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Within subject, double blind, examination of opioid sensitivity in participant-reported, observed, physiologic, and analgesic outcomes

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HIGHLIGHTS

- Opioid sensitivity was examined, compared to placebo, in opioid-naïve individuals.
- s1One in five participants did not detect hydromorphone based on "Drug Effect" rating.
- Opioid effects were not uniform or consistent across the various measures assessed.
- However, opioid responders displayed enhanced sensitivity for most measures.
- Analgesic effect was not associated with opioid responder status.

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ABSTRACT

Background: Inter-individual differences in opioid sensitivity may underlie different opioid risk profiles but have often been researched in persons who have current or past opioid use disorder or physical dependence. This study examined how opioid sensitivity manifests across various assessments of opioid effects in a primarily opioid-naïve population.

Procedures: Data were harmonized from two within-subject, double-blind trials wherein healthy participants (N = 123) received placebo and 4 mg oral hydromorphone. Demographics, self-report ratings, observer ratings, physiological, and cold pressor measures were collected. Participants were categorized as being responsive or nonresponsive to the opioid dose tested and compared using mixed-models, Pearson product correlations, and paired t-tests.

Findings: Participants were 49.6% female, mean 33.0 (SD=9.3) years old, and 44.7% Black/African American and 41.5% White, with 89.4% reporting no prior exposure to opioids. Within-subject sensitivity to opioids varied depending on the measure. One in five participants did not respond subjectively to the 4 mg hydromorphone dose based on their "Drug Effects" rating. Persons who were responsive showed more evidence of drug-dependent effects than did persons who were not responsive on ratings of Bad Effects (p= .03), feeling High (p= .01), Nausea (p= .03), pupil diameter (p< 0.01), and on the circular lights task (p< 0.001).

Conclusions: This study provides initial evidence that the experience of opioids may be domain specific. Data suggest potentially clinically meaningful differences exist regarding opioid response patterns, evident following one dose among opioid inexperienced individuals.

1. Introduction

Opioid use disorder (OUD) is a major societal issue that is contributing to substantial morbidity and mortality (Strang et al., 2020), including unprecedented rates of opioid-related overdose deaths (Centers for Disease Control and Prevention, 2021). In an effort to reduce these consequences, a series of societal initiatives have been enacted over the past decade focused on reducing person-level exposure to opioid products (Dowell et al., 2022). However, it is also the case that opioid medications are considered important and vital first-line

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treatments for pain management and that only a small minority of persons who are exposed to opioids develop problematic use behaviors. Preclinical literature has also documented vast individual variation in responses to first exposure of opioids (Horowitz et al., 1977; Belknap et al., 1989; Belknap et al., 1993; Phillips et al., 1994; Elmer et al., 1995; Elmer et al., 2010). Although there have been few studies of this phenomenon in humans, those that have examined it have observed wide variation in response to opioid products, as well as other substances such as amphetamine and alcohol (de Wit and Phillips, 2012; Bieber et al., 2008; Kirkpatrick et al., 2013; de Wit et al., 1986, 1987). Aside from self-reported risk stratifications tools, such as the ORT-OUD (Cheatle et al., 2019) that are based on history of problematic substance use and psychological comorbidities, our ability to accurately predict person-level risk for experiencing adverse events and developing problematic opioid use remains underdeveloped. As a result, broad sweeping policies that focus on general risk have been enacted; these have the potential to produce unintentional consequences by way of restricting access to opioid medications for persons who need them for pain management in lieu of reducing societal level harms from OUD (Manchikanti et al., 2022). This has led to a growing interest in being able to tailor opioid prescribing and/or care for patients who have pain and/or OUD (Volkow, 2020).

Our limited understanding of the individual differences that exist with regard to opioid response, prior to development of problematic use, may be hampering efforts to prospectively identify individual risk profiles. There has been little empirical evaluation of person-level experiences of opioid products, including whether variability in response is consistent across opioid metrics or are domain-specific (i.e., confined to one set of measures such as participant-reported, observed, physiological, or analgesic responses). Opioid sensitivity, or degree to which an individual can detect an effect of opioids, is one concept that may help elucidate understanding of opioid risk profiles. Existing characterizations of opioid sensitivity have primarily originated from persons who are opioid-experienced and have an established history of problematic opioid use; participants in these studies still experienced meaningful variability in their ability to detect opioid effects. For instance, the first study was a within-subject comparison of persons with OUD that found 39% of persons who received a double-blind dose of 30 mg oral oxycodone were unable to differentiate it from a placebo dose (Antoine et al., 2013). The second study was a within-subject laboratory evaluation within persons who had past (but not current) opioid physical dependence and who underwent a double-blind, double-dummy comparison of placebo, low, medium, and high doses each of intravenous and subcutaneous formulations of heroin and hydromorphone. Data revealed that participants displayed consistent effects within an individual, such that if the participant was deemed responsive to an opioid at one dose and formulation they also displayed dose-dependent changes to other doses and formulations across several outcomes measured. However, a subgroup of participants were deemed nonresponsive because they did not evidence any response to any of the doses and formulations independent of the outcome assessed (Dunn et al., 2019). The fact that opioid response patterns varied across individuals in these studies is particularly noteworthy because they were persons who all had a history of finding opioids reinforcing and thus had a history of subjectively detecting opioids; in the latter study they were also financially incentivized to accurately detect the opioid as part of the study methodology.

The current study builds upon prior research by examining differences in the detection of opioid effects across several domains within a large sample of individuals who are primarily opioid naïve and thus had no established history of subjectively detecting opioid effects. The aim of this proof-of-concept study is to expand understanding of how opioid sensitivity manifests across various assessments of opioid effects in the context of double-blind placebo and active opioid dose administrations. This is an important next step in this line of research because it addresses concerns that residual opioid physical dependence and/or tolerance may have impacted opioid responsiveness in prior studies. It also models the larger societal experience of being exposed to opioids in a naïve state (perhaps related to acute pain management) and can therefore help expand our understanding of how sensitivity may manifest at that level. Participants in these analyses received placebo and a dose of oral hydromorphone (4 mg) that is routinely prescribed for pain management. Participant-rated opioid effects, observer ratings, physiological outcomes, and measures of experimentally-induced pain and analgesia (via cold water immersion of the hand) were collected to provide a comprehensive assessment of opioid sensitivity. These analyses hypothesized that participants would demonstrate differences in responsiveness to hydromorphone versus placebo across several potential measures of opioid effects but that inter-individual differences in the effects produced by opioids would exist (though the magnitude and breadth of effects expected was unclear).

2. Methods

2.1. Project overview

This is a secondary analysis of two within-subject, double-blind, double-dummy, placebo-controlled, human laboratory trials (NCT02360371, NCT02901275 [Dunn et al. 2021]). Both studies utilized nearly identical research methodology so outcomes and results were harmonized here for analytic purposes. All study procedures were approved by the Johns Hopkins University IRB and participants provided voluntary informed consent to participate. Study 1 was a residential protocol that housed participants for the duration of their stay. Study 2 was an outpatient protocol. To be eligible for study sessions, participants had to test negative on a urine test for pregnancy and other drugs prior to the session start. Baseline measures were collected at approximately 08:00 and study drugs were administered by 09:30. Ratings were collected at regular intervals throughout the session day up to 6 h post-dosing; these analyses were restricted to the 60 min-post dose period to capture the peak effects of oral hydromorphone.

2.2. Participants

Healthy individuals with no recent opioid use or current/lifetime history of opioid use disorder were recruited from the community to participate in one of two within-subject studies between 06/2015 and 03/2020. To be eligible for the studies, participants across both trials were required to provide a negative breath ethanol test and a urine sample that tested negative for all substances (opioids, methadone, buprenorphine, oxycodone, amphetamine, cocaine, benzodiazepines, THC) and pregnancy. Participants were excluded if they endorsed current pain, reported opioid use or an opioid prescription in the past 5 days, reported use of illicit substances in the past 7 days, met DSM-5 criteria for current or lifetime alcohol or substance use disorder, were pregnant or breastfeeding, had known allergies to the study medications, or had a clinically significant medical and/or psychiatric illness deemed by medical staff to interfere with study participation. Study specific eligibility included being aged 21–50 and having a Body Mass Index (BMI) < 30 (study 1, $N = 98$) and being aged 18–75 with no history of seizure disorder or allergy to sesame seed oil (due to other study conditions that are not assessed here) (study 2, $N = 25$). The total harmonized sample size for this secondary analysis is $N = 123$.

2.3. Study medications

Participants in both trials received placebo and hydromorphone (4 mg, oral). Doses were over-encapsulated and administered in a double-blind, double-dummy manner with all participants receiving both doses. Strict double-blinding procedures were maintained for both studies. Neither the participant nor research staff knew the study drug under investigation and both were informed that participants may receive a

medication from one of the following categories: benzodiazepines, cannabinoids, opioids, stimulants, over-the-counter medications, and/or placebo at each visit.

2.4. Outcome measures

The following outcomes were all collected at the same timepoint, approximately 60 min post-dose.

Self-report Measures: General measures of drug effects were assessed using broad visual analog scale (VAS) ratings, consistent with Food and Drug Administration (FDA) guidance for assessing drug effects (FDA, 2017). These include "Drug Effects", "Good Effects", "Bad Effects", "High", "Like How I Feel", and "Nausea", rated on a 0 (not at all) to 100 (extremely) scale. In addition, opioid agonist effects were measured by summing the participant Likert ratings (0–5) on the Opioid Agonist and Antagonist Rating Scale using the following agonist symptoms: Flushing, Nodding, Good Mood, Skin Itchy, Relaxed, Dry Mouth, Coasting, Carefree, Friendly, Pleasant Sick, Energetic, Drive, Feel Limp or Loose, and Mentally Slowed Down (total score range 0–70). Given the opioid naïve sample, all items on the scales were explained to the participants.

Observer-Reports: Observers rated participant effects on VAS from 0 (not at all) to 100 (extremely) for the following statements: "Drug Effects", "Good Effects", "Bad Effects", and "High".

Physiological and Cognitive Endpoints: Vital signs, including systolic and diastolic blood pressure, heart rate, temperature (F), respiration rate (30 s), oxygen saturation, and pupil diameter (Neuroptics, Irvine, CA USA) were collected. In addition, a circular lights task, in which participants would repeat light patterns for 60 s, was completed as a measure of cognitive function and yielded a primary outcome of number of correct pattern reproductions.

Cold Pressor Pain Test: Cold water immersion of the hand (i.e., the "cold pressor" test) was selected for these analyses because it is a prototypical measure of pain response that is commonly used to assess opioid analgesic effects in laboratory settings (Posner et al., 1985; Reddy et al., 2012; Siebenga et al., 2019). For the cold pressor test, participants submerged their hand into a five degrees C circulating water bath (Thermo Scientific™ VersaCool™ Refrigerated Circulating Bath, Waltham, MA USA) for as long as they could tolerate, up to a maximum of five minutes. Primary outcomes were time to first detection of pain (i.e., cold pressor pain threshold) and time to removal of hand from water (i.e., cold pressor pain tolerance) (in seconds). Participants were also asked to rate their maximum pain and unpleasantness on VAS from 0 (none) -100 (worst imaginable) during hand immersion, and their pain and unpleasantness at 30 s post hand-withdrawal as a measure of central sensitization.

2.5. Analytic plan

This study hypothesized that participants would demonstrate differences in responsiveness to hydromorphone versus placebo across several potential measures of opioid effects. This was first assessed by comparing the degree to which severity ratings on different opioid assays (self-report, cold pressor, etc.) were associated. Next the study examined whether associations between measures differed as a function of opioid response. Being responsive (or sensitive to hydromorphone effects) was operationally defined as providing a >20-point difference in the response on the subjective "Drug Effect" VAS rating between baseline and the peak post-drug administration rating (collected at any time during the 6-hour post-dose period). This definition was based in part upon the strategy employed previously (Antoine et al., 2013). Persons who did not achieve a >20-point difference in response were categorized as being nonresponsive for the purpose of these analyses. Sensitivity status was then used as a between-groups variable to explore whether being responsive to hydromorphone on a subjective assay correlated with being responsive to hydromorphone on other opioid assays (i.e., participant-reported, observer report, physiological, analgesic). Analyses were conducted using mixed linear regressions fit with restricted maximum likelihood estimates, including a random intercept and an autoregressive covariance structure were used to examine the role of medication on outcomes. Pearson product correlations were conducted to examine associations between measures, collapsed across drug condition. Paired t-tests were used to conduct within-subject dose-based comparisons (0 and 4 mg) for the overall sample and separately within responder and nonresponder subgroups. Sex/gender, race, and body mass index were explored as covariates across analyses but were not found to substantively influence outcomes, so are not reported here. All analyses were conducting using SPSS version 28, with alpha set to 0.05.

3. Results

3.1. Participants

Participants were 49.6% female, 49.6% male, and 0.8% transgender. They were a mean 33.0 (StDev= 9.3) years old, and 44.7% Black/African American and 41.5% White. The majority (89.4%) of participants reported no prior lifetime exposure to opioids. Among the 13 participants who reported lifetime use of opioids, all reported having a past opioid prescription and none reported illicit opioid use. Only one participant reported past 30-day use of an opioid prescription. The most reported substances used by participants in the 30-days prior to admission were alcohol (56.1% of participants) and cannabis (7.3%). Between-study comparisons (i.e., NCT02360371, NCT02901275 [Dunn et al., 2021]) revealed no significant differences in demographic or prior drug/alcohol exposure.

3.2. Relationship between measures of opioid use

Mixed linear regression analyses revealed that almost all participant-reported measures demonstrated significant drug-dependent effects, including VAS ratings of Drug Effects ($F(1,98)= 24.7$, $p< 0.0001$), Good Effects ($F(1,98)= 16.0$, $p< 0.001$), Bad Effects ($F(1,98)= 6.2$, $p = 0.01$), High ($F(1,98)= 15.2$, $p< 0.01$), Nausea ($F(1,98)= 7.4$, $p< 0.01$), and the summed agonist symptoms ($F(1,99)= 46.6$, $p< 0.001$), but not the VAS rating of Like How I Feel ($p = 0.56$). Additional drug-dependent effects were also observed for cold pressor pain threshold ($F(1,99)= 4.6$, $p = 0.03$) but not other cold pressor-related measures; cold pressor pain tolerance, or pain and unpleasantness ratings. Regarding physiological effects, drug-dependent effects were observed for pulse ($F(1,99)= 11.3$, $p = 0.001$), pupil diameter ($F(1,98)= 13.1$, $p = 0.001$), and performance on the circular lights task ($F(1,84)= 48.6$, $p< 0.0001$), but not for other physiological measures such as blood pressure (systolic $p = 0.90$, diastolic $p = 0.70$) or respiration ($p = 0.80$). The only observer rating to show significant main effects of drug were VAS ratings of Drug Effects ($F(1,95)= 6.9$, $p = 0.01$).

Pearson product correlations were used to further explore the relationship between different opioid domains, independent of drug condition (Table 1). Cold pressor assessments of pain were highly associated with pulse and pupil diameter endpoints, suggesting there was an underlying physiological response occurring, though there were no significant associations between these ratings and cold pressor pain tolerance. However, despite showing significant associations with drug in the mixed model analyses, self-report ratings of general and specific drug effects were not robustly correlated with any cold pressor or observer ratings.

3.3. Opioid response profiles

Mean response on VAS Drug Effect scales were 7.7 (SD= 16.8) and 19.6 (SD= 24) for the placebo and 4 mg dose, respectively, demonstrating a statistically-significant difference overall and confirming the presence of a general drug-dependent difference in responding ($t(106)=$

Table 1
Correlations.

			Self-Reported Effects During QST						Observed Effects During QST			
	Drug	Opioid Responsivity	"Drug Effects" (VAS 0–100)	"Good Effects" (VAS 0–100)	"Bad Effects" (VAS 0–100)	"High" (VAS 0–100)	"Nausea" (VAS 0–100)	Sum of Agonist Effects (0–70)	Observed "Drug Effects" (VAS 0–100)	Observed "Good Effects" (VAS 0–100)	Observed "Bad Effects" (VAS 0–100)	Observed "High" (VAS 0–100)
Cold Pressor Outcomes												
Detection of Pain (seconds)	0.093	0.031	−0.109	−0.069	−0.058	−0.09	−0.049	−0.015	−0.082	−0.065	−0.054	−0.056
Hand Withdrawal (seconds)	0.017	−0.140*	−0.094	0.030	−0.104	−0.131*	0.008	−0.019	−0.127	−0.105	−0.024	−0.122
Peak Pain (VAS, 0–100)	−0.065	−0.190*	0.183*	0.036	0.073	0.109	0.179*	−0.047	0.123	0.155	0.176	0.119
Pain at Withdrawal, (VAS, 0–100)	−0.029	−0.075	0.102	−0.041	0.071	0.052	0.061	−0.074	0.095	0.117	0.054	0.118
Unpleasantness at Withdrawal (VAS, 0–100)	−0.036	−0.112	0.075	−0.018	0.014	0.015	0.025	−0.045	0.065	0.119	0.067	0.063
Maximum Pain Overall, (VAS, 0–100)	0.006	−0.126	0.147*	−0.024	0.104	0.088	0.085	−0.068	0.110	0.093	0.043	0.121
Maximum Unpleasantness Overall, (VAS, 0–100)	−0.025	−0.127	0.118	−0.017	0.042	0.064	0.039	−0.078	0.099	0.114	0.069	0.076
Pain 30 s after withdrawal, (VAS, 0–100)	−0.061	−0.168*	0.014	−0.012	−0.063	0.03	0.006	0.002	−0.012	0.056	0.046	−0.027
Unpleasantness 30 s after withdrawal, (VAS, 0–100)	−0.049	−0.198**	0.013	−0.083	−0.061	−0.018	0.03	−0.01	0.029	0.106	0.093	−0.019
Physiological Endpoints												
Systolic Blood Pressure	−0.009	−0.017	−0.054	−0.056	0.049	−0.047	0.089	−0.129	−0.015	−0.012	−0.002	0.001
Diastolic Blood Pressure	0.007	−0.041	0.09	0.037	0.147*	0.11	0.126	−0.04	0.124	0.109	0.154*	0.069
Heart rate (beats per minute)	−0.143*	0.100	0.07	0.038	0.089	0.04	0.101	0.042	0.096	−0.003	−0.034	0.065
Respiration rate	0.016	0.049	0.092	−0.072	0.114	−0.017	0.199**	−0.052	0.022	−0.070	−0.085	0.176**
Pupil Diameter (millimeters)	−0.168*	−0.105	−0.042	−0.046	−0.004	−0.094	0.004	−0.177**	−0.014	0.025	−0.001	0.058
Circular Lights	−0.252**	0.134	−0.103	0.027	−0.133	−0.099	−0.111	0.145*	−0.199**	−0.073	−0.049	−0.166*

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
VAS = visual analog scale.

5.07, $p< 0.001$). Seventy-nine percent ($n = 97$) of participants were responsive to the 4 mg hydromorphone dose and 21% ($n = 26$) were not responsive. Mean Drug Effect ratings compared among persons who were and were not responsive to hydromorphone revealed statistically-significant drug-dependent differences in ratings among persons who were responsive (placebo 7.0 [16.1] versus 4 mg hydromorphone 21.4 [25.3]; t(81)= 5.27, $p< 0.001$) but not among persons who were not responsive (placebo 10.4 [19.0] versus 4 mg hydromorphone 13.6 [23.1]; t(24)= 0.82, $p = 0.21$; Fig. 1).

Participants who were responsive on the Drug Effect scale also demonstrated drug-dependent differences in ratings on other subjective scales, including ratings of Good Effects (t(80)= 2.3, $p = 0.02$), Bad Effects (t(80)= 2.2, $p = 0.03$), feeling High (t(80)= 2.6, $p = 0.01$), Nausea (t(80)= 2.2, $p = 0.03$), and the sum of agonist symptoms (t(80)= 2.3, $p = 0.02$). Persons who were responsive subjectively also displayed prominent physiological ratings on measures of pulse (t(81)= 2.1, $p =$

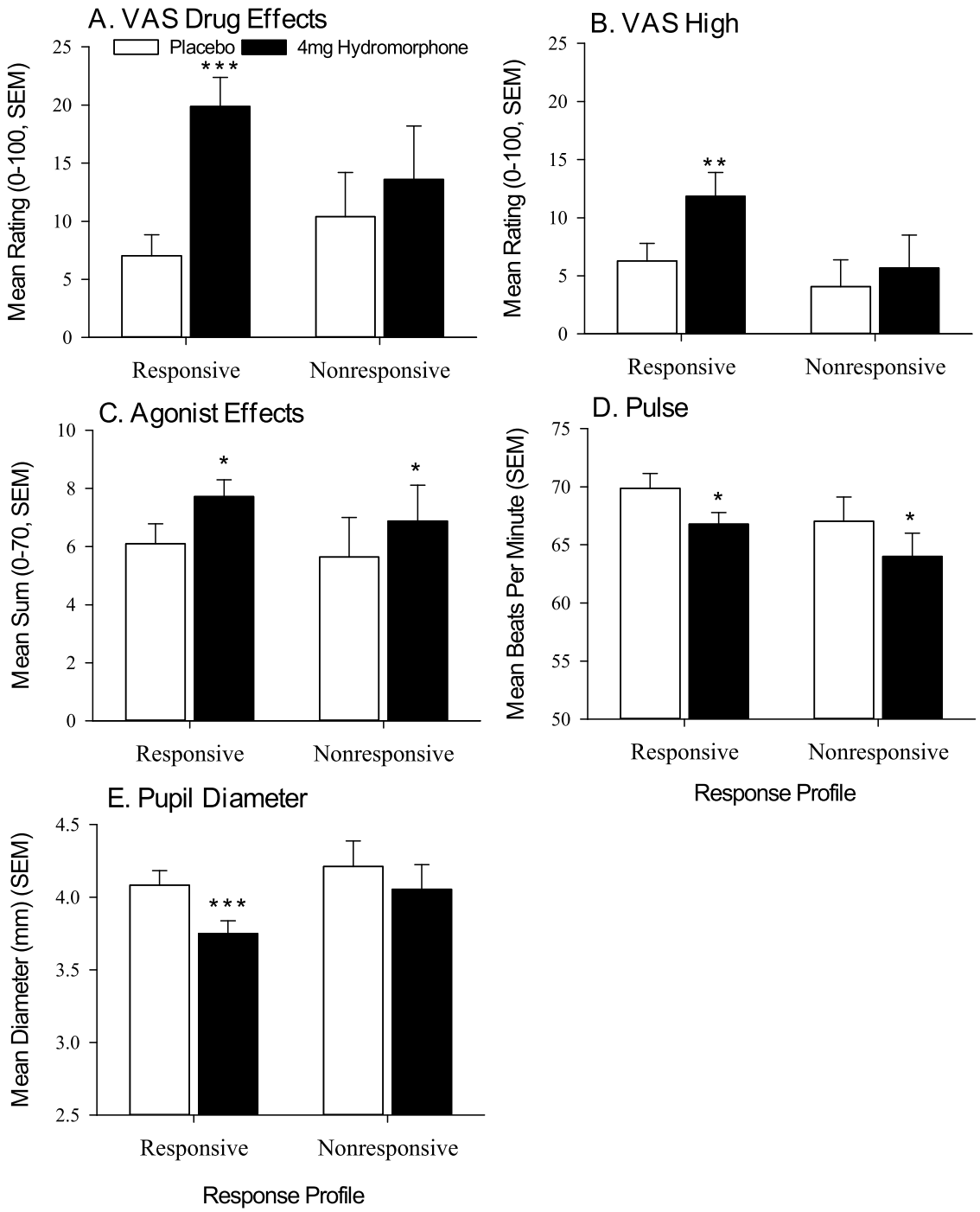

Fig. 1. Outcomes as a function of response profile.
Data represent outcomes as a function of response profile, defined as being responsive (> 20 point difference post-drug on visual analog scale [VAS] rating of drug effects) or nonresponsive as a function of placebo (open bars) and 4 mg oral hydromorphone (filled bars) for subjective ratings of Drug Effects (A) and High (B). Additional outcomes include mean summed values of subjective agonist rating scale (range 0–70, panel C), as well as physiological endpoints of pulse (D), and pupil diameter (E). Data represent mean values collected at the 60 min timepoint and standard error of the mean (SEM). * represents differences $p< 0.05$, ** $p< 0.01$, and *** $p< 0.001$.

0.04) and pupil diameter (t(80)= 2.9, $p< 0.01$), as well as cognitive performance on the circular lights task (t(81)= 3.9, $p< 0.001$). However, persons who were responsive to hydromorphone were not observed as displaying any prominent drug-dependent differences across any of the domains queried.

In contrast, persons who were nonresponsive on the Drug Effect VAS following hydromorphone administration were also much less likely to endorse an effect on other opioid outcomes. Specifically, persons with low subjective Drug Effect ratings only differentiated hydromorphone from placebo on ratings of Good Effects (t(24)= 2.4, $p = 0.03$), the summed agonist symptoms (t(24)= 2.6, $p = 0.02$), and pulse (t(24)= 2.2, $p = 0.04$) (Fig. 1).

Pearson product correlations revealed that opioid responsivity was significantly correlated with detecting opioid effects on several cold-pressor related outcomes including cold pressor tolerance (r(228)= −0.14, $p = 0.04$), peak pain ratings (r(127)= -1.9, $p = 0.03$), and VAS pain ratings at 30 s post hand-withdrawal (r(227)= -0.17, $p = 0.01$), but not with other participant-reported, observer-ratings, or physiological responses.

4. Discussion

These data add to growing evidence that persons experience meaningful differences in opioid response, and those differences are present around the time of opioid initiation (prior to the development of any problematic use behaviors). Participants in this study were generally opioid-naïve individuals with no current or prior history of opioid physical dependence or tolerance who received double-blinded doses of placebo and hydromorphone (4 mg, oral). Despite the lack of tolerance and an opioid dose that is considered moderately high in clinical settings, some individuals did not reliably, subjectively detect the effect of hydromorphone relative to placebo and demonstrated blunted responses across other opioid assays when compared to persons who were subjectively sensitive to hydromorphone.

When the sample was collapsed together, the dose of hydromorphone tested here (4 mg) was found to produce drug-dependent effects across several different opioid-related domains. Effects were most pronounced within self-reported outcomes relative to the observer-ratings, physiological endpoints, and analgesic response profiles, though not all participants who demonstrated a positive signal for opioids on one metric necessarily experienced a positive signal on another important opioid-related outcome. Moreover, none of the outcome domains assessed here (i.e., participant-reported, observed, physiological, analgesic responses) stood out as being uniformly associated with a participant's subjective experience of the drug when assessed across the total sample. This variation in response provides that the experience of opioids within an individual could be domain-specific, such that a dose that exerts an effect in one domain may not be detectable in other domains. This raises questions regarding the optimal assay on which to assess opioid effects or sensitivity.

The results from this study also suggest there may be a subgroup of individuals who demonstrated heightened subjective response to the opioid tested. Specifically, drug-dependent effects were more likely to emerge in persons who subjectively detected a drug effect of hydromorphone 4 mg. Persons within this subsample also evidenced higher ratings for hydromorphone versus placebo on other participant-reported, observed, physiological, and analgesic measures, all of which increased in the expected drug-dependent manner. In contrast, persons who were not subjectively responsive to the dose of hydromorphone tested displayed lower sensitivity to other opioid outcomes. There have been few empirical evaluations of opioid response profiles and this study now adds to those data by examining this question in persons who have a minimal or no history of prior opioid exposure, modeling the larger societal experience of receiving an opioid for the first time for analgesic purposes. It should be noted, however, that the focus here on point-prevalence outcomes, particularly with assays that were assessed at a single time such as the cold pressor, may have occluded our ability to detect changes in opioid sensitivity that emerged in all of the subjects at higher opioid doses or later time periods. Nevertheless, it may still be clinically valuable to know that differences in self-reported detection of effects might not align with expected peak effects or could vary widely across different individuals.

The results from this study support further evaluation into individual differences in opioid response profiles, including among clinical samples, to determine whether there may be a meaningful subgroup of persons who may have an unexpectedly lower clinical experience of opioid medications. It would also be valuable to more thoroughly examine the relationship between opioid assays, particularly the relationship between subjective reports and analgesic response profiles. The fact that time to first pain for the cold pressor task (a strong measure of analgesic effect) was not reliably associated with subjectively detecting an opioid drug effect could reveal a potential disconnect between analgesic effect and the subjective experience of drug effects. An important implication of this finding (if found to be true) is that some individuals might experience an analgesic benefit from opioids without having subjective awareness of the opioid effect whereas other individuals may experience only subjective drug effects without analgesic benefit. This variation in response underlies the importance of moving towards individualized opioid prescribing and reinforces the importance of early evaluation of risks and benefits, consistent with the CDC Clinical Practice Guideline for Prescribing Opioids for Pain, 2022 (Dowell et al., 2022).

These data are limited by the focus on a single opioid dose, which precludes any ability to examine underlying mechanistic contributors to the outcomes observed. In addition, participants were not excluded from the studies based on regular or current use of non-opioid analgesics, which may have had an effect on cold-pressor response, although we assume this limitation is minimal due to recruiting a healthy, pain-free population who presumably would have little need for use of analgesics. Cold pressor outcomes may have been influenced by documented variability in cold pressor response (Mitchell et al., 2004; Reddy et al., 2012) and perhaps even strengthened by conducting a pre-medication baseline, though this would have been applied uniformly to all participants. Data may also have been influenced by self-report recall bias or social desirability bias as well as variability in rating styles across the blinded observers. While the determination of opioid responsivity used here was based upon previous research and FDA guidance (FDA, 2017), it is important to clarify that there is no consensus operational definition of opioid sensitivity so the designation used here should be considered preliminary and for the purpose of these analyses only. We do also acknowledge that by analyzing responder data as a dichotomous between-group design, we were unable to examine the degree to which opioid response may actually vary along a continuum. Further research should be done to replicate the presence of opioid response profiles within various opioid assays and to examine potential characteristics and predictors of response, including within populations who have medical comorbidities or persons with previous opioid exposures.

5. Conclusion

These data provide initial evidence of prominent intra-individual and inter-individual differences in opioid response profiles in persons with no history of opioid use disorder, expanding upon prior research in this area. Outcomes are strengthened by the rigorous within-subject, highly-blinded, drug-dependent design, collection of a wide array of outcome measures, and diversity of participant population with regard to gender and race. Given the interest in exploring and refining non-mu opioid receptor agonists for the treatment of pain (Beck et al., 2019), further research should both continue examining opioid response profiles in response to mu receptor agonists and explore whether sensitivity might extend to other potential opioid receptor agonist targets (kappa).

Disclosures

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Contributors

Authors KED, PHF, CMC, and DGA obtained funding for the studies, CJD and KED led study analyses, all authors contributed to study conduct and manuscript development.

Declaration of Competing Interest

No authors have direct conflicts of interest to report. In the past 3 years, KED has consulted with MindMed Inc., DemeRx, and Cessation Therapeutics. ASH receives research funding from Indivior through his university. CLB receives funding from Canopy Growth Corporation and Pear Therapeutics through her university to conduct research studies. PHF is on the Scientific Advisory Board for Ninnion Therapeutics.

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