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Retrospectively assessed subjective effects of initial opioid use differ between opioid misusers with opioid use disorder (OUD) and those who never progressed to OUD: Data from a pilot and a replication sample

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Abstract

Attempts to identify opioid users with increased risk of escalating to opioid use disorder (OUD) have had limited success. Retrospectively assessed subjective effects of initial opioid misuse were compared in a pilot sample of opioid misusers (nonmedical use ≤60 times lifetime) who had never met criteria for OUD (N = 14) and heroin-addicted individuals in treatment for OUD (N = 15). Relative to opioid misusers without a lifetime OUD diagnosis, individuals with OUD reported greater euphoria and other positive emotions, activation, pruritus, and internalizing symptoms. Consistent with these findings, proxy Addiction Research Center Inventory (ARCI) Amphetamine Group, and Morphine Benzedrine Group scale mean item scores were significantly higher in those with OUD. Replication was attempted in opioid misusers with (N = 25) and without OUD (N = 25) who were assessed as part of an ongoing genetic study. We observed similar significant between-group differences in individual subjective effect items and ARCI scale mean item scores in the replication sample. We, thus confirm findings from prior reports that retrospectively assessed subjective responses to initial opioid exposure differ significantly between opioid users

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AUTHOR CONTRIBUTIONS

Conceptualization, A.A. and E.C.N.; *Investigation,* A.A. and E.C.N.; *Formal Analysis,* E.C.N. and P.W.J.; *Writing – Original Draft,* A.B.S. and E.C.N.; *Writing – Review & Editing,* A.A., P.W.J., A.B.S., V.V.M., M.T.L., A.C.H., and E.C.N.;*Project Administration*, A.A. and E.C.N.; *Funding Acquisition,* A.A. and E.C.N.

DECLARATION OF TRANSPARENCY

The authors, reviewers and editors affirm that in accordance to the policies set by the *Journal of Neuroscience Research*, this manuscript presents an accurate and transparent account of the study being reported and that all critical details describing the methods and results are present.

CONFLICT OF INTEREST

None of the authors have any conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

who do, and do not, progress to OUD. Our report extends these findings in comparisons limited to opioid misusers. Additional research will be necessary to examine prospectively whether the assessment of subjective effects after initial use has predictive utility in the identification of individuals more likely to progress to OUD.

Keywords

initial opioid use; opioid misusers; opioid use disorder; subjective effects

1 | INTRODUCTION

Markedly increased prescribing of opioids has contributed to spikes in prescription opioid and heroin misuse that have, in turn, led to increased mortality (Hedegaard, Miniño, & Warner, 2018; Kolodny et al., 2015; Rudd, Aleshire, Zibbell, & Gladden, 2016). CDC reports on opioid overdose deaths have observed interrelated trends with increased deaths initially due to prescription opioid analgesics followed by surges in deaths involving heroin and more recently synthetic opioids (i.e., primarily fentanyl and its derivatives) (Hedegaard et al., 2018; Rudd et al., 2016).

Given the morbidity and mortality associated with opioid use disorder (OUD), a means of identifying individuals exposed to opioids who are at increased risk for developing OUD would have substantial clinical utility. Attempts to do so have often relied on questionnaires documenting aberrant use or factors known to contribute to liability (e.g., depression, substance use disorder, and family substance use disorder history) (Butler, Fernandez, Benoit, Budman, & Jamison, 2008; Jamison, Butler, Budman, Edwards, & Wasan, 2010). Other research has hypothesized that the subjective effects of initial use could be useful to identify individuals who progress to addiction (Bieber et al., 2008; Haertzen, Kocher, & Miyasato, 1983). One early study of male drug abusers ($N = 42$) found that their retrospective report of the degree of reinforcement from their initial experience with a drug (including, but not limited to heroin and other opioids) was a strong indicator of their subsequent pattern of drug use (Haertzen et al., 1983). Other early studies have had inconsistent or even contradictory findings; however, methodological issues complicate their interpretation (Lasagna, Von Felsinger, & Beecher, 1955; McAuliffe, 1975; Zinberg, 1984).

A later report (Bieber et al., 2008), which provided the basis for the current investigation, used the modified short-form version (Martin, Sloan, Sapira, & Jasinski, 1971) of the Addiction Research Center Inventory (ARCI) to assess retrospectively the subjective effects of initial opioid use in two convenience samples of individuals who used opioid analgesics prescribed for chronic pain—individuals who did ($N = 20$), and did not ($N = 20$) develop DSM-IV opioid dependence. The ARCI was developed to measure a broad range of subjective effects that may be experienced with the use of drugs. The short form was adapted for retrospective use by Bieber and colleagues (2008). The current report includes five sub-scales: (1) the Morphine Benzedrine group (MBG) which contains primarily euphoria items with high scores indicative of feeling popular, happy, and expansive; (2) the Pentobarbital, chlorpromazine, and alcohol group (PCAG) which consists of items on

fatigue and low motivation with high scores indicative of fatigue, slowness, heavy feelings, and lack of motivation; (3) the Lysergic acid diethylamide group (LSDG) which includes items on anxiety, tension, depersonalization, and difficulty concentrating; (4) the Benzedrine group (BG) which includes items indicative of intellectual efficiency and energy; (5) the Amphetamine group (AG) which includes items selected from the other scales of the basis of their dose–dependent relationship to sympathomimetic amines (Haertzen, 1974; Martin et al., 1971). Bieber et al. (2008) found that opioid-dependent individuals reported having had greater euphoric and stimulating effects with initial opioid use than nondependent chronic pain patients.

A recent report (Bruehl et al., 2019) retrospectively assessed subjective effects of initial opioid exposure and then administered either morphine or placebo in a double-blinded manner to patients with chronic low back pain who were not using opioid analgesics on a daily basis. The authors found that those who had reported greater euphoric responses to initial opioid exposure had significantly less analgesia and sedation coupled with greater euphoria and increased desire to take the drug again in response to morphine administration.

The current investigation compares retrospective reports of initial subjective response to opioids in a pilot sample of individuals with a history of opioid misuse that never progressed to OUD (i.e., negative for lifetime OUD diagnosis) and a convenience sample of individuals in treatment for OUD involving heroin use. This report also examines whether these findings are replicated in a second sample that utilized consistent methods for ascertainment and assessment of cases and controls. This research was undertaken to extend prior reports (primarily, Bieber et al., 2008) by determining whether similar between-group differences in subjective effects are observed in samples that consist entirely of individuals with a history of opioid misuse (i.e., nonmedical opioid use and thus substantial liability for drug use disorders).

2 | MATERIALS AND METHODS

2.1 | Participants

Written informed consent was obtained from all participants in both samples as per the protocols approved by the institutional review boards of Washington University School of Medicine (WUSM) and the State of Missouri. Individuals from both sexes were included in each of these samples (see below for details). The replication sample includes the first 25 participants from each group recruited for a larger, ongoing genetic study (NIDA R01 DA042620 PIs ECN; AA). For both samples, we excluded individuals whose misuse history was not consistent with their diagnostic assessment (i.e., low-level misusers meeting criteria for OUD and individuals with high levels of lifetime misuse not meeting OUD criteria [details provided below]).

2.2 | Non-OUD opioid misusers

For both the pilot and replication samples, we recruited individuals with a lifetime history of opioid misuse (i.e., nonmedical use) who had never met criteria (lifetime) for OUD from various sources that included existing WUSM recruitment resources involving volunteer

lists and outreach efforts, electronic (e.g., Craigslist) and hard copy (poster) advertisements, prior participants in research projects focusing on other forms of substance dependence, and identification by other participants (i.e., snowball sampling) and key informants (e.g., leader of an opioid dependence advocacy group) (Korf, van Ginkel, & Benschop, 2010; Randesi et al., 2016; Zaaijer et al., 2014). A brief screening telephone call was conducted to determine potential participants' opioid misuse history. Inclusion criteria were age (18 or older), ethnicity (European American or African American), and opioid misuse (i.e., nonmedical use) 60 or fewer times lifetime. Exclusion criteria at screening, selected to reduce the likelihood of including individuals with substantial residual liability for progression to OUD, included greater than this level of past opioid misuse, a history of daily misuse, and any misuse during the past year.

For the pilot sample, in-person interviews were completed individually by an experienced interviewer (JS) using a modified Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (Bucholz et al., 1994; Hesselbrock, Easton, Bucholz, Schuckit, & Hesselbrock, 1999). This version of the SSAGA obtained the age of first, and most recent use, as well as DSM-5 substance use disorder diagnoses for prescription opioids, heroin, cannabis, amphetamines, sedatives, and cocaine. Two individuals found to meet the criteria for a lifetime diagnosis of OUD via interview were excluded resulting in 14 non-OUD misusers (8 M, 6 F) being retained for the current analyses.

For the replication sample, we report on the first 25 participants (9 M, 16 F) who reported having misused opioids 60 or fewer times lifetime and who did not meet criteria for OUD. We excluded 16 individuals (10 M, 6 F) who were enrolled during this period who reported having misused opioids 12–70 times lifetime, but were similarly found to meet DSM-5 criteria for OUD (see Tables S1–S3).

2.3 | OUD individuals

For the pilot sample, these individuals (N = 15; 8 M, 7 F) were ascertained from a local drug treatment facility where they were all currently enrolled in treatment for OUD (diagnosed by the treating physician and involving heroin use). The limited additional information obtained from these individuals included the duration of their daily or near daily heroin misuse (mean duration 13.2 years [SD 12.5]) and their primary route of use (via injection [12] or snorting [3]). Their history of other drug misuse was not assessed. For the replication sample, we ascertained these individuals (N = 25; 7 M, 18 F) from a number of local drug treatment facilities via poster advertisements as well as through the various sources described above for non-OUD controls. Their assessment included a modified SSAGA identical to that used for controls. Three individuals who reported extensive opioid misuse (ranging from 121 to more than 10,000 times lifetime), but failed to meet criteria for OUD, were excluded from these analyses.

2.4 | Measures

Basic demographic data including age, sex, and race were collected from all participants. Individuals were asked which opioid they first misused and instructed to respond to subsequent questions referring to that experience. In the pilot sample, subjective response to

initial opioid misuse was conducted with 31 items from the short form version of the ARCI (Haertzen & Hickey, 1987; Haertzen et al., 1983; Martin et al., 1971) and modified to enable retrospective assessment that were selected primarily based on case-control differences from Bieber et al. (2008). Two non-ARCI items ("I felt itchy." and "I did not like the way the drugs made me feel.") that have been found to be heritable (Angst et al., 2012) were also included. All items assessing subjective effects required responses of "true" or "false." For the non-OUD respondents, these items were included in the modified SSAGA administered by one experienced interviewer (JS). The OUD respondents were provided detailed verbal instructions by one individual (ECN) to enable completion of these items as a self-report questionnaire.

For the replication sample, all 46 ARCI items from the prior report (Bieber et al., 2008) and the two additional items were included in the modified SSAGA administered by trained interviewers.

2.5 | Data analysis

All analyses were conducted using SAS 9.4. For age, onset, and time since first misuse, non-OUD and OUD participants were compared using a nonparametric Mann–Whitney *U* test; similar comparisons for categorical data used a continuity-adjusted chi-square because of modest sample sizes. To enable broader comparison to the existing literature (which more commonly reports ARCI data as scale scores rather than individuals items), we calculated mean item endorsement for the five ARCI scales. For pilot data, these calculations were based on the subset of items that were assessed (i.e., 11/15 from the Morphine Benzedrine Group [MBG] scale, 10/15 from the Pentobarbital chlorpromazine alcohol group [PCAG] scale, 9/12 from the Lysergic acid diethylamide group [LSD] scale, 8/10 from the Amphetamine group [A] scale, and 6/12 from the Benzedrine Group [BG] scale); for the replication sample, all items from the prior report (Bieber et al., 2008) were included. For both samples, we used Mann–Whitney *U* tests to compare the mean item scores for each scale for those with and without OUD.

3 | RESULTS

In the pilot sample, the mean value for the number of times having misused opioids (lifetime) reported by the non-OUD opioid misusers was 18.6 (*SD* 17.5). These individuals also endorsed very high rates of lifetime misuse of other illicit drugs (Table 1). The prevalence of lifetime illicit drug use disorders in this group was also substantial (e.g., 50% met criteria for lifetime cocaine use disorder). The respective mean values for time elapsed since the initial and last opioid misuse for the non-OUD misusers were 13.1 years (*SD* 9.5) and 8.5 years (*SD* 8.9). The OUD and non-OUD groups did not differ significantly in age, sex, ethnicity, or whether the first opioid misused was a prescription or illicit opioid (i.e., heroin or opium).

The endorsement of subjective response items by non-OUD opioid misusers and OUD individuals is displayed in Table 2. While the majority in both groups endorsed some items expressing pleasure (e.g., "I felt as if something pleasant just happened to me") and sedation (e.g., "I felt drowsy"), individuals with OUD more frequently endorsed items indicative of

(1) experiencing greater levels of euphoria and other positive emotions (e.g., “I would be happy all the time if I felt as I felt then”); (2) activation (e.g., “My movements seemed faster than usual”; “I felt more excited than dreamy”); (3) pruritus (e.g., “I felt itchy”); and (4) internalizing symptoms (i.e., anxiety, moodiness, and avoidance). The largest observed between-group differences are striking both in terms of the degree of agreement with the prior report (Bieber et al., 2008) and their overall significance despite the modest sample size. Comparisons of mean item endorsement for ARCI scales in the two groups found the greatest differences in MBG and A scales with the BG Scale also reaching significance. The sub-scale findings also replicate the prior report and emphasize differences in measures of self-perceived euphoria, activation, and intellectual efficiency.

In the replication sample, individuals with OUD were somewhat younger than the non-OUD participants; the OUD group also included more African Americans (Table 1). The replication sample's OUD group reported a somewhat lower mean number of times having misused opioids 10.8 (*SD* 14.3) than that of the pilot sample. While non-OUD participants reported their first opioid misuse at a later age, time since first opioid misuse did not differ between groups with both groups reporting longer intervals than those in the pilot sample. The two groups again did not differ as to whether the first opioid misused was a prescription or illicit opioid (i.e., heroin or opium). The non-OUD group again had very high rates of lifetime misuse for other illicit drugs; their prevalence of illicit drug dependence was significantly less than that of the OUD group across drugs and somewhat lower than that of the pilot sample's non-OUD group. The excluded low-level misusers who met the criteria for OUD were predominately male and also reported very high rates of other drug misuse and substance use disorders (Table S1).

Comparisons of endorsement rates for individual items in the replication sample yielded results that were extremely consistent with that of the pilot sample (Table 2). Items endorsed more frequently by OUD individuals could similarly be categorized as involving euphoria and positive emotions (e.g., “I would be happy all the time if I felt as I felt then”), activation (e.g., “My movements seemed faster than usual”), internalizing symptoms (e.g., “I was moody”), and pruritus (“I felt itchy”). Greater inter-group differences observed for two potentially related items perhaps indicative of opioid sensitivity (“My speech was slurred”; “Some of my body parts were tingling”) appear to be a consequence of considerably lower endorsement by the replication sample's non-OUD individuals. The endorsement of subjective effects items by the excluded low-level misusers who met criteria for OUD suggests that this group may have had greater sensitivity to the diverse effects of opioids (Table S2). For example, while all endorsed their movements being faster than usual, nearly as many (87.5%) endorsed feeling anxious and upset and not liking how the drug made them feel.

Mean item scores for the ARCI scales (more completely assessed) in the replication sample revealed very similar inter-group differences. In the replication sample, between-group differences also reached significance for the LSD Scale as well as the BG Scale, but were once again strongest for the A and MBG scales (Table 3). The mean item scores for the excluded low-level misusers who met criteria for OUD had values that were consistently

intermediate between those of the low-level misusers who did not OUD criteria and the high-level misusers who did (Table S3).

4 | DISCUSSION

Despite potential differences in the type of opioid use (prescribed vs. recreational), the results from the comparison of our samples' non-OUD opioid misusers and OUD individuals are very consistent with the prior report (Bieber et al., 2008). The OUD individuals retrospectively reported greater levels of pleasure, activation, and internalizing symptoms after initial opioid use. The comparisons of mean item endorsement for ARCI scales found significant between-group differences that further replicate Bieber and colleagues' (2008) findings and confirm our characterization of patterns observed in the individual item data with the strongest differences in measures of self-perceived euphoria, activation, and intellectual efficiency. The degree of replication is particularly notable given the considerable inter-study differences in comparison group ascertainment (opioid misusers vs. chronic pain patients) and the first opioid used (heroin was the drug most commonly identified by both non-OUD misusers and OUD individuals in our pilot study). The mean interval between initial opioid misuse and assessment was more than 13 years for the current report's pilot non-OUD misusers and OUD individuals; the similar value for our replication sample was nearly two decades. In both samples, these intervals are longer than that of the prior report (Bieber et al., 2008) in which assessment followed initial prescribed opioid use by 8 years for cases and 12 years for controls.

The association of stimulant-like response to initial opioid exposure with greater addiction liability is consistent with an extensive literature focusing on differences observed between inbred mouse strains (Murphy, Lam, & Maidment, 2001; Oliverio & Castellano, 1974). Thus, genetic sources may be contributing to observed individual variation in initial response to opioids. Additional support for a genetic contribution to differences in how individuals respond to opioids is provided by a pharmacogenomics twin study that administered an opioid or saline placebo in a double-blind design. The authors observed both drug disliking and opioid-induced pruritus to be somewhat heritable (Angst et al., 2012).

A supplemental (i.e., non-ARCI) item that we included in our assessment found that OUD individuals also reported markedly higher prevalence of itching associated with their initial opioid misuse. Pruritus is a common adverse effect of opioids for which isoforms of the mu-opioid receptor have been demonstrated to play essential roles in mice (Liu et al., 2011; Miyamoto & Patapoutian, 2011) and humans (Liu, Ginosar, Yazdi, Hincker, & Chen, 2019). This class of isoforms (i.e., those with seven transmembrane domains) have also been implicated in morphine tolerance and reward in mice (Xu et al., 2017). One prior report (Azolosa, Stitzer, & Greenwald, 1994) administered morphine intramuscularly and assessed subjective response post-injection in two groups: (1) long-term heroin users, who were not currently physically dependent; and (2) individuals who were either opioid naïve or who had limited prescribed use. Consistent with our findings, those with a history of extensive heroin use reported more positive effects, less sedation, and more itchiness from morphine. However, the observation of these effects with re-exposure, while potentially

indicative of reassuring temporal stability, may also raise some concern for bias due to incorrect attribution of effects experienced with recent use as having occurred with initial use. Investigations that have also examined subjective response to opioid re-exposure have identified additional potential sources of bias including more positive opioid effects with higher doses and faster rates of infusion (Marsch et al., 2001; Zacny & Gutierrez, 2003). However, another study (Dunn, Barrett, Brands, Marsh, & Bigelow, 2019) of the abuse potential of opioids found that 85.5% of the explainable variance was due to between-subjects effects with the much smaller remainder attributable to within-subjects effects, results suggestive of a more stable trait. Additional research will be necessary to estimate the extent to which genetic factors contribute to differences in subjective responses to opioids and are protective against progression to OUD. Our results provide evidence for significant protective effects in non-OUD opioid misusers that extend beyond those observed in pain patients who do not misuse opioids which we would argue further supports the utility of nondependent opioid misusers as controls in genetic association studies of OUD (Agrawal, Lynskey, & Nelson, 2013; Nelson et al., 2013, 2016).

Our results are not without significant limitations. The ARCI has been used extensively for more than 50 years and has excellent psychometric properties (Haertzen & Hickey, 1987; Haertzen et al., 1983; Martin et al., 1971). However, we used a modified version that assesses subjective effects retrospectively and does not have similar psychometric data available. While some studies have provided the evidence of temporal stability of subjective effects with re-exposure to opioids (Dunn et al., 2019; Azolosa, Stitzer, & Greenwald, 1994), no reports have examined the test–retest reliability of retrospective assessment. Also, since the opioid misuse of our samples' OUD individuals was substantially greater, of longer duration, and had abated more recently, their responses may have been more prone to recall bias. Case-control differences in administration of subjective response items, overall assessment, and ascertainment in our pilot sample were corrected in the replication sample. Our samples, of modest size, were collected with no justification of sample size (i.e., no power analysis); larger samples may have identified further between-group differences and would have allowed examination of covariates (e.g., sex) and drug-specific effects. Our pilot study's OUD individuals were a convenience sample with a clinical, rather than an SSAGA-confirmed diagnosis; however, the extensive duration of their reported daily or near daily heroin misuse suggests misdiagnosis is unlikely. We used a diagnostic assessment for OUD individuals in the replication sample. We excluded low-level misusers who met criteria for OUD in our current design; future studies could be undertaken to determine whether this group is composed of individuals highly sensitive to a diffuse array of opioid effects. We could have employed alternative cut-offs for the number of times misused and duration of abstinence of non-OUD opioid misusers that might have impacted our findings. Additionally, prior reports (Marsch et al., 2001; Zacny & Gutierrez, 2003) have found evidence that subjective experience may vary with dose and rate of infusion (and by implication, method of administration) for which relevant data were not collected. Similarly, prescribed use was not queried in either group and thus any potential bias on subjective effect reports arising from prior prescribed use could not be evaluated. Finally, we report data without correction for multiple testing. We opted to do so, in part, since the ARCI contains a considerable number of items that are not independent (i.e., they were constructed

to assess closely related or, at times, opposing effects). It is important to note that our strongest findings, which represent the backbone of our results, would survive even the most stringent Bonferroni corrections.

We replicated and extended findings from a prior report (Bieber et al., 2008) demonstrating significant differences in subjective effects of initial opioid misuse retrospectively reported by misusers who never developed OUD and OUD individuals. Our findings further support the potential utility of the assessment of subjective responses to initial opioid use for the identification of individuals at increased risk for developing OUD. Given the long history (more than 50 years) of retrospective studies (Bieber et al., 2008; Haertzen et al., 1983; Lasagna et al., 1955; McAuliffe, 1975; Zinberg, 1984) conducted with similar goals and the tremendous clinical importance a simple questionnaire with this capacity could have, a prospective examination of this question is long overdue. For example, these measures could be administered prospectively with initial opioid dose in a large sample of young adult, opioid-naïve patients presenting for the treatment of acute injury. The sample then could be followed longitudinally to determine whether their reports of subjective effects are predictive of the development of OUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Significance

It is difficult to know which opioid users will progress to addiction. One study compared chronic pain patients, with and without opioid addiction, finding that these groups reported (years later) having had very different experiences with initial opioid use. We conducted a similar comparison in two samples of individuals with a history of nonmedical opioid use, with and without opioid use disorder. In both samples, we found significant between-group differences in responses to individual items (e.g., a new "itching" item) and for questionnaire sub-scales (e.g., measuring euphoria). Additional research could determine this measure's usefulness in closer proximity to initial use.

TABLE 1

Demographic and substance misuse characteristics for non-OUD and OUD individuals in pilot and replication samples

	Pilot (*N* = 29)			Replication (*N* = 50)		
Characteristics	**Non-OUD**	**OUD**	***p* Value**	**Non-OUD**	**OUD**	***p* Value**
Men (%)	57.1	53.3	1.00	36.0	28.0	0.76
Women (%)	42.9	46.7		64.0	72.0	
Mean age (*SD*)	38.6 (10.6)	40.5 (13.6)	0.71	50.0 (15.7)	39.8 (9.4)	0.03
Ethnicity—African American (%)	42.9	60.0	0.58	20.0	48.0	0.07
European American (%)	57.1	40.0		80.0	52.0	
First opioid used—Heroin/opium (%)	42.9	73.3	0.20	12.0	24.0	0.46
Other (%)	57.1	26.7		88.0	76.0	
Mean age first opioid misuse (*SD*)	25.5 (9.6)	–	–	29.4 (16.2)	20.9 (6.4)	0.05
Time (yrs) since first opioid misuse (*SD*)	13.1 (9.5)	–	–	20.6 (15.3)	19.0 (10.2)	0.88
Mean duration (yrs) of daily heroin misuse (*SD*)	–	13.2 (12.5)	–	–	–	–
Mean (*SD*) number of times misused opioids—lifetime	18.6 (17.5)	–	–	10.8 (14.3)	–	–
Lifetime misuse and use disorders—other drugs						
Any cannabis misuse	100	–	–	63.0	96.0	0.60
Cannabis use disorder (%)	35.7	–	–	16.0	56.0	0.008
Any stimulant misuse (%)	85.7	–	–	56.0	80.0	0.13
Stimulant use disorder (%)	21.4	–	–	12.0	40.0	0.05
Any cocaine misuse (%)	85.7	–	–	60.0	100	0.001
Cocaine use disorder (%)	50.0	–	–	12.0	64.0	0.0005
Any sedative misuse (%)	50.0	–	–	56.0	84.0	0.06
Sedative use disorder (%)	14.3	–	–	8.0	32.0	0.08

Note: Chi-square tests (continuity-adjusted) were performed for comparisons of binary variables; Mann–Whitney *U* tests were performed for comparisons of continuous variables.

TABLE 2

Subjective effects of initial opioid misuse endorsement by non-OUD and OUD individuals in pilot and replication samples

		Pilot (*N* = 29)			Replication (*N* = 50)		
		Endorsement (%)			Endorsement(%)		
Subjective response item	**ARCI scale(s)**	**Non-OUD**	**OUD**	***p* Value**	**Non-OUD**	**OUD**	***p* Value**
My speech was slurred	P	57.1	73.3	0.60	4.0	52.0	0.0005
I had a feeling of just dragging along rather than coasting	P	57.1	53.3	1.00	28.0	52.0	0.15
I felt like avoiding people although I usually did not feel this way	P	28.6	73.3	0.04	8.0	40.0	0.02
It seemed harder than usual to move around	P	64.3	60.0	1.00	36.0	56.0	0.26
I was moody	P	7.1	80.0	0.0004	4.0	64.0	<0.0001
People might have said that I was a little dull	P, B*	57.1	66.7	0.88	24.0	36.0	0.54
I felt dizzy	P	42.9	40.0	1.00	40.0	48.0	0.78
Things around me seemed more pleasing than usual	M	64.3	86.7	0.33	44.0	68.0	0.15
I felt drowsy	P, L*	78.6	80.0	1.00	68.0	88.0	0.17
I feared I would lose the contentment I had then	M	14.3	60.0	0.03	20.0	56.0	0.02
I felt in complete harmony with the world and those about me	M	28.6	66.7	0.09	32.0	76.0	0.005
I could completely appreciate what others were saying when I was in that mood	M	35.7	46.7	0.82	36.0	62.5	0.12
I would be happy all the time if I felt us I felt then	M	28.6	93.3	0.001	12.0	64.0	0.0005
I felt so good that I knew other people could tell it	M	42.9	66.7	0.36	32.0	68.0	0.02
I felt as if something pleasant just happened to me	M	78.6	73.3	1.00	40.0	80.0	0.009
I felt as if I would be more popular with people	A, M	21.4	73.3	0.02	20.0	60.0	0.009
I felt a very pleasant emptiness	A, M	42.9	53.3	0.85	16.0	48.0	0.03
My thoughts came more easily than usual	A, M, B	21.4	46.7	0.30	16.0	60.0	0.004
I felt less discouraged than usual	A, M	28.6	73.3	0.04	40.0	76.0	0.02
I felt more excited than dreamy	P*, A	7.1	46.7	0.004	24.0	48.0	0.14
My memory seemed sharper to me than usual	A, B	7.1	46.7	0.05	12.0	36.0	0.10
I felt as if I could write for hours	A, B	7.1	26.7	0.37	8.0	32.0	0.08
Some of my body parts were tingling	A, L, B	50.0	60.0	0.87	8.0	68.0	0.0006
I felt itchy	–	7.1	93.3	<0.0001	12.0	72.0	<0.0001
My movements seemed faster than usual	B	0	40.0	0.03	8.0	40.0	0.02
My hands felt clumsy	L	50.0	46.7	1.00	8.0	33.3	0.06
I noticed my hand shook when I tried to write	L	7.1	20.0	0.64	0.0	16.7	0.11
I had a disturbance in my stomach	L	14.3	53.3	0.07	28.0	44.0	0.38
I felt anxious and upset	L	7.1	40.0	0.10	20.0	32.0	0.52
I had unusual weakness of my muscles	L	64.3	46.7	0.56	16.0	45.8	0.05
A thrill had gone through me one or more times	P*, L	42.9	66.7	0.36	24.0	56.0	0.04
My movements were free, relaxed, and pleasurable	L*	71.4	93.3	0.28	40.0	96.0	<0.0001
I did not like the way the drug made me feel	–	28.6	20.0	0.92	44.0	28.0	0.38

		Pilot (*N* = 29)			Replication (*N* = 50)		
		Endorsement (%)			Endorsement(%)		
Subjective response item	**ARCI scale(s)**	**Non-OUD**	**OUD**	***p* Value**	**Non-OUD**	**OUD**	***p* Value**
I was not as active as usual	P	–	–	–	60.0	64.0	1.00
I felt sluggish	P	–	–	–	48.0	52.0	1.00
My head felt heavy	P	–	–	–	28.0	48.0	0.24
I was full of energy	P*	–	–	–	12.0	48.0	0.01
I said things in the easiest possible way	M	–	–	–	56.0	65.2	0.72
I had a pleasant feeling in my stomach	M	–	–	–	28.0	48.0	0.24
I felt more clearheaded than dreamy	P*, M, B	–	–	–	16.0	50.0	0.03
I was in the mood to talk about the feelings I had	M, B	–	–	–	32.0	52.0	0.25
I felt very patient	A, L*	–	–	–	52.0	56.0	1.00
I had a weird feeling	A, L	–	–	–	52.0	72.0	0.24
I had better control over myself than usual	B	–	–	–	12.0	48.0	0.01
My movements seemed slower than ritual	B*	–	–	–	44.0	52.0	0.78
I found it hard to keep my mind on a task or job	B*	–	–	–	32.0	56.0	0.15
I didn’t feel like reading anything then	B*	–	–	–	48.0	68.0	0.25
I felt an increasing awareness of bodily sensations	L	–	–	–	24.0	58.3	0.03

*Reverse coded in scale

P = Pentobarbital chlorpromazine alcohol group; A = Amphetamine group; M = Morphine Benzedrine group; L = Lysergic acid diethylamide group; B = Benzedrine group; Chi-square tests (continuity-adjusted) were performed.

TABLE 3

ARCI scale item mean scores for non-OUD and OUD individuals in pitot and replication samples

		Pilot (*N* = 29)		Replication (*N* = 50)	
Scale	**Group**	**Mean (*SD*)**	***p* Value**	**Mean (*SD*)**	***p* Value**
Morphine Benzedrine group	Non-OUD	0370 (0.28)	0.005	0.293 (0.27)	<0.0001
	OUD	0.673 (0.21)		0.624 (0.23)	
Pentobarbital chlorpromazine alcohol group	Non-OUD	0.543 (0.28)	0.82	0.448 (0.19)	0.23
	OUD	0.593 (0.19)		0.532 (0.29)	
Amphetamine group	Non-OUD	0.232 (0.22)	0.002	0.256 (0.21)	0.0001
	OUD	0.558 (0.25)		0.556 (0.26)	
Lysergic acid diethylamide group	Non-OUD	0.318 (0.11)	0.13	0.273 (0.17)	0.034
	OUD	0.400 (0.15)		0.407 (0.23)	
Benzedrine group	Non-OUD	0.214 (0.19)	0.022	0.310 (0.20)	0.017
	OUD	0.422 (0.27)		0.478 (0.26)	

Note: Items included in pilot and replication sample assessments–MBG 11/15; PCAG 10/15; AG 8/10; LSDG 9/12; BG 6/12; Mann–Whitney *U* tests were performed.