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Short Communication

Spontaneous reductions in smoking during double-blind buprenorphine detoxification

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HIGHLIGHTS

- We examined changes in smoking throughout a 12-week buprenorphine detoxification.
- Urinary cotinine levels significantly decreased throughout opioid detoxification.
- Reductions translated to a decrease of approximately 8 cigarettes per day.
- These data provide additional evidence that opioids influence smoking.

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ABSTRACT

Objective: Evidence suggests a positive association between administration of psychoactive drugs and rates of cigarette smoking. Prevalence of smoking among opioid-dependent individuals, for example, is four times greater than the general population. We recently completed a randomized double-blind trial evaluating outpatient buprenorphine taper for prescription opioid (PO) abusers, which provided a unique opportunity to examine naturalistic changes in smoking among participants who detoxified without resumption of illicit opioid use.
Method: Participants received no smoking-cessation services and were not encouraged to alter their smoking in any way. A subset of 10 opioid-dependent smokers, who were randomized to receive the same 4-week buprenorphine taper and successfully completed detoxification, were included in the present study. They provided staff-observed urine specimens thrice-weekly throughout the 12-week trial. Specimens were analyzed onsite via enzyme-multiplied immunoassay for urinary cotinine, a metabolite of nicotine that provides a sensitive biochemical measure of smoking status.
Results: Mean cotinine levels were significantly different across study phases, with significantly lower cotinine levels during taper (1317.5 ng/ml) and post-taper (1015.8 ng/ml) vs. intake (1648.5 ng/ml) phases (p"s < .05). Overall, mean cotinine levels decreased by 38% between intake and end-of-study, reflecting a reduction of approximately eight cigarettes per day.
Conclusions: These data provide additional evidence that opioids influence smoking and extend prior findings to include primary PO abusers, rigorous double-blind opioid dosing conditions and urinary cotinine. These results also suggest that, while likely insufficient for complete cessation, patients who successfully taper from opioids may also experience concurrent reductions in smoking and thus may be ideal candidates for smoking cessation services.

1. Introduction

In the United States, tobacco use is responsible for an estimated 443,000 premature deaths and $96.8 billion in lost productivity annually (CDC, 2008). While the rates of smoking in the general U.S. population have declined in recent years (CDC, 2012), smoking remains entrenched

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among individuals with concurrent substance abuse. Among patients receiving methadone or buprenorphine (Suboxone®) for the treatment of opioid dependence, for example, prevalence of smoking is 4-fold greater than the general population (Guydish et al., 2011).

One possible mechanism underlying the elevated smoking in opioid-dependent patients is a pharmacological interaction whereby opioids directly increase smoking (Chait & Griffiths, 1984; Mello, Lukas, & Mendelson, 1985; Mello, Mendelson, Sellers, & Kuehnle, 1980; Mutschler, Stephen, Teoh, Mendelson, & Mello, 2002; Pickworth, Lee, Abreu, Umbricht, & Preston, 2004; Schmitz, Grabowski, & Rhoades, 1994). It is also worth noting though, that similar associations have been observed between smoking and alcohol (e.g., Griffiths, Bigelow, & Liebson, 1976; Henningfield, Chait, & Griffiths, 1983) and psychomotor stimulants (e.g., Rush et al., 2005; Sigmon, Tidey, Badger, & Higgins, 2003). While the precise mechanism underlying these associations remains unknown, a growing literature suggests that shared genetic or neurobiological risk factors may underlie risk of poly-substance use (see Blum & Braverman, 2003; Blum, Cull, Braverman, & Comings, 1996). Nonetheless, this association holds significant clinical relevance considering that approximately 5% of Americans report recent opioid abuse (SAMHSA, 2013) and over 272,000 patients receive opioid maintenance treatment for opioid dependence annually (SAMHSA, 2011). Further, approximately five million adults are receiving long-term opioid treatment for acute or chronic pain, with over 256 million opioid prescriptions filled each year (Boudreau et al., 2009; Governale, 2010; Parsells Kelly et al., 2008).

Several controlled studies have examined the effects of opioids on smoking (Chait & Griffiths, 1984; Lofwall, Walsh, Bigelow, & Strain, 2007; Mello et al., 1980, 1985; Mutschler et al., 2002; Pickworth et al., 2004; Schmitz et al., 1994). Of those investigating the effect of opioids on the number of cigarettes smoked per day, all demonstrated a significant positive association between opioids and smoking (Chait & Griffiths, 1984; Mello et al., 1985; Mello et al., 1980; Mutschler et al., 2002; Pickworth et al., 2004; Schmitz et al., 1994). In the four studies that included breath carbon monoxide (CO) as a biochemical measure of smoking status, two demonstrated significant increases in breath CO during opioid administration (Chait & Griffiths, 1984; Lofwall et al., 2007), while two showed no effect (Pickworth et al., 2004; Schmitz et al., 1994).

Taken together, while opioids represent a widely-used approach for managing opioid dependence and pain, their possible effects on smoking warrant an improved understanding of this relationship. We present a secondary analysis of data from a double-blind trial evaluating duration of buprenorphine detoxification for treating PO dependence (Sigmon et al., 2013). Participants did not receive any smoking-cessation services and were not encouraged to alter their smoking in any way. Participants' urine specimens were analyzed for urinary cotinine as an objective measure of smoking, permitting us to examine whether naturalistic changes in smoking occurred among participants who successfully tapered. We hypothesized that successful opioid detoxification would be associated with a reduction in smoking, as evidenced by reductions in urinary cotinine.

2. Methods

2.1. Participants

Participants were PO-dependent adults enrolled in a NIDA-funded clinical trial investigating the efficacy of buprenorphine detoxification and subsequent oral naltrexone therapy (Sigmon et al., 2013). Eligible participants met DSM-IV criteria for opioid dependence, provided an opioid-positive urine at intake, endorsed an illicit PO as their primary drug of abuse (e.g., oxycodone) and were interested in opioid detoxification. Participants were excluded if they were pregnant or nursing, required opioid therapy for pain, or had a significant psychiatric or medical illness. The local institutional review board approved the study, and participants provided written informed consent prior to participating.

2.2. Study design

Complete methods of the clinical trial have been described previously (Sigmon et al., 2013). Briefly, participants received an initial buprenorphine stabilization (approximately 2 weeks) wherein they were inducted onto a buprenorphine dose sufficient to achieve withdrawal suppression (Johnson, Strain, & Amass, 2003). Once stabilized, participants were randomized to receive a 1-, 2- or 4-week buprenorphine taper. Following randomization, the study was 12 weeks in duration. During each taper, buprenorphine doses were gradually reduced until placebo (0 mg) was reached. Participants who successfully tapered without resuming illicit opioid use were transitioned to oral naltrexone for the remainder of the study. All medications were administered in a double-blind, double-dummy manner to ensure that participants and staff remained blind to dose, taper duration, and the point at which naltrexone began. Thus, participants received 5.5 sublingual (active buprenorphine and/or color-matched placebo buprenorphine) and 3 capsules (active naltrexone and/or placebo naltrexone) at each study visit.

For the present analyses, our aim was to characterize naturally occurring changes in smoking during successful opioid detoxification. Three criteria were used to identify appropriate participants. First, smokers were defined as those who self-reported smoking $\geq$10 cigarettes per day at intake, which is a commonly-used criterion for identifying regular smokers (Schmitz et al., 1994; Tidey, O'Neill, & Higgins, 2000). Second, to minimize confounding related to illicit opioid use, we included only those participants who successfully tapered off of buprenorphine without resumption of illicit opioid use. Finally, to minimize confounding related to varying taper durations and because results from the parent trial determined that the 4-week taper provided the most complete data for analysis (Sigmon et al., 2013), we focused on participants who were randomly assigned to the 4-week taper duration. While these criteria translated to a limited sample size, they also provided a rigorous evaluation of change in smoking throughout detoxification.

2.3. Biochemical monitoring

Urine specimens were collected under same-sex staff observation thrice weekly (MWF) and analyzed immediately onsite for cotinine using enzyme multiplied immunoassay (EMIT) (MGC240; Microgenics; Fremont, CA).

2.4. Data analysis

Mean urinary cotinine levels were compared across intake, stabilization, taper and post-taper study phases. The stabilization phase was defined as the last seven days of the buprenorphine stabilization. The buprenorphine taper phase was defined as Weeks 1–5 (note: participants received active buprenorphine taper during Weeks 1–4, yet Week 5 was included in this phase to permit buprenorphine to clear the system prior to naltrexone induction in Week 6). The post-taper phase was defined as Weeks 6–12 during which all participants received placebo buprenorphine and active naltrexone. Repeated measures analysis of variance was used to compare mean cotinine values collapsed across study phase. Due to skewed cotinine distributions, values were log-transformed prior to analysis, therefore all means presented represent geometric means and their associated standard errors, which were computed based on the Delta method. Temporal changes in mean cotinine values across study week were analyzed using repeated-measures analysis of variance (PROC MIXED). The paired t-tests were used to compare self-reported number of cigarettes smoked at intake with those smoked at the end of the 12-week study. Pairwise comparisons were performed using Fisher's LSD. All analyses were performed