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Individual differences in human opioid abuse potential as observed in a human laboratory study

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ABSTRACT

Background: Opioids have high abuse potential and pose a major public health concern. Yet, a large percentage of individuals exposed to opioids do not develop problematic use. Individual differences in opioid abuse potential are not well understood.

Methods: This within-subject (N = 16), double-blind, double-dummy, human laboratory study evaluated individual differences in response to dose (placebo, low, medium, high) following administration of heroin and hydromorphone through intravenous and subcutaneous routes, in opioid-experienced but non physically-dependent participants. Outcomes were self-reported visual analog scale (VAS) ratings (High, Liking, Drug Effect, Good Effect, Rush), pupil diameter change from baseline, and crossover point on the Drug vs. Money questionnaire. The degree to which results were consistent across measures within an individual was assessed using a mixed-effects model from which an intraclass correlation coefficient measure of between and within-subject variance was derived.

Results: The mixed effects model fit was significant ($p < 0.0001$) and revealed that 85.5% of the explainable variance was due to between-subject effects, suggesting the responses within an individual were highly consistent. Visual inspection reveals a myriad response pattern across participants, with some demonstrating classic dose-effect responses and others not differentiating any active doses from placebo.

Conclusions: Data suggest the abuse potential of opioids is significantly different between individuals but that the experience within an individual is highly consistent. Research to prospectively characterize and evaluate mechanisms underlying these differences is warranted and may provide a foundation to help identify persons at heightened risk of transitioning from opioid exposure to misuse and/or opioid use disorder.

1. Introduction

North America is in the midst of an opioid crisis that has been acknowledged by government and health agencies in the United States and Canada as public health emergencies. The need to appropriately balance the prescribing of opioid analgesics for pain management with the potential risk for promoting problematic opioid use and eventual development of opioid use disorder represents a significant conundrum for the research and clinical communities. Risk of opioid misuse can be evaluated using abuse liability studies, which are controlled human laboratory paradigms that expose participants to one or more dose of the drug of interest and examine a variety of outcomes (Carter and Griffiths, 2009). The Food and Drug Administration (FDA) has identified self-reported ratings of "Drug Liking" and "High" as primary outcomes upon which to base determinations of opioid abuse potential (US Food and Drug Administration, 2017), and results from abuse liability studies are generally reported as mean ratings as a function of dose.

A plethora of abuse liability studies have demonstrated that opioids, on average, have a high potential for abuse (Walsh and Babalonis, 2016), yet epidemiological data indicate that a large number of people who take prescribed opioids do not develop problematic use (Higgins et al., 2018), for reasons unknown. Closer examinations of opioid abuse liability studies reveal large differences in individual abuse potential ratings (Bickel et al., 1989; Strain et al., 1992; Walsh et al., 1996). The

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magnitude of difference ranges from persons not being able to differentiate an opioid from placebo to persons experiencing strong opioid agonist effects (e.g., vomiting) at subtherapeutic low doses. For instance, in the only study to formally report on this phenomenon, 61% of participants who received a 30 mg dose of oxycodone were able to differentiate it from placebo, but 31% could not discriminate between oxycodone and placebo on any measure (Antoine et al., 2013). The inability for persons to differentiate between an opioid and placebo happens so often that the FDA has recommended in its 2017 guidance to industry that opioid abuse liability studies include "qualifying" sessions wherein a test doses of the opioid of interest is administered to potential study participants to ensure they can detect opioid effects before being admitted into the study (McColl and Sellers, 2006; Schoedel and Sellers, 2008, 2008; Comer et al., 2012, 2012; US Food and Drug Administration, 2017). This observed variability in opioid response is not limited to studies of abuse potential; many studies have also reported pronounced and reliable differences in how patients respond to opioids for pain management (Kaiko et al., 1983; Portenoy et al., 1990).

Understanding more about different opioid abuse liability profiles, or the magnitude of individual differences that exist with regard to opioid effects, would directly support research into the mechanisms underlying those differences and the degree to which they contribute to the transition from opioid use to misuse. Such information could ultimately be used to inform clinical decisions with regard to opioid analgesic treatment strategies and to help advance the use of precision medicine in the areas of pain management and opioid use disorder. The aim of the current report is to contribute to the literature on differences in opioid abuse liability ratings between and within individuals, to help provide a foundation upon which future empirical studies examining this phenomenon can be premised. These data are taken from a rigorous, within-subject, double-blind, double-dummy, placebo-controlled, human laboratory study that collected outcomes related to opioid abuse potential following administration of the two opioid mu agonists heroin and hydromorphone, administered through both intravenous and subcutaneous routes and at four dose levels (placebo, low, medium, high) (Dunn et al., 2018).

2. Methods

2.1. Participants

Sixteen opioid-experienced users were recruited between 2000 to 2001 from newspapers and word of mouth. To be eligible for the study, participants had to report monthly intravenous use of opioids for > 6 months and provide a urine sample that tested positive for opioids, but show no signs of opioid physical dependence following a 48 -h opioid-free observation period. Participants were excluded from study participation if they were physically dependent on opioids or other substances except nicotine; had a history of seizures, cardiovascular disease, liver disease, or diabetes; were taking prescribed medications; had abnormal blood chemistry, hematology, medical urinalysis, or electrocardiogram (ECG) readings during an eligibility screening; or had other significant medical and/or psychiatric disorders as assessed by clinical interviews. The study was conducted at the University of Toronto and at Johns Hopkins University and participants were compensated up to $1040 for participation and task performance. Both sites received IRB approval for study conduct and subjects provided voluntary informed consent to participate. Only methods relevant to the current analyses are presented below; a full report of the study measures and primary outcomes is available elsewhere (Dunn et al., 2018).

2.2. Experimental sessions

Eligible participants were admitted to a closed residential research unit for six weeks. Participants completed 16 experimental sessions that were scheduled > 48 h apart to minimize carry-over effects and control for potential acute opioid tolerance following drug administration (Bickel et al., 1988; Heishman et al., 1989, 1990; Kirby et al., 1990). Each session day began at 08:00 when participants consumed a calorie-controlled breakfast and provided a urine sample that was tested for evidence of recent drug use. Participants who were cigarette smokers were permitted to smoke a single cigarette prior to study drug administration (and a second cigarette after 2 h elapsed). Participants then received double-blind and double-dummy intravenous (IV) and subcutaneous (SC) injections of the study drugs described below. Participants received both injections during each session but only one active drug was administered per session. A crash cart with supplemental oxygen, a defibrillator, and the opioid antagonist naloxone was available onsite for emergencies.

2.3. Measures

Self-report ratings were collected using visual analog scales (VAS) for High, Rush, Liking, Good Effects, and Drug Effects. VAS were rated on a scale 0 (not at all) to 100 (extremely) and were collected prior to drug administration (baseline), once per minute for the first 15 min, and then at 30-, 45-, 60-, 90-, 120-, 150-, and 180- minutes post-dosing. Higher ratings were conceptualized as indicating stronger drug effects and more potential for abuse. Pupil diameter in millimeters (mm) was collected as a physiological measure of opioid agonist activity under consistent lighting using a customized pupillometry device or with a Polaroid camera at baseline and 16-, 30-, 60-, 90-, 120, 150- and 180-minutes post-dosing. Doses that led to greater miosis (constriction) were generally interpreted as having greater agonist activity. Participants also completed the drug vs. money choice question at the 30- and 150-minute time points. This was a computer-based item for which participants moved a cursor along a $0 - $50 continuum to indicate the dollar values at which, in a choice situation, they would have selected money over that day's drug exposure. The lowest dollar value at which money was preferred, defined as the crossover point, was understood to be the equivalent dollar value of the drug and dose tested that day. Doses assigned higher dollar values were interpreted as having greater abuse potential.

2.4. Study drugs

Participants received IV or SC injections of placebo, low, medium, and high doses of heroin or hydromorphone at every study session. The order of drug administration was quasi-randomized within individual participants and the largest dose was never administered first. Heroin was administered IV at 0 mg, 2.5 mg, 5 mg, and 10 mg and SC at 0 mg, 5 mg, 10 mg, and 20 mg. Hydromorphone was administered IV at 0 mg, 0.63 mg, 1.25 mg, and 2.5 mg and SC at 0 mg, 1.25 mg, 2.5 mg, and 5 mg. IV doses were administered slowly over 30 s through a 23-guage butterfly cannula via an indwelling intravenous catheter in an identical volume of fluid (2 ml), followed by a saline flush of the cannula line (2 ml). All SC doses were injected into the upper arm. Both medications were prepared independently at each site by research pharmacists. Hydromorphone was purchased from domestic commercial sources and heroin was obtained commercially from international pharmaceutical suppliers.

2.5. Data analysis

The goal of these secondary analyses was to characterize individual differences in the human abuse potential response to two prototypic mu opioid agonists. Peak self-report ratings, pupil diameter change-from-baseline in mm, and drug vs. money crossover point (e.g., assigned dollar value) were analyzed as primary outcomes. Pupil diameter change from baseline was calculated by subtracting the pre-drug pupil size from each post-drug pupil size at each time point; this was done to

control for physiological differences in pupil size across participants. A mixed-effects linear model was then fit to assess the degree to which the dose response to study drugs varied between participants (as a measure of between-subject difference) and remained internally consistent within a participant (as a measure of within-subject consistency). Responses were nested within subjects, and the mixed-effects linear model was fit using the following equation:

response ~ 1 + drug + route + dose + measure + (1 + dose + measure || ID)

This model estimated separately, for each participant, the intercept and slope for effect of dose and measure on response. All measures (VAS values for High, Rush, Liking, Good Effecs Drug Effects, pupil change from baseline, drug vs. money crossover point) were included in the model to ensure individual differences were not limited to the domain being measured. The resulting intraclass correlation coefficient (ICC) provided a ratio of between-subject variance explained by the model to the total variance explained by the model (Raudenbush and Bryk, 2002). An equivalent fixed-effects model that did not nest responses within-measure or within-subject was also conducted to compare model fit indices between the mixed and fixed effects models, using Akaike's information criterion (AIC; Akaike, 1974) and Bayesian Information Criterion (BIC; Schwarz, 1978) measures. AIC and BIC are measures of model fit that account for different numbers of parameters between models by penalizing the number of parameters in the given models and lower AIC and BIC values indicate better model fit. Data were standardized within measure (across all participants) using z-score transformations to remove influence from between-measure differences in response scales. The models were then re-calculated without standardizing the response data; those results are not reported because they were quantitatively very similar and qualitatively identical to the results discussed below. Analyses were conducted using the R statistical software v3.5.0 (R Core Team, 2018) and the *lme4* package (Bates et al., 2015), and alpha was set to 0.05.

3. Results

3.1. Participants

Participants were Caucasian (50%) and African American (50%), 100% male, were a mean (SD) of 37 (6.2) years old, had a mean education of 12.4 (2.2) years, weighed 172.1 (25.3) pounds, reported using heroin for approximately 6.5 (6.1) years, and had used heroin an average of 5.8 (4.5) days in the past 30.

3.2. Evaluation of individual differences

Evaluation of model fit ($\Delta\chi^2[23] = 1401$, $p < 0.00001$) suggested the mixed effects model had a better fit (AIC = 2624.1, BIC = 2800.2, df = 33) than the fixed effects model (AIC = 3979.0, BIC = 4032.4, df = 10). The ICC calculated from the mixed-effects model was 0.855, indicating that 85.5% of the variance explained by the model could be attributed to between-subject differences in drug response and that no more than 14.5% of the variance could be explained by within-subject variance. These results indicate there was significant within-subject reliability with regard to self-report, physiological, and drug valuation ratings at each dose level and that outcomes were not specific to the measure under evaluation.

Fig. 1 displays the individual dose-effect results of the self-report, pupil diameter, and drug vs. money choice question, as a function of dose; results are collapsed across drug and route because a previous analysis found the elements did not significantly impact participant response relative to dose (Dunn et al., 2018). Fig. 1 provides visual confirmation that some participant ratings (e.g., participant 1) displayed classic dose-response patterns whereby outcomes increased in a conventional dose-dependent manner. In contrast, other participants (e.g., participant 16) showed almost no evidence of a dose-related response on any measure, indicating little to no dose-dependent effect of the study drugs. Moreover, although participant 1 shows prototypical dose effect changes whereby self-report and drug vs. money responses and the magnitude of pupil change from baseline increase as the dose increases, participant 16 shows no change in self-reported responses and very minimal variations in pupil size as a function of dose. Additional participants showed evidence of a strong effect that was not dose-dependent. The high level of correspondence across the myriad outcomes (VAS, pupil, drug vs. money) illustrated in Fig. 1 supports the results of the ICC analyses and provides visual confirmation that response varied between individuals but that an individual participant had consistent dose-dependent effects across measures.

4. Discussion

This study expands upon previous research (Bickel et al., 1989; Strain et al., 1992, 1992; Walsh et al., 1996, 1996; Antoine et al., 2013) and provides evidence of remarkable internal consistency within an individual with regard to their opioid mu agonist response pattern despite significant variability between individuals. Specifically, this analysis shows that the majority of variance in dose-dependent responding to different opioid drugs, doses, and routes was attributed to individual differences between participants, whereas an individual participant's experience was highly consistent. This pattern was true despite several different domains (e.g., self-report ratings, physiological effects, drug preference) being included in the model, which suggests the effect is robust and unrelated to idiosyncratic responding on a particular measure. Moreover, the fact that this level of difference was evident among individuals who had an established history of using opioids, which suggests they already have a history of finding opioids reinforcing, is especially intriguing.

It should be noted that this is a secondary analysis from a parent study that was conducted in 2000 and that very limited data on participant characteristics were collected. It is therefore not possible to determine whether the participant ratings were correlated with different demographic, drug use, or physiological characteristics. We know of no studies that have prospectively evaluated the mechanisms underlying individual differences in opioid abuse liability in humans, and retrospective analyses of laboratory and/or treatment outcome studies have not yet revealed any consistent demographic, drug use, and/or treatment characteristics that can reliably predict opioid abuse potential (McLellan et al., 1994; Brewer et al., 1998; Franken and Hendriks, 1999; Morral et al., 1999; Gossop et al., 2002; Raby et al., 2009). Chronic exposure to opioids may also alter the interoceptive cues through which an individual detects an opioid, thereby changing his or her individual likelihood of abusing opioids.

The majority of studies reporting differences in opioid effects have been conducted in the context of analgesia and these studies have reported prominent differences in analgesic response as a function of sex, genetics, and cytochrome P450 enzyme metabolism (Kaiko et al., 1983; Portenoy et al., 1990; Lee and Ho, 2013; Matic et al., 2017; Solhaug and Molden, 2017; Huhn et al., 2018). These same targets have not yet been thoroughly examined with regard to opioid abuse potential risk, though these data suggest those studies are warranted. The degree to which differences in opioid abuse potential correspond to differences in opioid analgesic efficacy is also unknown. However, understanding more about the mechanisms underlying the differences in how persons experience opioids has the potential to inform efforts to refine opioid prescribing and also reduce risk for opioid misuse. These approaches would be consistent with the field of personalized medicine, which uses individual response profiles to tailor prescribing in order to maximize treatment outcomes and minimize related adverse effects (Branford et al., 2012). The ability to prospectively reduce risk of opioid misuse while still providing patients with adequate pain management would

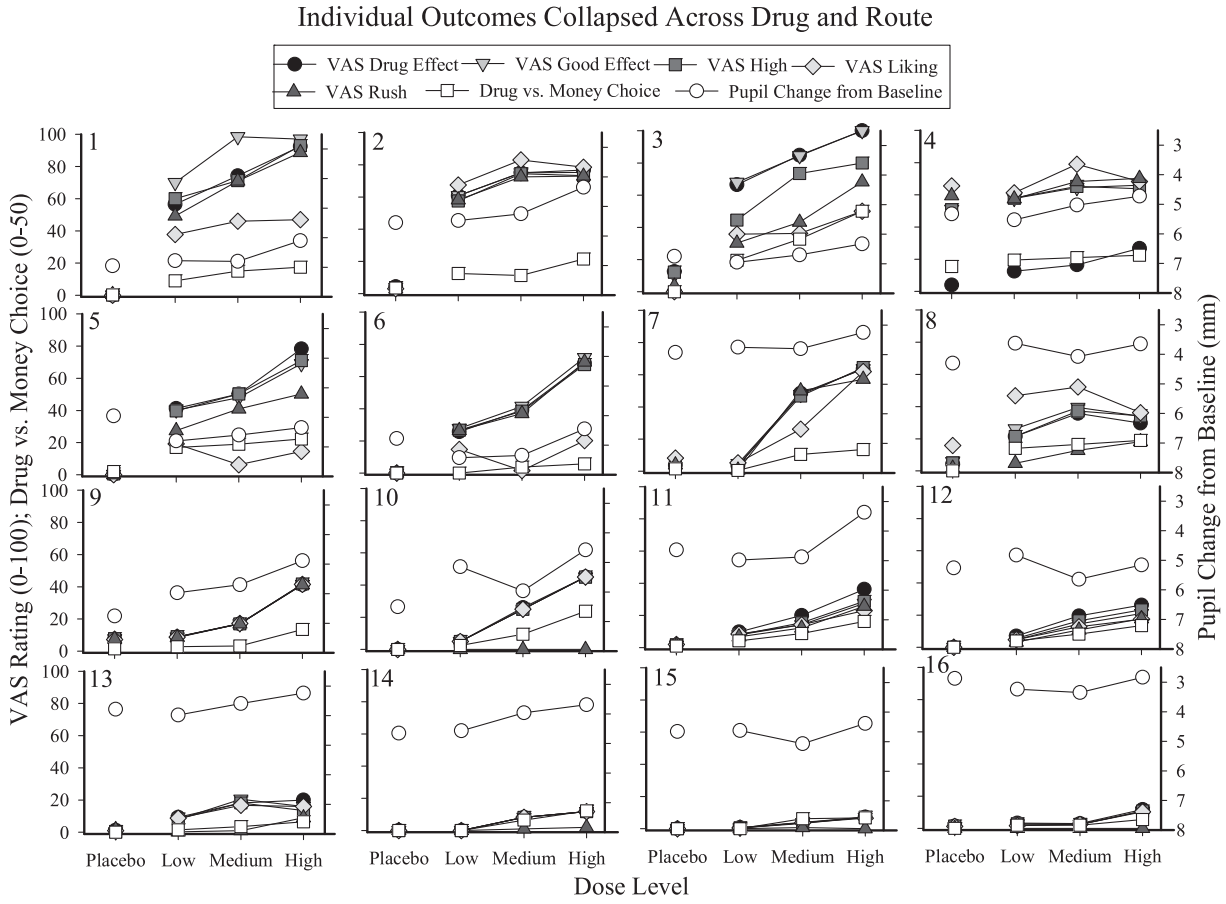

Fig. 1. Individual Outcomes Collapsed Across Drug and Route. Values represent the peak rating during each drug administration session for five independent visual analog scales (VAS; Drug Effect, High, Good Effect, Drug Liking, Rush; gray-scale symbols), the drug vs. money choice crossover value (open square), and pupil diameter change from baseline in millimeters (mm; open circle). The left Y-axis represents peak ratings for the VAS (scale 0–100) and the drug vs. money choice procedure (scale 0–50). The right Y-axis represents pupil size in mm; since pupillary constriction is measured for evidence of an effect, the direction of the right Y-axis is descending so data will move in the same direction as the other outcomes. For all three outcomes, higher rankings represent greater effects. Results are collapsed across drug (heroin, hydromorphone) and route (intravenous, subcutaneous) and presented as a function of dose (placebo, low, medium, high) along the X-axis. Each graph represents a different participant (range 1–16), as designated by the number in the upper left corner. A mixed effects model ($p < 0.0001$) that transformed all seven outcomes to the same scale for comparison yielded an intraclass correlation coefficient (ICC) of 0.855, indicating 85.5% of explainable variance in the model resulted from between-subject comparisons, suggesting a high degree of within-subject consistency in response patterns.

support providers who are trying to balance opioid need and risk in their patients. Data from highly-controlled, double-blinded, within-subject abuse liability studies might also provide important contributions to the development of risk algorithms, a concept that has gained recent traction in the research community to help providers assess risk of problematic opioid use in their patients (Brenton et al., 2017).

It is important to note that participants had to report a history of non-medical opioid use to be eligible for this study, which suggests that even the low responders in this study had a history of finding opioids reinforcing. It is therefore possible that the individuals who did not demonstrate a significant dose-response in this study did not receive a dose that was large enough to be physiologically detectable for them (though this finding is also of scientific interest). Participants who have a history of illicit opioid use but are currently abstaining may differ in important ways from other subpopulations of persons using opioids, so it is not clear how well these data will generalize to these other groups. Studies examining the opioid abuse liability profile of abstinent individuals with and without a history of opioid use disorder would help advance our understanding of opioid abuse liability risk. Additional limitations include that this is a secondary analysis of a parent study that was not prospectively designed to support intense investigation of individual differences, that only men volunteered to participate in this study, and that the doses selected for this study aimed to be equipotent across drugs and routes (Dunn et al., 2018) so the degree to which these results will extend to other drugs and doses is unknown. Finally, the small sample size in this study (n = 16) may have obscured the full distribution of participant responses. It is important that this study be replicated to inform whether the pattern of participant responses adhere to a normal (suggesting that persons fall along a continuum of responses) or bimodal (suggesting that persons either do or do not detect opioids) distribution, which will help inform future efforts to elucidate individual differences in opioid response.

Overall, these results provide evidence that an individual may have high reliability in his or her own experience of opioids but that the opioid response pattern across people differs in ways that may be clinically significant. The fact that several outcomes (self-report, physiological, drug preference) relevant to opioid abuse potential showed the same response profile supports the robustness of the results. A primary goal of this report is to prompt more focused exploration into the breadth and determinants of individual differences in opioid abuse potential, including evaluation of the correlates and mechanisms underlying these results and any associations that might exist between responses on abuse potential metrics and opioid analgesic efficacy. A more refined and thorough understanding of the basis upon which people experience opioids could ultimately be used to help providers better tailor individual opioid dosing strategies and identify persons at risk for developing problematic opioid use following opioid exposure via prescription. Empirical evaluation of mechanisms underlying

individual differences in opioid abuse potential could ultimately contribute to addressing society's current opioid crisis.

Contributors

Authors BB, DM, and GB developed and conducted the study. KD developed the first draft of the current manuscript and conducted the analyses. FB conducted the statistical analyses. All authors reviewed and approved the manuscript for submission. Bruna Brands conducted this work prior to becoming a Health Canada employee.

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Declaration of Competing Interest

None of the authors have any conflicts of interest relevant to the analyses in this manuscript.

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