Addictive Behaviors 51 (2015) 93–99

Contents lists available at ScienceDirect

Addictive Behaviors

Rate of Nicotine Metabolism and Smoking Cessation Outcomes in a Community-based Sample of Treatment-Seeking Smokers☆

Amanda Kaufmann [a], Brian Hitsman [b], Patricia M. Goelz [a], Anna Veluz-Wilkins [b], Sonja Blazekovic [a], Lindsay Powers [b], Frank T. Leone [c], Peter Gariti [a], Rachel F. Tyndale [d,e,f], Robert A. Schnoll [a,*]

[a] Department of Psychiatry, University of Pennsylvania, 3535 Market Street, Suite 4100, Philadelphia, PA 19104
[b] Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 N Lakeshore Drive, Chicago, IL 60611
[c] Pulmonary, Allergy, & Critical Care Division, University of Pennsylvania Presbyterian Medical Center, 51 N. 39th Street, Philadelphia, PA 19104
[d] Centre for Addiction and Mental Health, 1 King's College Circle, University of Toronto, Toronto, Ontario, Canada, M5S 1A6
[e] Department of Pharmacology & Toxicology, 1 King's College Circle, University of Toronto, Toronto, Ontario, Canada, M5S 1A6
[f] Department of Psychiatry, 1 King's College Circle, University of Toronto, Toronto, Ontario, Canada, M5S 1A6

HIGHLIGHTS

- Nicotine metabolism and smoking cessation was examined in a community sample
- Faster nicotine metabolizers showed lower quit rates than slower metabolizers
- Faster metabolizers reported higher anxiety levels than slower metabolizers
- Rate of nicotine metabolism can individualize treatment for nicotine dependence

ARTICLE INFO

Article history:
Received 11 March 2015
Received in revised form 16 June 2015
Accepted 21 July 2015
Available online 26 July 2015

Keywords:
Smoking cessation
Nicotine dependence
Pharmacogenetics
Biomarker
Anxiety
Nicotine metabolite ratio

ABSTRACT

Background: In samples from controlled randomized clinical trials, a smoker's rate of nicotine metabolism, measured by the 3-hydroxycotinine to cotinine ratio (NMR), predicts response to transdermal nicotine. Replication of this relationship in community-based samples of treatment-seeking smokers may help guide the implementation of the NMR for personalized treatment for nicotine dependence.
Methods: Data from a community-based sample of treatment seeking smokers (N = 499) who received 8 weeks of transdermal nicotine and 4 behavioral counseling sessions were used to evaluate associations between the NMR and smoking cessation. Secondary outcomes included withdrawal and craving, depression and anxiety, side effects, and treatment adherence.
Results: The NMR was a significant predictor of abstinence (OR = .56, 95% CI: 0.33-0.95, p = .03), with faster metabolizers showing lower quit rates than slower metabolizers (24% vs. 33%). Faster nicotine metabolizers exhibited significantly higher levels of anxiety symptoms over time during treatment, vs. slower metabolizers (NMR x Time interaction: F[3,357] = 3.29, p = .02). NMR was not associated with changes in withdrawal, craving, depression, side effects, and treatment adherence (p's > .05).
Conclusions: In a community-based sample of treatment-seeking smokers, faster nicotine metabolizers were significantly less likely to quit smoking and showed higher rates of anxiety symptoms during a smoking cessation treatment program, vs. slower nicotine metabolizers. These results provide further evidence that transdermal nicotine is less effective for faster nicotine metabolizers and suggest the need to address cessation-induced anxiety symptoms among these smokers to increase the chances for successful smoking cessation.

1. Introduction

Several studies suggest that a genetically-informed biomarker that characterizes smokers by their rate of nicotine metabolism may be useful for selecting pharmacotherapy to maximize treatment efficacy for smokers interested in cessation (Bough, Lerman, Rose, et al., 2013; Schnoll & Leone, 2011). This biomarker, referred to as the nicotine metabolite ratio (NMR) and formed using a ratio of the two primary

☆ Funding: This research was supported by grants from the National Institute on Drug Abuse (R01 DA025078 and R01 DA033681) and from the National Cancer Institute (R01 CA165001 and P30 CA16520).
* Corresponding author.
E-mail address: schnoll@mail.med.upenn.edu (R.A. Schnoll).

http://dx.doi.org/10.1016/j.addbeh.2015.07.019
0306-4603/

metabolites of nicotine (3-hydroxycotinine and cotinine), is a surrogate marker for the rate of nicotine clearance, representing genetic (CYP2A6) and demographic influences (e.g., race, gender) on the rate of nicotine metabolism (Lea, Dickson, & Benowitz, 2006). Three independent randomized clinical trials (Ho, Mwenifumbo, Al Koudsi, et al., 2009; Lerman, Tyndale, Patterson, et al., 2006; Schnoll et al., 2009) have shown that smokers characterized as having faster nicotine metabolism (higher NMR values) are significantly less likely to quit smoking using transdermal nicotine than smokers with slower nicotine metabolism (lower NMR values); in a fourth clinical trial (Patterson, Schnoll, Wileyto, et al., 2008), bupropion offset the relapse risk among faster nicotine metabolizers, suggesting that bupropion may help fast nicotine metabolizers to quit smoking. Most recently, a randomized clinical trial that prospectively stratified allocation to transdermal nicotine or varenicline showed that varenicline can effectively treat nicotine dependence among fast nicotine metabolizers (Lerman, Schnoll, Hawk, et al., 2015).

Should the NMR be used clinically to determine treatment selection to maximize therapeutic benefit, the relationship between the NMR and response to transdermal nicotine should be replicated among community samples of smokers who may differ in important ways (e.g., higher rates of comorbid psychiatric conditions) from the participants in the efficacy clinical trials which form the basis for knowledge regarding the effects of the NMR on treatment response. In this study, data from a community-based effectiveness trial of transdermal nicotine patches were used to assess the replication of the relationship previously found between NMR and response to transdermal nicotine (Ho et al., 2009; Lerman et al., 2006; Schnoll et al., 2009). In addition, this study examined how the rate of nicotine metabolism predicted secondary outcomes relevant to cessation outcomes: withdrawal, craving, depression and anxiety symptoms, side effects, and treatment adherence (West, Hajek, & McRobbie, 2011). Assessment of secondary outcomes between slow and fast nicotine metabolizers may elucidate potential mechanisms through which the NMR influences response to treatments for nicotine dependence and offer insight into targets for adjunctive treatment to help offset the heightened relapse risk documented among fast nicotine metabolizers. The results from this study may provide further support for, and enhance understanding of, the potential use of the NMR to guide the personalization of treatment for nicotine dependence.

2. Methods

Data for this study were from an effectiveness study designed to evaluate long-term use of transdermal nicotine for nicotine dependence (ClinicalTrials.gov Identifier: NCT01047527). Community smokers were recruited through media advertisements and the trial was conducted at the University of Pennsylvania and Northwestern University, which provided Institutional Review Board oversight and approval. Potential participants called to inquire about the study; an evaluation of study interest and initial eligibility was completed by phone. An in-person visit confirmed eligibility and participants were randomly selected for either 8, 24, or 52 weeks of transdermal nicotine patch therapy; all participants received 12 standardized, manual-based behavioral smoking cessation counseling sessions based on established guidelines (Fiore, Jaen, Baker, et al., 2008). For the present analysis, only data up to 8 weeks were used to standardize treatment across participants (i.e., all participants received 8 weeks of nicotine patch treatment and four behavioral counseling sessions) and to remain consistent with previous studies (Ho et al., 2009; Lerman et al., 2006; Schnoll et al., 2009).

2.1. Participants

Consistent with an effectiveness trial, inclusion and exclusion criteria were limited to increase generalizability of findings (e.g., 20% of the present sample had current or past major depression and 5% had current substance abuse). Eligible participants were > 18 years of age, reported smoking > 10 cigarettes/day, and were interested in quitting smoking. Participants were excluded if they had a current medical problem for which transdermal nicotine is contraindicated (e.g., allergy to latex), had a lifetime DSM-IV diagnosis of psychosis or bipolar disorder, reported current suicidality as identified by the Mini International Neuropsychiatric Interview (MINI) (Sheehan, Lecrubier, Sheehan, et al., 1998), or were unable to communicate in English. Female participants were excluded if they were pregnant, planning a pregnancy, or lactating.

2.2. Procedures

All participants received 8 weeks of 21 mg transdermal nicotine patches (Nicoderm CQ; GlaxoSmithKline, Research Triangle Park, NC). Participants received one in-person pre-quit counseling session at week -2 (baseline), which focused on preparing for cessation, and then set a quit date for week 0, at which time they were instructed to start using the nicotine patch. At weeks 0, 4, and 8, participants received behavioral counseling over the telephone. These sessions were based on standard smoking cessation behavioral treatment guidelines (Fiore et al., 2008) focusing on managing urges and triggers to smoking and developing strategies to avoid relapse. Assessments, described below, were conducted at baseline (in-person) and at weeks 0, 4, and 8 (by telephone). Week 8 self-reports of smoking cessation (for the 7 days preceding this assessment) were biochemically confirmed using breath carbon monoxide (CO).

2.3. Measures

2.3.1. Covariates

At baseline, participants self-reported demographics (e.g., age, race, sex) and smoking history and behavior (e.g., cigarettes per day; the Fagerström Test for Nicotine Dependence [FTND]) (Heatherton, Kozlowski, Frecker, & Fagerström, 1991).

2.3.2. Nicotine Metabolite Ratio

Saliva samples (5 ml) were collected during eligibility assessment to determine NMR using liquid chromatography with tandem mass spectrometry (Dempsey, Tutka, Jacob, et al., 2004). Individual NMR values remain stable over time, and saliva NMR results correlate strongly with plasma NMR results (St Helen, Novalen, Heitjan, et al., 2012).

2.3.3. Nicotine Withdrawal

The Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 1986) assesses 7 DSM-IV items of nicotine withdrawal (e.g., restlessness, irritability) and items were summed.

2.3.4. Nicotine Craving

The 10-item brief Questionnaire of Smoking Urges (QSU) (Cox, Tiffany, & Christen, 2001) contains 2 subscales (anticipation of reward, relief from negative affect).

2.3.5. Depression

The Inventory of Depressive Symptomatology (IDS) is a 30-item self-report measure used to assess the severity and frequency (past 7-days) of depressive symptoms, consistent with the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders – 4th Edition diagnosis of a major depressive episode (American Psychiatric Association, 2000; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996; Rush et al., 1986).

2.3.6. Anxiety

The 21-item Beck Anxiety Inventory (BAI) assessed anxiety symptoms over the past week (Beck, Epstein, Brown, & Steer, 1988). Items were summed to obtain a total score.