Published in final edited form as:

Drug Alcohol Depend. 2015 January 1; 0: 89–96. doi:10.1016/j.drugalcdep.2014.11.016.

Predictors of buprenorphine initial outpatient maintenance and dose taper response among non-treatment-seeking heroin dependent volunteers

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Abstract

Background—Buprenorphine (BUP) is effective for treating opioid use disorder. Individuals' heroin-use characteristics may predict their responses to BUP, which could differ during maintenance and dose-taper phases. If so, treatment providers could use pre-treatment characteristics to personalize level of individual care and possibly improve treatment outcomes.

Methods—Non-treatment-seeking heroin-dependent volunteers (N=34) initiated outpatient BUP maintenance (8-mg/day) and submitted urine samples thrice weekly tested for opioids (non-contingent result). After completing three programmatically-related inpatient behavioral pharmacology experiments (while maintained on 8-mg/day BUP), participants were discharged and underwent a double-blind BUP dose taper (4-mg/day, 2-mg/day and 0-mg/day during weeks 1-3, respectively) with an opioid-abstinence incentive (\$30 per consecutive opioid-negative urine specimen, obtained thrice weekly).

Results—Participants who reported less pre-study (past-month) heroin use and shorter lifetime duration of heroin use were more likely to submit an opioid-negative urine sample during initial outpatient BUP maintenance. Participants who reported more lifetime heroin-quit attempts and provided any opioid-free urine sample during initial outpatient maintenance sustained longer

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Conflict of Interest MKG has received compensation as a scientific consultant to Reckitt-Benckiser Pharmaceuticals, Inc., which manufactures and markets buprenorphine products, and Titan Pharmaceuticals, Inc., which manufactures a buprenorphine product. All other authors declare no conflict of interest with respect to the conduct or content of this work.

Contributors EW was responsible for conceptualizing and performing this data analysis, drafting the manuscript, and producing the data tables and figures. LHL contributed to psychiatric screening and edited the manuscript. MKG contributed to study design, data coordination, figure production, and edited the manuscript. All authors have reviewed content and approved the final version for publication.

continuous opioid-abstinence during the BUP dose taper. Participants who reported >3 lifetime quit attempts abstained from opioid use nearly one week longer (14 vs. 8 days to opioid-lapse) and nearly half (46.7%) refrained from opioid use during dose taper.

Conclusions—Number of prior heroin quit attempts may predict BUP dose taper response and provide a metric for stratifying heroin-dependent individuals by relative risk for opioid lapse. This metric may inform personalized relapse prevention care and improve treatment outcomes.

Keywords

Buprenorphine; Maintenance; Dose Taper; Heroin; Abstinence; Relapse

1. INTRODUCTION

Long-acting *mu* opioid agonist medications are first-line interventions for treating and preventing relapse to use of heroin and other shorter-acting opioids (Meador, 2010). Buprenorphine (BUP) is a partial *mu* receptor agonist with dose-related clinical efficacy and good safety profile (Ling et al., 1998; Pani et al., 2000; Greenwald et al., 2014). BUP maintenance treatment of opioid use disorder typically includes a plan for eventual medication withdrawal *via* dose tapering. A recent meta-analysis (Dunn et al., 2011) of 28 BUP treatment trials that culminated with outpatient dose tapering found that participant retention was modest (median: 65%, range: 4-100%), while urinalysis-verified opioid abstinence was low during maintenance treatment (median: 41%, range: 1-94%), at the end of dose tapering (median: 30%, range: 22-41%), and at a post-taper follow-up assessment (median: 23%, range: 8-52%). Several methodological factors were associated with better outcomes of BUP dose tapering: higher pre-taper BUP maintenance dose (16-32 mg/day vs. <16 mg/day; Fareed et al., 2012), longer BUP maintenance (median: 5 days; range: 0-56; Dunn et al., 2011), longer dose taper (median: 17 days; range: 0-120; Dunn et al. 2011) and opioid-abstinent contingent reinforcement (Amass et al., 1994; Becker et al., 2001; Marsch et al., 2005; Greenwald, 2008).

In addition, pre-treatment opioid use-related characteristics have been found to predict BUP maintenance and dose taper response in treatment-seeking opioid dependent individuals; specifically, older age at onset of opioid use (Soyka et al., 2008), shorter duration of continuous opioid use (Soyka et al., 2008), less frequent opioid use (Ziedonis et al., 2009; Warden et al., 2012; Hillhouse et al., 2013) and non-injection opioid use (Subramaniam et al., 2011) were related to positive BUP outcome (opioid-negative urine at follow-up or greater treatment retention, depending on the study).

Treatment-seeking individuals to varying extents concede their substance use is beyond their control. However, the population of problematic substance using/abusing individuals in most countries far exceeds those who seek or receive treatment (SAMHSA, 2012; UNODC, 2013). Thus, studies that examine non-treatment-seeking (NTS) individuals may offer unique generalizability to substance using populations. While NTS individuals surpass treatment-seeking individuals in number, they are generally similar to treatment-seeking individuals in addiction severity and duration of use (Rounsaville and Kleber, 1985, Carroll and Rounsaville, 1992). Additionally, NTS heroin dependent individuals have been found to

partly endorse motivation to quit using heroin and report prior attempts to do so (Papke and Greenwald, 2012).

The present study investigated lifetime and current heroin use-related predictors of sublingual BUP response among opioid dependent NTS individuals. Two phases of outpatient BUP response were examined: initial outpatient maintenance and dose taper. The primary outcome during initial outpatient maintenance in this NTS subject sample was submitting any opioid-negative urine specimens without an abstinence contingency, which may reflect an individual's intrinsic motivation to abstain and whether a moderate BUP dose (8-mg/day) can manage withdrawal symptoms and heroin craving. The primary outcome during the BUP dose taper, which included an abstinence-contingent monetary incentive, was continuous opioid-abstinence, which might partly reflect an individual's extrinsic motivation (by the incentive) to abstain. In addition to examining predictor variables identified in previous studies, we hypothesized that number of lifetime heroin quit attempts and initial outpatient maintenance UDS result would predict days to opioid lapse during BUP dose taper. The present study is novel for two reasons; the study sample (non-treatment-seeking) and use of lifetime heroin quit attempts as a predictor of dose taper response.

2. METHODS

2.1. Participants

The local Institutional Review Board approved this study, which was conducted according to the Declaration of Helsinki. Advertisements and word-of-mouth referrals were used to recruit volunteers for three source studies (Greenwald and Steinmiller, 2009; Greenwald, 2010; Greenwald et al., 2013).

Volunteers were males and females aged 18 to 55 years who self-identified as regular heroin users not *currently* seeking treatment for their substance use. Participants were referred to treatment if they desired to reduce or halt their substance use. Candidates provided informed consent before completing screening procedures. All candidates met DSM-IV criteria for Opioid Dependence. Candidates were excluded if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for current Axis I disorders except Opioid and Nicotine Dependence based on SCID (First et al., 1996) or reported chronic health problems. Candidates whose urine samples at screening tested negative for opioids (< 300 ng/ml), or positive for methadone (> 300 ng/ml), benzodiazepines (> 300 ng/ml), barbiturates (> 200 ng/ml) or whose breath sample was positive for alcohol (> .002%) were ineligible, whereas samples positive for cocaine (> 300 ng/ml) or cannabinoids (> 50 ng/ml) were allowed. Eligible participants provided separate written consent to enroll in each source study.

2.2 Experimental protocol

2.2.1. Initial outpatient maintenance—Starting from day 1, participants received BUP mono 8-mg/ day sublingual tablets (open-label; one daily 8-mg Subutex™ tablet; Reckitt-Benckiser, Hull, UK) for 10 but < 30 outpatient days (variable length due to participant, laboratory and inpatient unit availability and schedule) before inpatient admission (Table 1).

On weekdays, laboratory research staff watched the participant take the 8-mg dose. On Saturdays, a clinic nurse observed the participant take a 16-mg dose (two 8-mg tablets), as the laboratory and clinic were closed on Sunday.

Thrice weekly [Monday, Wednesday, Friday (M-W-F)], participants provided staff-monitored, temperature-tested urine samples and completed symptom questionnaires (section 2.3.2). Participants were informed their inpatient study participation did not depend on being opioid abstinent during the initial outpatient maintenance period. Length of initial outpatient maintenance (and thus number of BUP doses received) varied across participants; therefore, maintenance duration was examined as a potential confound for dose taper response.

2.2.2. Inpatient maintenance—All participants continued maintenance on BUP 8 mg/day (open-label, observed by inpatient staff at 8:00pm) during the residential portion of each source study (10-20 nights). This dose minimized opioid withdrawal symptoms while participants lived on the inpatient unit without access to heroin. Staff observation and daily urinalyses ensured abstinence from unsanctioned drug use during this period.

Inpatient experimental procedures varied slightly across the three programmatically-related source studies, but each involved two hydromorphone fixed-dose sampling sessions followed by six sessions during which participants could work on a behavioral choice task to earn units of money and/or hydromorphone (Greenwald and Steinmiller, 2009; Greenwald, 2010; Greenwald et al., 2013). The total amount of hydromorphone administered varied across studies due to differences in experimental design (see Table 1) and variability in participants' choice responding. We grouped participants across source studies because recruitment, inclusion/exclusion criteria, BUP dosing procedures, initial outpatient maintenance and dose taper methodology, and outcome measures were identical. Number of days on the inpatient unit, total experimental hydromorphone amount administered during the inpatient phase, and source study were examined as potential confounds for dose taper response.

2.2.3. Dose taper—After a weekend washout period to clear residual hydromorphone from the final experimental session (urinalysis confirmed), participants were discharged and underwent outpatient BUP dose taper under double-blind conditions using small (2-mg or matched-placebo) mono tablets: 4 mg/day (Week 1; two active tablets) to 2 mg/day (Week 2; one active and one matched-placebo tablet) to 0 mg/day (Week 3; two matched-placebo tablets); this taper was identical across source studies. Abstinence-contingent reinforcement (\$30 per consecutive opioid-negative urine sample measured thrice weekly M-W-F) was used to discourage opioid lapse during BUP dose taper, based on prior work (Stitzer et al., 1980; Greenwald, 2008). The abstinent-contingent incentive was explained to participants during the informed consent procedures and prior to inpatient discharge, and was identical across source studies.

2.3. Measures

2.3.1. Baseline—Participants completed a comprehensive substance use history questionnaire that was reviewed for accuracy and completeness by graduate-level clinical

psychology students (supervised by LHL). Participants were asked an extensive series of questions regarding licit and illicit substance use, including: ‘How old were you when you first used heroin to get high?’ [age at initial use]; ‘How old were you when you first began to use heroin regularly (at least three times weekly)?’ [age at regular use]; ‘Have you ever taken heroin intravenously or subcutaneous (‘skin popping’)?’ [administration route: injection vs. non-injection]; ‘In the past 30 days, on how many DAYS did you take heroin?’ [past month use days: range 0-30]; and ‘How many times have you tried to quit using heroin?’ [quit attempts: range 0-100]. Duration of regular heroin use (years) was a calculated score: age at screening *minus* age at regular use. The Addiction Severity Index (McLellan et al., 1985) was used to assess severity of drug, alcohol and psychiatric symptoms.

2.3.2. Initial outpatient maintenance—Thrice weekly (M-W-F) urine samples were analyzed for presence of opioids (> 300 ng/ml). We analyzed both the presence of any (binary) and percentage of total opioid-negative urine samples (continuous measure). Participants completed the Opioid Symptom Questionnaire (OSQ) (Schuster et al., 1995), consisting of two subscales: Agonist (16 items) and Withdrawal symptoms (16 items). Item responses (each scored 0-4) were summed and expressed as a percentage of maximum score (64) separately for each subscale.

2.3.3. Dose taper—Following inpatient discharge, thrice weekly (M-W-F) urine samples were analyzed for first opioid-positive result (lapse) during the dose taper. Days to lapse (range: 0-19; where 19 days indicated completion of dose taper without lapse) was quantified by combining two data sources: urinalysis result (objective) and self-reported (subjective) opioid use. An *objective* window of lapse [bounded by last opioid-negative UDS and first opioid-positive UDS] was established by urinalyses that were performed M-W-F [not providing a urine sample on a scheduled day was considered an opioid lapse]. If self-reported day of opioid use was within the objective (urinalysis-established) lapse window, those data were analyzed. If not, the last opioid-negative urine sample (last day of verified abstinence; most conservative approach) was used in analyses. In addition to the OSQ, participants reported heroin craving thrice weekly (M-W-F) *via* a brief 10-item survey (S.T. Tiffany, personal communication, 11/23/99) derived from the 34-item Heroin Craving Questionnaire (Schuster et al., 1995).

2.4 Data analyses

2.4.1. Data preparation—Skewness and kurtosis statistics were used to evaluate distribution normality. Any variable that did not approximate a normal distribution (West et al., 1995) was transformed ($\log_{10}$) and normality was verified prior to outcome analyses that required normality. Descriptive statistics presented are mean (M) $\pm$ one standard deviation (SD). ANOVAs and chi-square tests were used to contrast non-hypothesized relationships and are presented solely for descriptive purposes. All analyses were conducted using SPSS v. 22. Criterion to reject the null hypothesis was $p < .05$.

2.4.2. Methodological variance—Length of initial outpatient maintenance and inpatient stay (thus number of BUP doses), and total experimental hydromorphone amount

administered varied across participants and source study. These variables could influence initial outpatient maintenance and dose taper UDS results, and thus were evaluated as potential confounds. Analysis of variance (ANOVA) was used to evaluate number of BUP doses by initial outpatient maintenance UDS result and source study. Bivariate correlations were used to assess statistical relationships between number of BUP doses and percentage of opioid-negative urine samples during initial outpatient maintenance, as well as total hydromorphone received and days to opioid lapse.

2.4.3. Initial outpatient maintenance—Analyses predicting group membership (any opioid-negative vs. no opioid-negative urine samples) were evaluated using forward conditional logistic regression. Hypothesis-driven predictors were selected *a priori* based on published data and included: age at regular heroin use, duration of regular heroin use, heroin administration route, and days of past-month heroin use.

2.4.4. Dose taper—Number of days to opioid lapse was evaluated using two statistical approaches. Stepwise linear regression was used to evaluate continuous (and/or ordinal) variables and days to lapse. Predictors included: age at regular heroin use, duration of regular heroin use, lifetime number of heroin-quit attempts ($\log_{10}$ transformed), days of past-month heroin-use ($\log_{10}$ transformed), and percentage of opioid-negative urine samples ($\log_{10}$ transformed) during initial outpatient maintenance.

Kaplan-Meier survival curves contrasted binary predictors using the Breslow (Generalized Wilcoxon) test. Predictors used in survival analyses included: lifetime number of heroin-quit attempts (median split), past-month heroin use (daily vs. less than daily), heroin administration route (injection vs. non-injection), and initial outpatient maintenance UDS result (any opioid-negative vs. no opioid-negative urine samples).

2.4.5. Power analyses—Power analyses for sample size estimates were conducted using G*Power 3.1 (Erdfelder et al., 1996; Faul et al., 2007). Results indicated that 34 participants was sufficient to detect large effect sizes (Cohen's $f^2 = 0.46$) for linear multiple regression analyses with five predictors at recommended power = .80 and $\alpha = .05$ (Cohen, 1988). Further, a sample of 34 participants was sufficient to detect large effect sizes (Cohen's $f = .50$) for independent samples group differences ($\alpha = .05$) at recommended power = .80 (Cohen, 1988).

3. RESULTS

3.1. Participant characteristics

The sample ($N=34$) was 51.5% African-American and 48.5% Caucasian, 82.4% male, with an average age of 41 years (Table 2). Participants reported using heroin ~3 times daily (90.8 ± 50.6 total past-month uses; 61.8% reported daily past-month use) and half the sample (50%) reported injection heroin use (Table 3). Initial heroin use was 24.0 ± 8.0 years old, followed closely by regular use at 26.8 ± 8.1 years old. Participants reported 14.7 ± 9.8 years of heroin use.

3.2. Initial outpatient maintenance

During initial outpatient maintenance participants received 15.5 ± 5.0 BUP doses (range: 10-28) and provided 7.6 ± 1.6 urine samples (range: 5-10). Eleven participants (32.4%) submitted at least one opioid-negative urine sample (Figure 1). Mean percent-of-maximum withdrawal and agonist symptom scores throughout initial outpatient maintenance were modest (14.3% and 16.6%, respectively). Number of BUP outpatient doses received was not significantly related to UDS result, $F(1,33) = 0.38$; $p = .54$; Spearman $\rho = -.23$, $p = .20$.

Four heroin-use characteristics (age at regular use, duration of regular use, administration route, and past-month use days) were entered as predictors of initial outpatient maintenance UDS result in a forward conditional logistic regression model. Duration of regular heroin use (Wald[1] = 5.14, $p = .023$, $\beta = -.16$, SE = .07) and past-month heroin use days (Wald[1] = 4.43, $p = .035$, $\beta = -.53$, SE = .25) accurately (82.4%) and significantly predicted initial outpatient maintenance UDS result, $\chi^2(2) = 11.14$, $p = .004$. Participants with any opioid-negative UDS reported fewer years of heroin use (9.9 ± 9.2 vs. 17.0 ± 9.4 years) and less frequent past-month use (27.5 ± 3.9 vs. 29.1 ± 1.7 days; 23.8% vs. 76.2% daily past-month users) compared to individuals with no opioid-negative UDS. Years of use and past-month use days were not correlated ($p = .30$).

3.3. Dose taper

Overall, median time to opioid lapse was 11 days (during 2 mg/day). Ten participants (29.4%) remained opioid-abstinent while completing the dose taper (Figure 2). Half (50%) remained opioid-abstinent throughout active BUP dosing. Nearly two-thirds of participants (61.8%, $n = 21$) submitted every urine sample, even after being disqualified from earning the abstinent-contingent incentive due to an opioid positive UDS. Withdrawal symptom scores were very low at the onset of dose taper (4.0%) and increased minimally over time with decreasing BUP dose (Figure 2). Agonist symptom scores reported during dose taper were comparable to those reported during initial outpatient maintenance (range: 12.1-19.5%).

Length of inpatient stay (and number of BUP doses) varied across source studies; however, days to lapse did not differ by source study ($F[1,33] = 1.54$; $p = .22$), and was not correlated with total number of BUP doses received or number of inpatient days ($p = .38$; $p = .89$; respectively). Total experimental hydromorphone amount administered inpatient varied by participant responding on the drug/money choice task (144.4 ± 56.0 mg; range: 38-236mg), but was not related to days to lapse ($p = .55$).

Five heroin use-related characteristics (% opioid-negative urine samples during initial outpatient maintenance, lifetime heroin-quit attempts, age at onset and duration of regular heroin use, and past-month heroin-use days) were included in a stepwise linear regression model to predict days to opioid lapse during dose taper. Two significant predictors ($F[2,32] = 4.66$, $p = .017$) accounted for 23.7% of the variance: lifetime heroin-quit attempts ($r^2 = .13$) and proportion of opioid-negative urines during initial outpatient maintenance ($r^2 = .11$). Pearson correlations revealed significant positive relationships between days to lapse, and quit attempts and opioid-negative urines ($r_s = .36$ and $.24$, respectively). Quit attempts and opioid-negative urines were not correlated ($p = .19$).

Kaplan-Meier survival analyses were used to evaluate probability of opioid lapse throughout the BUP dose taper. Four binary variables [route of administration, initial outpatient maintenance UDS result, past-month days using heroin, and lifetime heroin quit attempts] were considered individually in survival analyses. Lifetime heroin quit attempts (median split) was significantly related to opioid lapse probability during dose taper ($\chi^2[1] = 4.61, p = .032$): individuals who reported > 3 quit attempts lapsed later than those who reported ≤ 3 quit attempts (13.5 vs. 8.2 days; $F[1,32] = 4.76, p = .037$; Figure 3). Among participants with more quit attempts, 46.7% completed the dose taper without lapse (vs. 16.7% with fewer quit attempts). No other variables approached significance ($ps > .20$).

Withdrawal and agonist symptomatology were unrelated to initial outpatient maintenance UDS result and days to lapse. Mean withdrawal and agonist symptoms during the first two weeks of initial BUP outpatient maintenance did not differ by initial outpatient maintenance UDS result ($ps > .10$). Moreover, symptom scores and heroin craving during week one of dose taper, and just prior to an individual's lapse, were evaluated by week of lapse, revealing no significant relationships ($ps > .15$).

Exploratory analyses examined the relationship between dose taper retention and heroin use characteristics. Lifetime quit attempts were significantly related to length of retention (Spearman $\rho = .35, p < .05$). We replaced 'days to lapse' with 'retention,' and replicated the Kaplan-Meier survival analyses above. Only heroin quit attempts (median split) was significantly related to dose taper retention ($\chi^2[1] = 3.87, p = .049$): those who reported more quit attempts remained in the dose taper longer (18.0 vs. 14.8 days).

4. DISCUSSION

This secondary analysis examined heroin use-related characteristics as predictors of response to both initial BUP outpatient maintenance and dose taper in heroin dependent, non-treatment-seeking (NTS) adults. There were two primary findings. First, less frequent past-month heroin use and shorter lifetime duration of regular heroin use predicted individuals who refrained from opioid use (UDS verified) during initial outpatient maintenance, without abstinence contingencies. Second, individuals who reported more lifetime heroin-quit attempts and submitted more opioid-negative urine samples during initial outpatient maintenance remained continuously opioid-abstinent longer during outpatient dose tapering. Importantly, source study methodological variance, number of BUP doses received, total experimental hydromorphone administered inpatient, and length of inpatient stay (BUP maintenance) were unrelated to initial outpatient maintenance or dose taper response.

This NTS sample reported comparable (Hillhouse et al., 2013) or more-frequent (Soyka et al., 2008) opioid use, comparable rates of injection (Soyka et al., 2008; Hillhouse et al., 2013), higher ASI Drug Severity scores (Soyka et al., 2008), and older age at onset of heroin use (Gerra et al., 2004; Soyka et al., 2008; Hillhouse et al., 2013) than similar research studies with treatment-seeking opioid dependent samples. Although these participants denied *current* interest in treatment, they endorsed prior attempts to quit using heroin. Therefore, this NTS sample differs in degree along a continuum, but is not categorically

different than treatment-seeking samples, consistent with prior studies (Rounsaville and Kleber, 1985; Carroll and Rounsaville, 1992).

Results from the non-incentivized initial outpatient maintenance period urine screens indicate about one-third of participants submitted at least one opioid-negative UDS while stabilized on BUP 8 mg/day. Years of heroin use (duration) and number of past-month heroin-use days (frequency) predicted UDS result: shorter lifetime duration and less frequent recent use were related to opioid-negative urine specimen. These findings replicate prior research (Soyka et al., 2008; Ziedonis et al., 2009; Warden et al., 2012; Hillhouse et al., 2013). These results indicate some NTS individuals can refrain from opioid use without an abstinence contingency while maintained on a moderate BUP dose, and that duration and frequency of use are relevant factors. One hypothesis is that an individual's heroin-use duration and frequency may be related to the magnitude of heroin-induced allostasis (Koob and Le Moal, 1997) and related neurobiological changes (Sim-Selley et al., 2000; Nestler, 2001; Colpaert, 2002; Raehal and Bohn, 2005). Although we did not examine neurobiological changes directly, indirect support for this explanation might be obtained if participants who gave opioid-negative UDS reported milder opioid withdrawal symptoms than those who were not opioid abstinent. Our findings did not support this explanation. However, these data cannot rule out associations that may emerge during protracted abstinence. A second plausible explanation is that lifetime duration and recent frequency of use reflects the degree to which heroin is embedded in the participant's life (e.g., increased drug cue exposure, easy access); however, we were unable to test this hypothesis in the present study.

Results from the incentivized BUP dose taper indicated the median participant lapsed at day eleven. About one-third of all participants remained opioid-abstinent throughout the dose taper (including placebo). Importantly, pre-taper total length of initial outpatient maintenance, inpatient stay and experimental hydromorphone administered were unrelated to days to opioid lapse. Regression analyses indicated initial outpatient maintenance UDS result and lifetime heroin-quit attempts predicted days to opioid lapse and accounted for nearly one-quarter of the total variance. Participants who reported more quit attempts and provided more opioid-negative urine samples during initial outpatient maintenance were subsequently less likely to lapse to opioid use, and those who lapsed did so significantly later during the dose taper. Survival analyses reaffirmed the regression findings in that days to opioid lapse differed significantly by quit attempts (median split): participants with more quit attempts lapsed nearly one week later (14 vs. 8 days).

The present findings indicate that self-reported (quit attempts) and objective (initial outpatient maintenance UDS result) measures of prior opioid discontinuation predicted continuous opioid abstinence during outpatient BUP dose tapering following a brief period of inpatient maintenance dosing and monitored heroin abstinence. It is important to note that we did not measure the success (i.e., length) of the self-reported quit attempts. These indices may be proxy measures of: 1) an individual's ability to manage heroin craving and tolerate withdrawal symptoms during heroin abstinence, and/or 2) the degree to which they are motivated to abstain. The first hypothesis seems unlikely as results indicated heroin craving and withdrawal symptom scores were generally low and unrelated to lapse. The second

hypothesis is possible. Days to opioid lapse was predicted by lifetime heroin quit attempts and non-incentivized initial outpatient maintenance UDS result, which may reflect intrinsic motivation to abstain.

To our knowledge, this is the first study to assess and relate self-reported lifetime heroin-quit attempts and BUP dose taper response. Initial outpatient maintenance UDS result predicted BUP dose taper response in this study and is comparable to treatment studies that demonstrated 'lead-in' UDS result predicted treatment outcome (Alterman et al., 1997; Ehrman et al., 2001; Bisaga et al., 2005). The present findings could be used to improve BUP treatment retention and abstinence by personalizing level of care provided, e.g., higher BUP dose, longer maintenance period, more gradual dose taper, and/or more intensive relapse prevention treatment. We hasten to note the present findings do not reflect treatment efficacy *per se* but, instead, provide a metric for stratifying heroin-dependent individuals by likelihood for opioid lapse. Clinical trials are needed to evaluate the effectiveness of personalized care for individuals at higher risk for lapse based on number of prior quit attempts. These preliminary findings warrant consideration and further investigation due to the tremendous societal and economic costs of heroin (and non-medical opioid) use disorder (Mark et al., 2001).

Several limitations of this study require mention. First, the study sample was compiled from several source experiments; however, between-study methodological variance was unrelated to the primary outcomes. Second, sample size in this study is small, but not unprecedented for this line of inquiry (Cameron et al., 2001; Sigmon et al., 2009, 2013). Moreover, we used a hypothesis-driven approach that sought to replicate existing findings. Third, this study did not randomly assign participants to treatment conditions, nor did it include a comparison/control condition. Fourth, NTS samples (by definition) are not actively seeking substance use treatment; thus, it is not clear how these findings will generalize to treatment-seeking individuals. However, because far greater numbers of substance using/abusing individuals do not seek treatment, understanding the behavioral propensities of these individuals is of great societal importance. Finally, this study included a relatively brief outpatient BUP dose taper (19 days), which limits the clinical significance of these results, but is comparable to similar studies (median: 17 days; Dunn et al., 2011). Because of the brief dose taper, we selected a rigorous outcome measure (length of continuous opioid-abstinence).

In conclusion, pre-treatment heroin use-related characteristics can accurately predict BUP response and may offer a convenient tool for stratifying treatment interventions to improve individual outcomes and delay opioid lapse in heroin-dependent individuals. In this study, less frequent past-month and shorter duration of lifetime heroin use predicted non-contingent opioid abstinence during initial BUP outpatient maintenance in NTS heroin-dependent individuals. A higher number of lifetime heroin quit attempts and opioid-negative UDS samples during initial outpatient maintenance predicted longer continuous opioid abstinence during outpatient BUP dose taper. Additional research is needed to replicate these preliminary findings in larger treatment-seeking samples, and to investigate the effectiveness of personalized relapse prevention strategies based on these predictors.

Acknowledgements

The authors thank Ken Bates for recruiting participants; and Debra Kish, Joi Moore, Melissa Williams, Lisa Sulkowski and Elorie Eggleston for data collection and management.

Role of funding source NIH R01 DA015462 from the National Institute on Drug Abuse (to MKG), a research grant (Joe Young, Sr./Helene Lycaki Funds) from the State of Michigan, and the Detroit Wayne Mental Health Authority supported this research. Data for this study were obtained under NIH clinical trials NCT00218361, NCT00608504, and NCT00684840.

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Highlights

- Individuals' heroin-use characteristics may predict their responses to BUP, which may differ across dosing phases.
- Out-of-treatment, heroin-dependent volunteers underwent BUP outpatient maintenance and double-blind, placebo-controlled BUP dose taper.
- Participants reporting shorter lifetime and less pre-study heroin use demonstrated opioid-abstinence during initial outpatient maintenance.
- Self-reported (number of lifetime heroin quit attempts) and objective (opioid-negative urine samples) measures of opioid discontinuation predicted continuous abstinence during outpatient BUP dose taper.

Figure 1. Initial buprenorphine (BUP 8 mg/day) outpatient maintenance responses for cumulative percentage opioid-negative urine drug screens (UDS; negative samples are carried forward), opioid percent-of-maximum scale score withdrawal symptoms and opioid agonist symptoms as a function of consecutive thrice weekly (M-W-F) UDS.

Figure 2.

Buprenorphine (BUP) dose taper responses for percentage opioid-negative urine drug screens (UDS), percent-of-maximum scores for opioid withdrawal symptoms and opioid agonist symptoms, and percent retention as a function of consecutive thrice weekly (M-W-F) UDS.

Figure 3. Survival curve analysis of percent opioid-abstinent subjects as a function of number of days of buprenorphine dose tapering using a median split for subjects differing in lifetime number of self-reported heroin quit attempts (≤ 3 vs. > 3 quit attempts).

Table 1

Methodological details by experiment phase

	Initial Outpatient Maintenance	Inpatient Maintenance	Outpatient Dose Taper
Buprenorphine Dose	8 mg/day	8 mg/day	4 mg/day (Week 1); 2 mg/day (Week 2); 0 mg/day (Week 3)
Methodology	Open-label	Open-label	Double-blinded; Placebo-controlled
Dose Administration	Self-administer single sublingual tablet	Self-administer single sublingual tablet	Self-administer two sublingual tablets (0 or 2 mg BUP)
Length	10-30 days; varied by participant and inpatient schedule	10-20 days; varied by source study	19 days
Opioid Use Assessment	UDS collected M-W-F	24/7 monitoring; daily UDS collected	UDS collected M-W-F; self-reported opioid use
Other Medications	None	Experimental hydromorphone (M±SD = 144.4±56.0mg; range: 38-236mg); ibuprofen/nausea medications (as needed)	None

Table 2

Participant demographic characteristics contrasted by buprenorphine response

	Overall Overall (N=34)	Initial Outpatient Maintenance			Dose Taper		F or χ^2	p
		Not Abstinent (n=23)	Opioid Abstinent (n=11)	Lapsed during 4mg/day dose (n=13)	Lapsed during 2mg/day dose (n=7)	Placebo or No Lapse (n=14)		
	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)		
Age (yrs)	41.4 (9.9)	43.0 (8.3)	38.1 (12.6)	41.2 (9.5)	39.7 (12.9)	42.4 (9.4)		0.84
Race (% African American) [#]	51.5%	54.5%	45.5%	38.5%	42.9%	69.2%		0.26
Gender (% male) [#]	82.4%	82.6%	81.8%	100.0%	42.9%	85.7%		0.005
Education (yrs)	12.4 (1.8)	12.4 (1.9)	12.3 (1.7)	12.9 (2.2)	11.7 (1.7)	12.3 (1.4)		0.41

[#] Note: Indicates a Chi Square Test of Independence was performed to evaluate group membership allocation differences for non-parametric variables. BOLD rows indicate a significant difference between groups (p < .05).

Table 3

Participant heroin use characteristics contrasted by buprenorphine response

	Overall (N=34)	Initial Outpatient Maintenance			Dose Taper		
		Not Abstinent (n=23)	Opioid Abstinent (n=11)	F or χ^2	Lapsed during 4mg/day dose (n=13)	Lapsed during 2mg/day dose (n=7)	Placebo/No Lapse (n=14)
	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)	p	M ($\pm$ 1 SD)	M ($\pm$ 1 SD)	F or χ^2
Addiction Severity Index (range 0-9)							
Drug Severity	5.7 (1.6)	6.5 (1.6)	5.4 (1.5)	0.16	5.4 (1.3)	5.0 (1.0)	6.4 (1.9)
Alcohol Severity	0.1 (0.2)	0.0 (0.0)	0.1 (0.3)	0.51	0.0 (0.0)	0.3 (0.6)	0.0 (0.0)
Psychiatric Severity	1.3 (2.0)	2.3 (2.9)	0.8 (1.4)	0.14	1.1 (2.5)	1.7 (1.5)	1.4 (1.9)
Heroin Use Characteristics							
Administration Route (% injection) [#]	50.0%	56.5%	36.4%	0.27	61.5%	42.9%	42.9%
Use Days Past Month (max 30)	28.6 (2.7)	27.5 (3.9)	29.1 (1.7)	0.09	28.5 (3.1)	29.6 (0.8)	28.1 (2.8)
Use Frequency Past Month	90.8 (50.6)	73.8 (54.4)	98.9 (47.8)	0.18	90.0 (54.1)	87.7 (49.9)	93.0 (51.4)
Age of First Use	24.0 (8.0)	25.6 (10.6)	23.3 (6.6)	0.44	24.2 (5.8)	25.4 (11.1)	23.3 (8.6)
Age of Regular Use	26.8 (8.1)	28.2 (9.9)	26.1 (7.2)	0.49	27.2 (5.3)	27.3 (10.0)	26.1 (9.7)
Duration of Regular Use (yrs)	14.7 (9.8)	17.0 (9.4)	9.9 (9.2)	0.05	14.1 (10.9)	12.4 (9.5)	16.4 (9.4)
Lifetime Quit Attempts [*]	9.3 (18.4)	5.5 (8.8)	11.1 (21.6)	0.20	4.3 (5.8)	4.4 (2.7)	15.9 (26.8)
Use Consequences [*]	8.6 (4.4)	9.1 (5.5)	8.3 (3.8)	0.65	7.8 (3.8)	10.3 (4.6)	8.5 (4.8)

[#]Note: Indicates a Chi Square Test of Independence was performed to evaluate group membership allocation differences for non-parametric variables.^{*}Indicates a log10 transformation was applied prior to ANOVA to normalize variable distribution. BOLD rows indicate a significant difference between groups ($p < .05$).