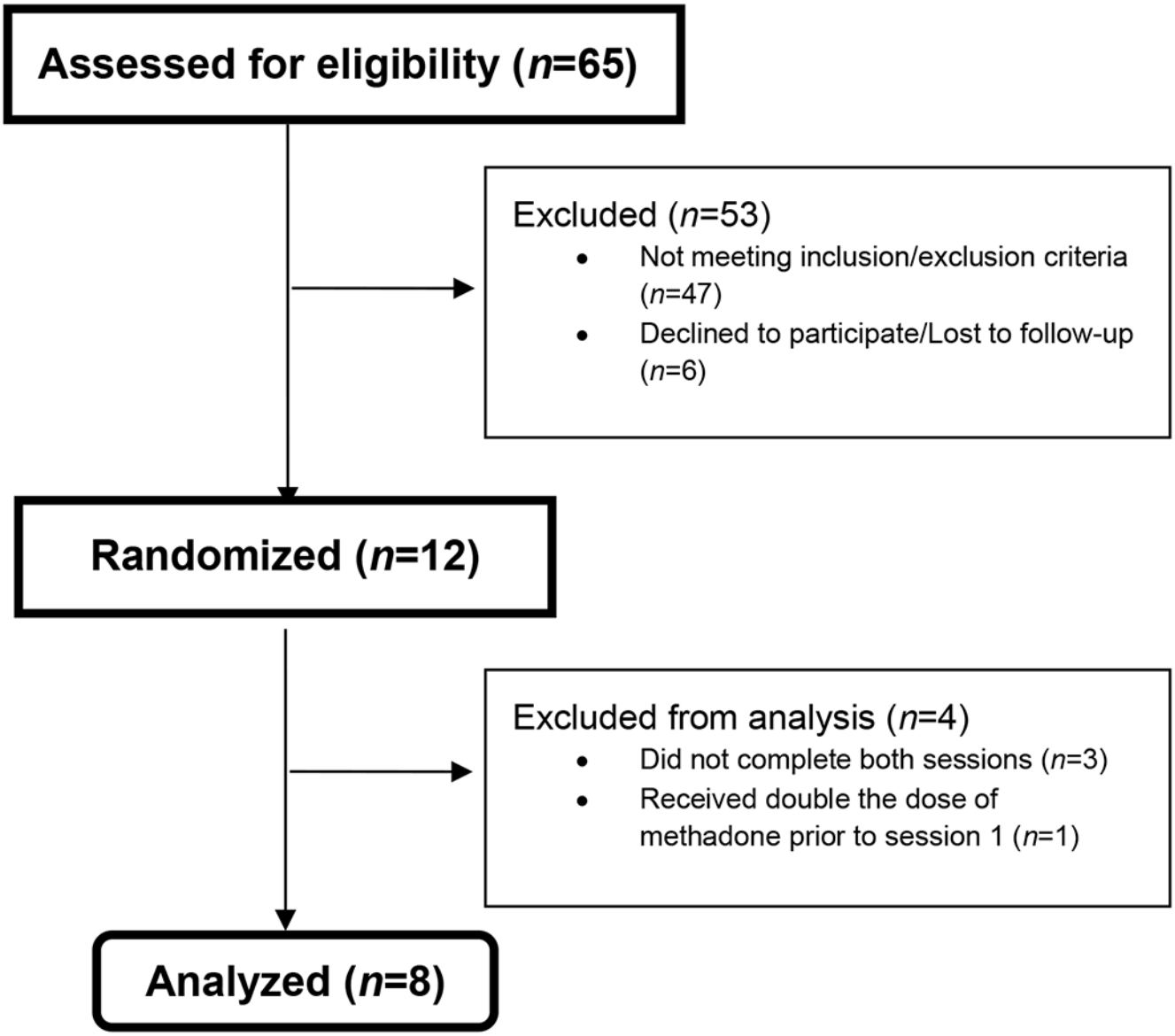

Fig. 1.
CONSORT Diagram

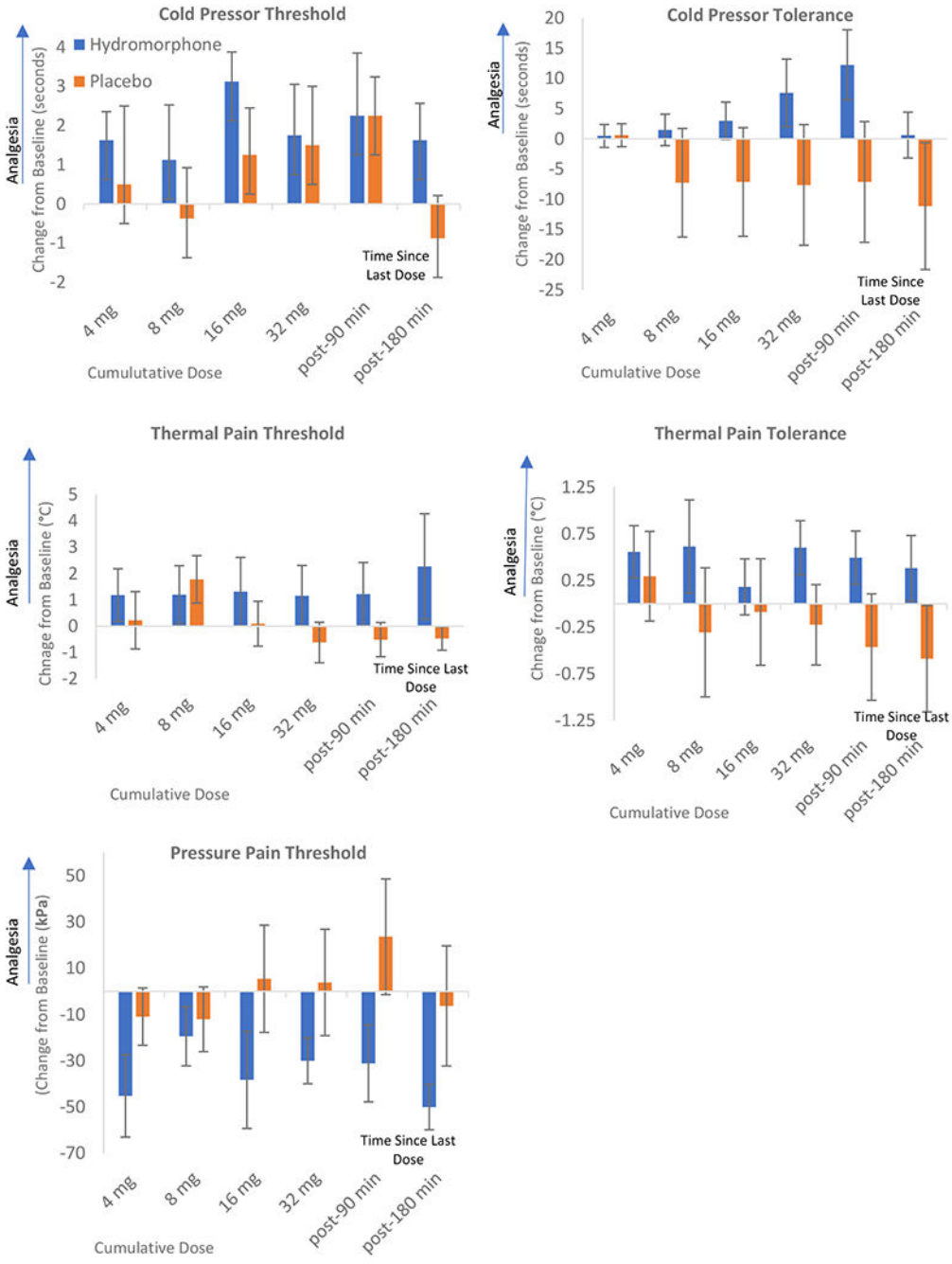

Fig. 2.

Change from baseline and subsequent mean values for cold pressor, thermal pain, and pressure pain testing, which began 15 min after each injection (4-, 4-, 8-, and 16-mg individual doses of hydromorphone or placebo given 90 min apart, corresponding to cumulative doses of 4, 8, 16, and 32 mg hydromorphone or placebo, respectively), as well as 90 and 180 min after final drug administration. Bars represent sample means, and error bars represent standard error. No significant differences were detected in these pain testing modalities.

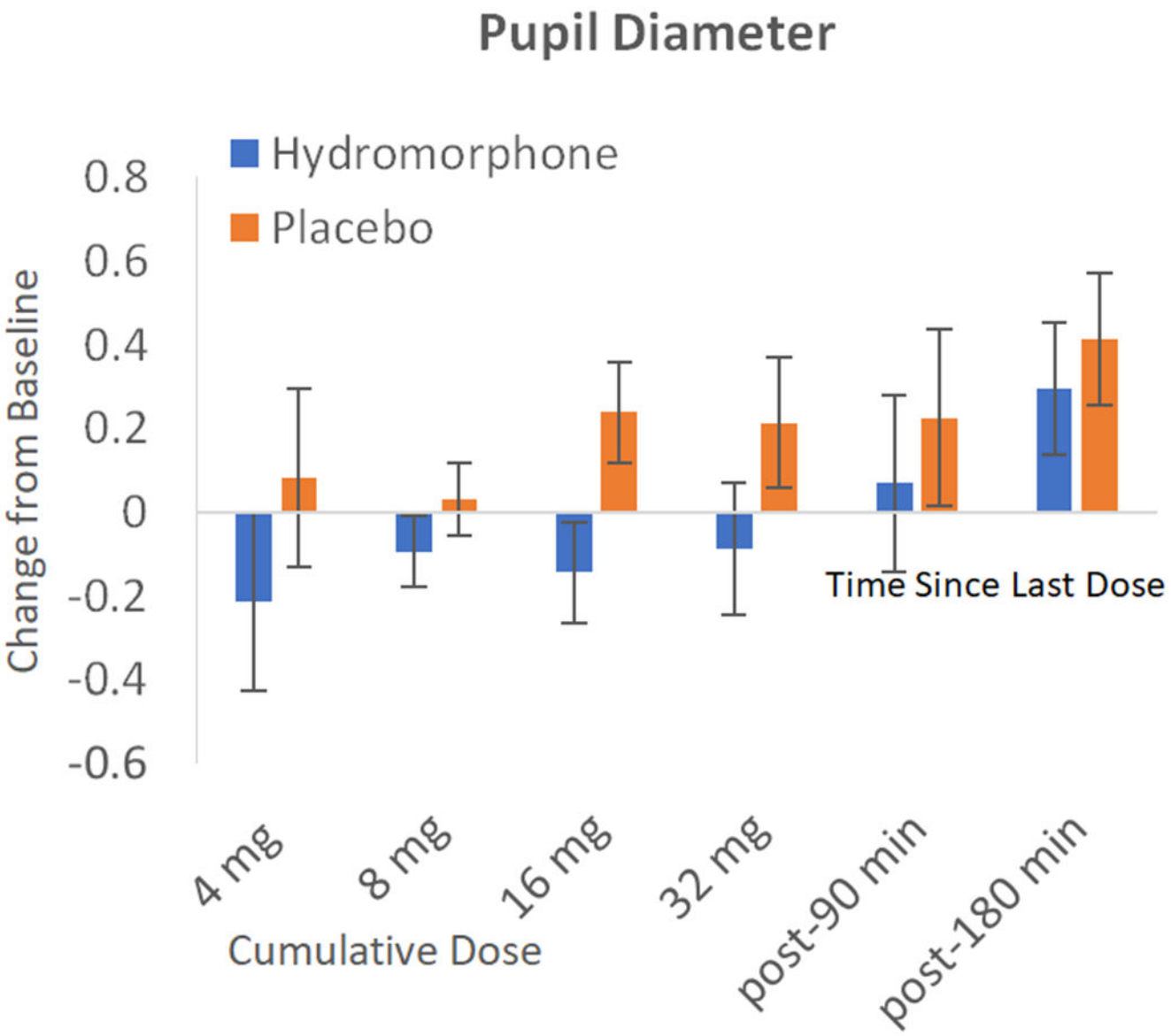

Fig. 3.

Change from baseline and subsequent mean values for pupil diameter, which was performed 15 min after each injection (4-, 4-, 8-, and 16-mg individual doses given 90 min apart, corresponding to cumulative doses of 4, 8, 16, and 32 mg, respectively), as well as 90 and 180 min after final drug administration. Bars represent sample means, and error bars represent standard error. No significant differences were detected.

Table 1.

F-Tests Assessing for Condition x Time Interactions

Measure	F (*P* value)
Quantitative Sensory Testing (QST)	
Δ Cold pressor threshold	0.44 (.821)
Δ Cold pressor tolerance	1.41 (.231)
Δ Thermal pain threshold	0.89 (.491)
Δ Thermal pain tolerance	0.79(.558)
Δ Pressure pain threshold	0.42 (.833)
Physiological Measures	
Δ Percent oxygen saturation	0.32 (.863)
Δ Heart rate, beats per minute	0.54 (.706)
Δ Systolic blood pressure, mmHg	0.40 (.806)
Δ Diastolic blood pressure, mmHg	0.23 (.866)
Δ Pupil diameter	0.60 (.700)
Abuse Liability (0-100 VAS)	
High	1.67 (.152)
Liking	1.31 (.269)
Drug Effect	2.07 (.173)
Good Effects	0.68 (.640)
Bad Effects	1.14 (.348)
Sick	0.37 (.866)

Values shown are F statistics (*P* values). There were no significant condition-by-time interactions on any quantitative sensory testing (QST), physiological, or abuse liability Visual Analog Scale (VAS) measure.

Note: The values for QST and physiological measures are change from baseline.

Table 2.

Abuse Liability Measures

	Placebo	Hydromorphone	t (*P* value)
VAS Mean Values after 4th injection [◊]			
High	10.5 ± 11.2	1.9 ± 4.5	−2.3 (.053)
Liking	7.3 ± 10.3	2.5 ± 5.6	−2.0 (.081)
Drug Effects	10.9 ± 12.1	2.5 ± 6.7	−2.1 (.075)
Good Effects	9.3 ± 13.9	2.6 ± 7.0	−1.7 (.126)
Bad Effects	1.1 ± 2.5	1.8 ± 2.8	−0.9 (.420)
Sick	0.9 ± 1.8	1.0 ± 2.1	−0.1 (.901)
Next Day Questionnaire [*]			
Drug Liking	8.2 ± 12.3	7.0 ± 19.0	−0.3 (.818)
Strength of Drug	12.9 ± 15.2	7.2 ± 15.7	−1.4 (.214)
Good Effects	13 ± 22.4	6.8 ± 19.1	−1.5 (.181)
Bad Effects	7.0 ± 11.1	3.4 ± 6.5	−1.5 (.173)
Take Again	6.9 ± 8.9	5.5 ± 10.3	−0.3 (.759)
Money versus Drug [Ω]	15.9 ± 18.8	7.3 ± 10.0	−1.9 (.106)

[◊]Values shown are mean ± SD (VAS 0–100). Session peak values for abuse liability testing were taken after 4th injection (placebo or a cumulative dose of 32 mg of hydromorphone). Pairwise comparisons are shown for comparison between placebo and hydromorphone. No significant differences were detected in these measures. VAS = Visual Analog Scale.

[*]Values shown mean ± SD (VAS 0-100) for the Next Day Questionnaire administered on the day following study sessions. Pairwise comparisons are shown for comparison between placebo and hydromorphone. No significant differences were detected in these measures.

[Ω]Values shown mean ± SD for the Money versus Drug Questionnaire administered on the day following study sessions. Pairwise comparisons are shown for comparison between placebo and hydromorphone. No significant differences were detected in these measures.

Table 3.

Frequency of Adverse Events

Event	Placebo	Hydromorphone
Nausea	2 (25%)	1 (20%)
Hypoaesthesia	1 (12.5%)	0
Infusion site pain	0	1(20%)
Pruritis	0	1 (20%)
Headache	2 (25%)	1 (20%)
Hives/rash	1 (12.5%)	1 (20%)
Somnolence	1 (12.5%)	0

Columns indicate the frequency counts and percentages of participants reporting an adverse event (AE) in each study condition. AEs were coded according to terms in the Medical Dictionary for Regulatory Activities (Brown et al., 1999*)*. There were no significant differences between groups. Note: There were four participants who experienced more than one AE during the study. One participant experienced hives after hydromorphone and somnolence after placebo. A second participant experienced infusion site pain and pruritis during the hydromorphone session. A third participant experienced nausea on two occasions throughout the placebo session. A final participant experienced headache on two occasions throughout the placebo session. All AEs reported were mild in severity.