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Short communication

Nicotine biomarkers and rate of nicotine metabolism among cigarette smokers taking buprenorphine for opioid dependency

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ABSTRACT

Background: Individual differences in the rate of nicotine metabolism contribute to differences in tobacco use, dependence, and efficacy of smoking cessation treatments and can be assessed using the nicotine metabolite ratio (NMR), a validated biomarker for CYP2A6 activity. Despite the high cigarette smoking rates observed in opioid users, no data have been reported on NMR among this population as they has been largely excluded from previous studies that have examined the relationship between tobacco use characteristics and rate of nicotine metabolism.

Methods: A linear regression model was used to examine the relationship between tobacco use characteristics and NMR among smokers taking buprenorphine for opioid dependency (N = 141). The relationship between buprenorphine dose and NMR was also examined. All participants were enrolled in an intervention designed to promote cigarette-smoking cessation, though participants did not need to stop smoking to enroll.

Results and conclusions: Rate of nicotine metabolism assessed using the NMR was positively associated with cigarettes smoked in the past 24 h, but was not related to time to first cigarette or past year quit attempts. Dose of buprenorphine was not associated with NMR, suggesting no association with rate of nicotine metabolism. Our results suggest that NMR is related to tobacco use among persons enrolled in opioid treatment, as reported in general population smokers and may be a useful biomarker to include in future research assessing efficacy of tobacco cessation interventions in this population.

1. Introduction

There is a high prevalence of tobacco use among opioid users, estimates ranging from 84% to 94% (Clemmey et al., 1997; Nahvi et al., 2006; Richter et al., 2001). Individuals with opioid dependence smoke more cigarettes per day, have greater nicotine dependence, and have poorer smoking cessation outcomes (Clemmey et al., 1997; Okoli et al., 2010). Higher doses of methadone have been found to be associated with heavier smoking (Chait and Griffiths, 1984; Schmitz et al., 1994; Stark and Campbell, 1993). Tobacco-related diseases remain a leading cause of premature death in individuals with substance abuse (Bandiera et al., 2015; Hurt et al., 1996) and there is an urgent need to improve smoking cessation interventions in this population.

Differences in the rate of nicotine metabolism may contribute to differences in tobacco use and dependence. Individuals with faster rates of nicotine metabolism smoke more cigarettes per day (Benowitz et al., 2003; Tyndale and Sellers, 2001), have greater nicotine withdrawal symptoms (Rubinstein et al., 2008; Sofuoglu et al., 2012), and decreased efficacy of nicotine replacement therapy (NRT) for smoking cessation (Lerman et al., 2006, 2015).

Nicotine is primarily metabolized into cotinine by the enzyme CYP2A6, which is further metabolized to *trans*-3′-hydroxycotine (3HC) nearly exclusively by the same enzyme (Benowitz et al., 2009). Rate of nicotine metabolism can be assessed using the ratio of 3HC/cotinine, termed the nicotine metabolite ratio (NMR), a validated biomarker for CYP2A6 activity that can be measured in blood, saliva or urine. (Dempsey et al., 2004). A higher NMR indicates greater CYP2A6 enzyme activity and faster rate of nicotine metabolism. In vitro and rodent studies indicate that buprenorphine can weakly inhibit CYP2A6 enzyme activity (Ohtani et al, 1993; Ohtani, 2007; Umehara et al., 2002; Zhang et al., 2003), which could result in a lower rate of nicotine metabolism.

Despite the high rates of smoking in individuals with substance abuse problems, most studies that have assessed NMR have been conducted in populations that exclude such individuals. To our knowledge, there are no published data on NMR in opioid dependent smokers and this is the first study to examine the relationship between

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buprenorphine dose and rate of nicotine metabolism in humans. It is important to understand the relationship between rate of nicotine metabolism and cigarette consumption and dependence in an opioid treatment population, as this knowledge may help to inform future smoking cessation interventions in this population.

Thus, the goals of the current study were: (1) to characterize saliva NMR levels in buprenorphine maintained cigarette smokers, (2) to examine the relationship between NMR and tobacco use behaviors and dependence measures in cigarette smokers in opioid treatment and (3) to determine if buprenorphine dose was associated with differences in NMR. It was hypothesized that in an opioid treatment population, a faster rate of nicotine metabolism would be associated with greater cigarettes smoked per day, as is found in the general population.

2. Methods

2.1. Participants

The parent study assessed the efficacy of a smoking cessation intervention in buprenorphine maintained cigarette smokers and was conducted in the Integrated Buprenorphine Intervention Service (IBIS), a buprenorphine treatment program operated under the San Francisco Department of Public Health (SFDPH). Details of parent study recruitment and procedure are published in (Hall et al., 2017; Clinicaltrials.gov, NCT01350011). Eligible participants had to smoke ≥5 cigarettes per day during the past week (at the time of screening) but did not need to want to quit smoking to be eligible for the study. Participants had to have been in IBIS for at least three months, reflecting stabilization on buprenorphine and be 18 years of age or older, have a diagnosis of opioid dependence, and live in San Francisco, and eligible for treatment through SFDPH. Patients dependent on benzodiazepines or alcohol, had an uncontrolled medical or psychiatric condition, had a pain syndrome requiring opioid analgesics, or were pregnant or planning to become pregnant, were treated elsewhere in the SFDPH system. Individuals with a history of schizophrenia, bipolar disorder, cardiovascular disease (myocardial infarction within 3 months, uncontrolled high blood pressure) were excluded. All study procedures were approved by the Institutional Review Board of the University of California, San Francisco.

The current analyses included 141 buprenorphine maintained cigarette smokers with complete biomarker data; excluded were 16 participants that did not provide a saliva sample, and 5 participants that had 3HC levels below the level of quantification. A saliva cotinine cutoff of 10.0 was used for the current analysis to ensure participants were active smokers (6 participants with salivary cotinine levels < 10 were excluded).

2.2. Procedure and measures

Demographic variables included age, sex, race, body mass index (BMI) and education. Number of days in the past month drinking alcohol or using (cocaine, amphetamine, marijuana, heroin); having a doctor recommendation for treatment for hepatitis C; being prescribed medication to treat a psychological/emotional problem in the past 30 days; and current dose of buprenorphine (mg/day) were also assessed. Usual cigarettes smoked per day, cigarettes smoked during the past 24 h, and number of past year cigarette quit attempts (lasting at least 24 h) were assessed by self-report. Individuals also reported time to first cigarette (TTFC) smoked after waking, which was used as a measure of nicotine dependence (Baker et al., 2007). Saliva samples were collected at the end of the baseline assessment session to ensure that participants had not smoked or eaten for at least 30 min before sample collection.

2.3. Analytical chemistry

Saliva samples were analyzed for concentrations of cotinine and *trans*-3′-hydroxycotinine (3-HC) using liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) as previously described (Dempsey et al., 2004; Jacob et al., 2011). Biochemical analyses were conducted in the Clinical Pharmacology Laboratory at Zuckerberg San Francisco General Hospital.

2.4. Data analysis

NMR was calculated as the ratio of 3HC/cotinine. Log-transformed NMR was used in the regression model because NMR was not normally distributed and Log-transformed NMR has been found to be a better predictor of nicotine clearance (Levi et al., 2007). A linear regression model was used to determine if NMR was associated with tobacco use variables adjusting for other factors (Table 2). Three subjects had NMR values there were greater than 2.5 standard deviations above or below the sample mean. The regression model was run with and without these 3 outliers. The model, reported in the manuscript, excluding these outliers was found to better predict cigarettes in the past 24 h. As expected, usual cigarettes smoked per day and cigarettes smoked in the past 24 h were correlated ($r = 0.81$. $p < 0.001$). Number of cigarettes smoked in the past 24 h (versus usual cigarettes smoked per day) was found to be a better predictor of NMR. For this reason, the regression model only included cigarettes smoked in the past 24 h.

Means are presented ± standard deviation (SD). Associations were considered significant at an alpha level of 0.05 or less. All statistical analyses were performed using SPSS 24 (IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Sample characteristics

The baseline demographic and smoking variables for the sample (N = 141) are shown in Table 1.

Mean age of the sample was 40.6 ± 10.3, and the majority were male (74.5%) and White (69.5%). The mean dose of buprenorphine was 16.1 ± 7.4 (range 2–32 mg/day). Mean usual cigarettes smoked per day was 14.9 ± 7.3, and mean cigarettes smoked in the past 24 h was 14.1 ± 7.6. Overall 64.3% smoked their first cigarette of the day within 30 min of waking and the mean number of past year quit attempts (lasting at least 24 h) was 1.8 ± 4.9.

3.2. Biomarkers and rate of nicotine metabolism

For the sample, mean saliva cotinine was 273.6 ± 209.8 ng/ mL, saliva 3HC levels was 134.1 ± 139.9 ng/ mL, and NMR was 0.53 ± 0.37 (see Table 1).

3.3. Relationship between NMR and tobacco use characteristics in individuals in opioid treatment

In the regression model (Table 2), log-transformed NMR was only a significant predictor of cigarettes smoked in the past 24 h. Controlling for demographic characteristics, higher NMR (faster rate of nicotine metabolism) was associated with smoking more cigarettes ($b = 0.009$, $p = 0.007$). The mean number of cigarettes smoked in the past 24 h by NMR quartiles was NMR Q1 (mean = 11.03, SD = 6.20), NMR Q2 (mean = 15.66, SD = 6.66), NMR Q3 (mean = 15.03, SD = 7.68), and NMR Q4 (mean = 14.86, SD = 9.07).

NMR was not found to be significantly related to time to first cigarette smoked in the morning, the number of quit attempts made in the past year, or other demographic characteristics. NMR was not associated with dose of buprenorphine that participants were taking.