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Opioid withdrawal, craving, and use during and after outpatient buprenorphine stabilization and taper: A discrete survival and growth mixture model

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HIGHLIGHTS

- Antecedents of first post-detoxification opioid use were simultaneously modeled.
- Opioid users were parsed into classes during and after agonist pharmacotherapy.
- Four classes were characterized on craving, withdrawal, and opioid-free survival.
- Odds ratios showed significant differences in time-to-first use across classes.
- Future research may allow timely interventions to extend time-to-first opioid use.

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ABSTRACT

Introduction: Most patients relapse to opioids within one month of opioid agonist detoxification, making the antecedents and parallel processes of first use critical for investigation. Craving and withdrawal are often studied in relationship to opioid outcomes, and a novel analytic strategy applied to these two phenomena may indicate targeted intervention strategies.
Methods: Specifically, this secondary data analysis of the Prescription Opioid Addiction Treatment Study used a discrete-time mixture analysis with time-to-first opioid use (survival) simultaneously predicted by craving and withdrawal growth trajectories. This analysis characterized heterogeneity among prescription opioid-dependent individuals (N = 653) into latent classes (i.e., latent class analysis [LCA]) during and after buprenorphine/naloxone stabilization and taper.
Results: A 4-latent class solution was selected for overall model fit and clinical parsimony. In order of shortest to longest time-to-first use, the 4 classes were characterized as 1) high craving and withdrawal, 2) intermediate craving and withdrawal, 3) high initial craving with low craving and withdrawal trajectories and 4) a low initial craving with low craving and withdrawal trajectories. Odds ratio calculations showed statistically significant differences in time-to-first use across classes.
Conclusions: Generally, participants with lower baseline levels and greater decreases in craving and withdrawal during stabilization combined with slower craving and withdrawal rebound during buprenorphine taper remained opioid-free longer. This exploratory work expanded on the importance of monitoring craving and withdrawal during buprenorphine induction, stabilization, and taper. Future research may allow individually tailored and timely interventions to be developed to extend time-to-first opioid use.

1. Introduction

A majority of patients (>70%) receiving treatment for opioid dependence relapse to opioids within 6 months following detoxification from

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agonist therapy (Chutuape, Jasinski, Fingerhood, & Stitzer, 2001; Tuten, DeFulio, Jones, & Stitzer, 2011), and most relapses occur within 1 month (Gossop, Stewart, Browne, & Marsden, 2002). Despite clinical guidelines for opioid-dependent patients to remain on long-term pharmacotherapy (Amato, Davoli, Ferri, Gowing, & Perucci, 2004; Stotts, Dodrill, & Kosten, 2009), many patients seek, and community treatment providers often insist upon, agonist detoxification (Mannelli et al., 2009; Peterson et al., 2010). Data support that sustained opioid abstinence is an attainable goal with appropriate intervention (Amato, Minozzi, Davoli, & Vecchi, 2011; Donovan et al., 2012; Smyth et al., 2005; Stotts et al., 2012); however, relapse rates are still quite high (Amato et al., 2011).

Opioid agonist treatment and detoxification encompasses numerous stages, including pharmacotherapy induction, stabilization, taper, and ultimately pharmacological cessation. The first use of an illicit opioid following initiation of agonist detoxification is often an indicator that a relapse to pre-treatment opioid use is imminent (Gossop, Marsden, Stewart, & Treacy, 2001; Gossop et al., 2002; Gruber, Delucchi, Kielstein, & Batki, 2008; Kertesz, Horton, Friedmann, Saitz, & Samet, 2003). While not discounting individuals who engage in isolated one-time use (i.e., a "slip") or several slips and then re-establish abstinence (Gossop et al., 2002), the overwhelming majority of opioid users who engage in a first "slip" will go on to relapse. Thus, a better understanding of the antecedents and parallel processes that accompany first use may assist in meaningfully advancing opioid-dependence treatment.

Craving and withdrawal have long been studied as potential moderators and mediators of opioid-use outcomes (Gowing, Ali, & White, 2009; Hyman, Fox, Hong, Doebrick, & Sinha, 2007; Kosten, Schottenfeld, Ziedonis, & Falcioni, 1993; Krupitsky et al., 2011; McMillan & Gilmore-Thomas, 1996; Rounsaville, Kosten, & Kleber, 1985; Scherbaum, Heppekausen, & Rist, 2004; Sinha, 2007; Soyka, Zingg, Koller, & Kuefner, 2008; Strobbe, Brower, & Galen, 2003; Wasan et al., 2009; Whitley et al., 2010; Ziedonis et al., 2009). Craving is hypothesized to play a central role in relapse to opioids (Hyman et al., 2007; McMillan & Gilmore-Thomas, 1996; Ren, Shi, Epstein, Wang, & Lu, 2009; Sinha, 2007; Wasan et al., 2009). For example, individuals on non-therapeutic doses of medications used to treat opioid dependence (e.g., 1 mg of buprenorphine), placebo, or medications currently considered less efficacious (e.g., clonidine) often report greater levels of craving and experience earlier dropout or relapse (Fudala et al., 2003; Krupitsky et al., 2011; Ling et al., 2005; Ling et al., 1998) compared to individuals on therapeutic doses of opioid-agonist medications (Dole, 1994).

Similar to craving, withdrawal symptoms tend to be lower in groups receiving efficacious opioid-agonist treatment compared to those on inadequate or no pharmacotherapy (e.g., Oreskovich et al., 2005). Many studies have reported that withdrawal severity may significantly relate to opioid-use outcomes (Gowing et al., 2009; Kosten et al., 1993; Soyka et al., 2008; Whitley et al., 2010; Ziedonis et al., 2009), such that individuals with withdrawal symptoms that quickly abate or decline after receiving treatment often fare better, especially when receiving buprenorphine (Gowing et al., 2009; Whitley et al., 2010). Also, Ziedonis et al. (2009) showed that individuals with *higher* baseline withdrawal levels who received buprenorphine–naloxone fared better than those with fewer symptoms.

Opioid users demonstrate significant variability across craving (e.g., McMillan & Gilmore-Thomas, 1996; Ren et al., 2009) and withdrawal experiences (e.g., Nielsen, Hillhouse, Mooney, Fahey, & Ling, 2012). Furthermore, craving and withdrawal appear to be distinct, yet related, phenomena (e.g., Swift & Stout, 1992). For example, Schuster, Greenwald, Johanson, and Heishman (1995) found that craving increased following naloxone-precipitated withdrawal in a sample of methadone-maintained patients. Taken as a whole, investigations to date suggest associations between craving, withdrawal, and opioid use outcomes; however, more sophisticated statistical tools are needed to fully explore these relationships and potentially adapt the information for interventions. Longitudinal models may help characterize the timing and magnitude of changes in withdrawal and craving related to first opioid use during and after a buprenorphine stabilization and taper.

Latent class analyses (i.e., mixture modeling) have shown promise for explaining heterogeneous substance dependence treatment outcomes and offer novel targets for clinical intervention. Stated simply, latent class analyses (LCAs) create subgroups of individuals (classes) from a larger diverse population based on constructs of interest, such as substance use patterns (e.g., frequency, polysubstance use), routes of administration, and patterns of health-risk behaviors (Trenz et al., 2013). Several latent class analyses with opioid-dependent populations have been conducted. Monga et al. (2007) examined latent classes of opioid users on drug use, depression, pain, HIV/Hepatitis infection, and homelessness; Banta-Green, Merrill, Doyle, Boudreau, and Calsyn (2009) examined health and pain; and, Shand, Slade, Degenhardt, Baillie, and Nelson (2011) explored abuse/dependence symptom subtypes. However, none has modeled craving, withdrawal, and opioid use concurrently.

In a broader context, this exploratory research is relevant to the national agenda to find approaches to "individualize medicine." Organizations such as the Patient-Centered Outcomes Research Institute (PCORI) support evidence-based approaches to improve health care delivery and patient outcomes. Identifying trends during and after opioid-agonist stabilization and taper may help generate hypotheses about how different subgroups (and ultimately individuals) respond to treatment. Empirically based latent class analyses are an important first step.

This secondary data analysis of the Prescription Opioid Addiction Treatment Study (POATS; Weiss et al., 2010, 2011) explored latent classes of prescription opioid users. Specifically, we used discrete-survival, growth mixture modeling with time-to-first opioid use (survival) predicted by growth trajectories of craving and withdrawal (Muthen & Muthen, 2012) during and after stabilization and taper from buprenorphine/naloxone. Exploring heterogeneity across these constructs may better characterize the variability in opioid use outcomes and provide direction for intervention (Amato et al., 2011).

2. Methods

POATS was a multisite, randomized clinical trial (NCT00316277) funded through the NIDA Clinical Trials Network. The institutional review boards at each of the 10 study sites approved the study, and all participants gave written informed consent. Full details of the trial design and primary outcome are published elsewhere (Weiss et al., 2011; Weiss et al., 2010).

2.1. Participants & procedures

Sociodemographic and clinical characteristics of the population separated by intervention condition have previously been reported (see Weiss et al., 2011). Briefly, 653 participants were randomized to standard medical management (SMM) alone or SMM plus individual opioid dependence counseling (SMM + ODC). A majority of the sample was male (60.0%), White (91.3%), and employed full-time (62.9%). The average age was 33.2 years ($SD = 10.2$) with a mean education of 13.0 years ($SD = 2.2$). The average number of days of opioid analgesic use in the past 30 days at baseline was 28.1 ($SD = 4.0$), while that of heroin was 0.1 ($SD = 0.6$).

The main trial consisted of 2 phases, and only phase 1 data were used in the current study. Phase 2 had differing aims and methods and a smaller sample size, precluding its use in current investigation. In phase 1, following screening and completion of baseline assessments, participants underwent a 1-day buprenorphine/naloxone induction (participants received between 4 and 12 mg [in 4 mg doses] on the day of induction, depending on initial response). Participants continued to increase their dosage based on opioid use, withdrawal symptoms, side effects, and craving (consistent with standard dosing guidelines) up to a maximum dose of 32 mg/day (SAMHSA, 2004). A 2-week stabilization period (weeks 1 and 2) was followed by a 2-week taper (weeks