BRIEF REPORT

Clinical Significance of Early Smoking Withdrawal Effects and Their Relationships With Nicotine Metabolism: Preliminary Results From a Pilot Study

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ABSTRACT

Introduction: Although the early time course of smoking withdrawal effects has been characterized, the clinical significance of early withdrawal symptoms and their predictors are unknown. This study evaluated the relationships of early smoking withdrawal effects with quit attempt outcomes and the rate of nicotine metabolism.

Methods: Eleven treatment-seeking smokers abstained from smoking for 4 hr in the laboratory before a quit attempt. Withdrawal measures included heart rate, sustained attention, and self-report. Following baseline assessment, withdrawal measures were administered every 30 min. At the conclusion of the 4-hr early withdrawal session, participants received a brief smoking cessation intervention and then returned 1 week and 12 weeks later for outcome assessments that included biochemically confirmed smoking abstinence, cigarettes smoked in the past 24 hr, and self-reported withdrawal symptoms. The rate of nicotine metabolism was estimated at intake with the nicotine metabolite ratio (trans-3'-hydroxycotinine/cotinine) measured in saliva.

Results: Greater self-reported negative affect and concentration difficulty during early withdrawal, most notably anxiety, were related with poorer quit attempt outcomes. There was some indication that although a faster increase in craving and greater hunger during early withdrawal were associated with more favorable outcomes, a greater decrease in heart rate during this time was associated with poorer outcomes. Faster nicotine metabolism was related to a faster increase in anxiety but a slower increase in craving during early withdrawal.

Conclusions: These findings lend support to the clinical significance of early smoking withdrawal effects. The rate of nicotine metabolism may be a useful predictor of early withdrawal symptoms.

INTRODUCTION

Despite an extensive literature on smoking withdrawal (Ashare, Falcone, & Lerman, 2013; Baker et al., 2012; Bidwell et al., 2013; Etter, Ussher, & Hughes, 2012; Evans et al., 2013; Hendricks & Leventhal, 2013), few studies have evaluated early withdrawal effects—those that emerge during the first minutes and hours after the last cigarette. To the best of our knowledge, only two studies have systematically evaluated the early time course of smoking withdrawal effects (Brown et al., 2013; Hendricks, Ditte, Drobles, & Brandon, 2006). However, these studies did not address the clinical significance of these symptoms (e.g., their relationships with quit attempt outcomes such as abstinence or later withdrawal symptoms; Hughes, 2007a), which could serve as predictors of treatment success

and provide valuable information for clinicians in designing tailored interventions.

Predictors of early withdrawal effects are also unknown. A viable candidate is the rate of nicotine metabolism, which can be estimated in smokers using the nicotine metabolite ratio (NMR; the ratio of trans-3'-hydroxycotinine to cotinine) measured in saliva, urine, or plasma. Greater ratios indicate faster clearance (St. Helen, Jacob, & Benowitz, 2013) and might be expected to associate with more prominent withdrawal symptoms. One study found that greater NMR is associated with greater craving 1 week postquit (Lerman et al., 2006), but this finding failed to replicate (West, Hajek, & McRobbie, 2011). In a study of adolescent light smokers, greater NMR was associated with more severe withdrawal symptoms following 24 hr of supervised abstinence (Rubinstein, Benowitz, Auerback, & Moscicki, 2008). Nevertheless, no

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investigation has examined the relationship between NMR and early withdrawal effects, which could help inform the utility of NMR-based treatments (West et al., 2011).

In this study, withdrawal effects were monitored during the first 4 hr of abstinence among adult cigarette smokers, preceding a quit attempt. The relationships of early withdrawal effects with abstinence, cigarette consumption, and withdrawal symptoms at follow-up were estimated in an initial attempt to establish their clinical significance. Furthermore, the relationships of NMR with early withdrawal effects were examined as a first step in determining the contribution of the rate of nicotine metabolism to early withdrawal phenomena.

METHODS

Participants

Participants were 11 treatment-seeking cigarette smokers who responded to community advertisements. Eligibility criteria were (a) fluent in English, (b) ≥ 18 years old, (c) smoking ≥ 10 cigarettes/day for at least the past year, (d) a score of ≥ 8 on the Contemplation Ladder (Biener & Abrams, 1991), and (e) willing to set a quit date within 48 hr after participation in a 4-hr experimental session. Exclusion criteria were (a) expired breath carbon monoxide (CO) < 10 parts per million (ppm) at intake, (b) currently participating in a smoking cessation treatment program, (c) currently using pharmacotherapy for smoking cessation, and (d) presence of any condition contraindicating use of the nicotine patch. This study was approved by the institutional review boards of the University of Alabama at Birmingham and the University of California, San Francisco.

Procedures

Procedures for assessing early withdrawal effects followed those of an earlier study (Hendricks et al., 2006). Participants who met inclusion criteria during a telephone interview were scheduled for individual appointments at an inpatient research unit located at the San Francisco General Hospital between noon and 9:00 p.m. and were instructed to smoke as usual before their appointment. They were further instructed that the study requires between 4 and 6 hr of their time and may require abstaining from smoking. Upon obtaining informed consent, the order of procedures was as follows: (a) confirmation of smoking status via CO; (b) collection of saliva sample for NMR analysis; (c) completion of intake measures; (d) participants smoked one of their own cigarettes; (e) baseline withdrawal assessment; (f) participants were instructed to abstain from smoking. Participants' cigarettes were collected to ensure abstinence, the duration of which was not revealed so that participants could not anticipate smoking availability. Early withdrawal assessments required approximately 5 min each to complete and occurred at 30-min intervals over 4 hr after baseline assessment (i.e., at baseline and at 30, 60, 90, 120, 150, 180, 210, and 240 min post-baseline), for a total of nine assessments. Between assessments, participants had the opportunity to read a variety of magazines or personal material (e.g., books brought from home) as well as use their personal electronic devices. Participants were paid \$50 for completing the 4-hr experimental session.

Following the 4-hr experimental session, participants received a brief smoking cessation intervention consisting of

cognitive-behavioral counseling, a standard 10-week supply of the nicotine patch, and self-help material. Participants returned 1 and 12 weeks after the experimental session for outcome assessments. Participants were reimbursed \$20 for completing outcome assessments at Weeks 1 and 12.

Early Withdrawal Measures

Withdrawal measures were those that demonstrated sensitivity to early smoking abstinence in a prior study (Hendricks et al., 2006). The order of administration at each of the nine early withdrawal assessments was as follows.

Heart Rate

Decreased heart rate is an effect of smoking abstinence (Hughes, 2007b). Heart rate in beats per minute was measured over a 30-s period via a telemetry monitor at each assessment. A research assistant recorded heart rate every 3 s during this 30-s period, and average heart rate was determined by computing a mean of these 10 observations.

Rapid Visual Information Processing Task

The Rapid Visual Information Processing (RVIP) is a task of sustained attention, which is impaired by abstinence from cigarettes (Wesnes & Warburton, 1983). A series of single digits appear on a computer screen, and participants are told to press a response button whenever they notice three consecutive odd or even digits. Greater mean reaction time latency reflects poorer sustained attention.

Wisconsin Smoking Withdrawal Scale

The Wisconsin Smoking Withdrawal Scale (WSWS) is a self-report questionnaire that contains seven scales (Anger, Anxiety, Concentration difficulty, Craving, Hunger, Sadness, and Sleep disturbance) (Welsch et al., 1999). As in Hendricks et al. (2006), participants were instructed to complete the WSWS with reference to their current experience; items on the Sleep disturbance scale were removed due to their inapplicability to early withdrawal; and the response scale was expanded from the original 0–4 to 0–8 to increase the measure's sensitivity. Greater scale scores represent more severe symptomatology.

Outcome Measures

Outcome measures at Weeks 1 and 12 follow-up included the following: (a) 7-Day point prevalence smoking abstinence verified by CO levels of < 10 ppm; (b) self-reported cigarettes smoked in the past 24 hr; and (c) withdrawal symptoms, as measured by the WSWS (reference period of previous week; original 0–4 response scale; Sleep disturbance scale included).

Nicotine Metabolite Ratio

Concentrations of cotinine and trans-3'-hydroxycotinine in saliva were measured by liquid chromatography–mass spectrometry (Jacob et al., 2011).

Data Analysis

As in Hendricks et al. (2006), early withdrawal analyses focused on both mean withdrawal symptoms and the rate of change (i.e., slope) of these symptoms. Mean values were

computed from the eight abstinent ratings of each withdrawal measure, whereas empirical Bayes estimates of linear slope (Oberfeld & Franke, 2013; Speer & Greenbaum, 1995) were computed from all nine ratings (baseline plus the eight abstinent ratings) of each withdrawal measure. To test the main effects of abstinence, dependent sample *t* tests compared mean abstinent values to nonabstinent baseline values, and one-sample *t* tests evaluated slope values for significant departure from zero. Cohen's *d* was computed by dividing the mean difference by the standard deviation of the difference scores.

As the small pilot sample precluded complex modeling (e.g., multiple regression; Bewick, Cheek, & Ball, 2005; Green, 1991), primary analyses evaluated the relationships of withdrawal effect means and slopes to outcome measures and NMR with nonparametric correlations (Kendall's τ). Given the small sample's reduced power to detect statistically significant associations, we did not require that results be statistically significant to warrant inclusion in this report. However, because the strength of association per se is not affected by sample size, only τ s of .40 or greater (i.e., those exceeding the conventional cutoff of .30 that corresponds to a moderate effect; Cohen, 1988) are reported to identify potentially meaningful relationships.

RESULTS

Participants were six men and five women with a mean age of 46.1 (*SD* = 7.5, range = 30–57). Four were White, four were African American, two were Asian American, and one was American Indian. Participants smoked for a mean of 22.6 years (*SD* = 13.1, range = 6–43), smoked a mean of 17.7 cigarettes/day (*SD* = 6.6, range = 10–30), and had a mean Fagerström Test of Cigarette Dependence (Fagerström, 2012) score of 4.0 (*SD* = 1.7, range = 2–8). Mean NMR was 0.46 (*SD* = 0.35, range = 0.11–1.23).

During early withdrawal, there were significant mean differences, each in the expected direction, between abstinent and nonabstinent Anger (mean difference = 1.03, *t* = 2.5, *p* = .03, *d* = 0.76), Anxiety (mean difference = 0.72, *t* = 2.2, *p* = .04, *d* = 0.68), Craving (mean difference = 1.83, *t* = 2.7, *p* = .02, *d* = 0.83), Hunger (mean difference = 2.41, *t* = 3.6, *p* = .005, *d* = 1.09), and heart rate (mean difference = –5.16, *t* = –2.9, *p* = .01, *d* = –0.89). Though abstinent and nonabstinent Concentration difficulty (mean difference = 0.81, *t* = 2.1, *p* = .053, *d* = 0.66), Sadness (mean difference = 0.35, *t* = 1.2, *p* = .25, *d* = 0.37), and RVIP reaction time (mean difference = 55.21, *t* = 1.48, *p* = .16, *d* = 0.45) mean values did not differ significantly, trends were in the expected direction and effect sizes were in the moderate range. There also were significant departures from zero, each in the expected direction, for the early withdrawal slopes of Anxiety (mean difference = 0.15, *t* = 2.6, *p* = .02, *d* = 0.79), Craving (mean difference = 0.38, *t* = 3.5, *p* = .005, *d* = 1.06), Hunger (mean difference = 0.31, *t* = 3.13, *p* = .01, *d* = 0.94), and heart rate (mean difference = –0.74, *t* = –3.2, *p* = .009, *d* = –0.96). Although the slopes of Anger (mean difference = 0.13, *t* = 1.6, *p* = .12, *d* = 0.50), Concentration difficulty (mean difference = 0.09, *t* = 1.8, *p* = .09, *d* = 0.55), Sadness (mean difference = 0.03, *t* = 1.4, *p* = .16, *d* = 0.45), and RVIP reaction time (mean difference = 1.99, *t* = 1.4, *p* = .17, *d* = 0.44) did not differ significantly from zero, effects were in the anticipated direction and effect sizes were in the moderate range.

At Week 1, 4/11 (36%) of participants were abstinent with none lost to follow-up. At Week 12, 2/10 (20%) of participants were abstinent with one lost to follow-up and coded as missing. As shown in Table 1, greater mean Anger, Anxiety, Concentration difficulty, and Sadness during early withdrawal were associated with a range of poorer outcomes. Greater mean Craving during early withdrawal was associated only with more Sadness at Week 12. Greater mean Hunger was associated with

Table 1. Correlations (τ) of at Least .40 Between Early Withdrawal Effect Means and Smoking Abstinence, Cigarettes Smoked in the Past 24 Hours, and Self-reported Withdrawal Symptoms at Weeks 1 and 12 Follow-up

Early withdrawal effect mean		Abstinence	Cigarettes	1	2	3	4	5	6	Sleep disturbance
1. Anger	Week 1	–.40	—	.62	.65	.40	—	—	.42	.50
	Week 12	–.54	—	.45	.55	—	—	—	.55	.59
2. Anxiety	Week 1	–.44	.49	.64	.90	—	—	—	.61	.66
	Week 12	–.52	.48	.58	.64	.41	—	—	.86	.75
3. Concentration difficulty	Week 1	–.48	.49	.49	.71	.67	—	—	.57	.51
	Week 12	–.45	—	.68	.42	.46	.52	—	.67	.80
4. Craving	Week 1	—	—	—	—	—	—	—	—	—
	Week 12	—	—	—	—	—	—	—	.42	—
5. Hunger	Week 1	—	—	—	—	—	—	—	—	—
	Week 12	—	—	–.53	—	—	—	—	–.40	–.48
6. Sadness	Week 1	–.44	.53	.60	.82	.56	—	—	.65	.62
	Week 12	–.45	.43	.58	.55	—	—	—	.72	.79
RVIP reaction time	Week 1	—	—	—	—	—	–.49	—	—	—
	Week 12	—	—	—	—	—	—	–.45	—	—
Lower heart rate	Week 1	—	—	—	–.41	—	—	—	—	–.51
	Week 12	—	—	—	–.51	—	—	—	—	—

Note. Early withdrawal effect mean values were computed from 8 ratings assessed during the first 4 hr of abstinence at 30-min intervals. Anger, Anxiety, Concentration difficulty, Craving, Hunger, Sadness, and Sleep disturbance are scales of the Wisconsin Smoking Withdrawal Scale. RVIP = Rapid Visual Information Processing task; Abstinence = biochemically confirmed 7-day point prevalence smoking abstinence; Cigarettes = cigarettes smoked in the past 24 hr. Findings in bold are significant (*p* < .05).

less Anger, Sadness, and Sleep disturbance at Week 12; greater mean RVIP reaction time during early withdrawal was associated with less Craving at Week 1 and less Hunger at Week 12; and lower mean heart rate during early withdrawal was associated with less Anxiety at Weeks 1 and 12 and less Sleep disturbance at Week 1.

As shown in Table 2, a faster increase in Anxiety during early withdrawal was associated with a range of poorer outcomes. Moreover, a faster decrease in heart rate during early withdrawal was related to a lower likelihood of abstinence, more cigarettes smoked in the past 24 hr, and more Craving at Week 12. Faster increases in Anger, Concentration difficulty, Sadness, and RVIP reaction time during early withdrawal were associated with greater withdrawal symptoms at follow-up in some cases. Unexpectedly, a faster increase in Craving during early withdrawal was associated with a greater likelihood of abstinence and fewer cigarettes smoked in the past 24 hr at Week 1 as well as less Concentration difficulty at Week 12. A faster increase in Hunger during early withdrawal was associated with fewer cigarettes smoked per day and less Sadness at Week 1 but more Craving at Week 1 and more Hunger at Week 12.

Two participants' NMR data were missing due to inadequate volume of saliva. NMR was not associated with mean early withdrawal effects. However, although greater NMR was associated with a faster increase in Anxiety ($\tau = .48$, $p = .08$), it was related to a slower increase in Craving ($\tau = -.49$, $p = .07$). To place these findings in a larger context, the relationships between NMR and outcome measures also were evaluated; greater NMR was associated with greater Craving ($\tau = .40$, $p = .14$) and Hunger ($\tau = .40$, $p = .14$) at Week 1 and greater cigarettes smoked in the past 24 hr ($\tau = .62$, $p = .03$), Anger ($\tau = .44$, $p = .13$), and Anxiety ($\tau = .50$, $p = .08$) at Week 12.

DISCUSSION

Greater self-reported negative affect and concentration difficulty during early withdrawal were associated with poorer quit attempt outcomes at Weeks 1 and 12 follow-up, including lower likelihoods of abstinence, with anxiety evincing the most robust pattern of relations. A faster increase in craving during early withdrawal, conversely, was associated with more favorable outcomes at follow-up, including a higher likelihood of abstinence. As faster declines in craving measured over the first days and weeks postquit typically predict greater probabilities of abstinence (Wray, Gass, & Tiffany, 2013), our finding may suggest that change in craving during early withdrawal reflects a unique process not captured by later assessment. Consistent with work on longer term withdrawal effects (Javitz, Lerman, & Swan, 2012), there was some evidence that greater hunger during early withdrawal was related to more favorable outcomes. Perhaps hunger is protective with regard to smoking cessation because it is readily mollified via eating. Finally, although mean heart rate during early withdrawal appeared to relate to indices of autonomic arousal at follow-up, a faster decline in heart rate during early withdrawal was associated with a decreased probability of abstinence, more cigarettes smoked in the past 24 hr, and greater craving at Week 12. Performance on a task of sustained attention had few and inconsistent relationships with outcome. In total, these findings provide preliminary support for the clinical significance of early smoking withdrawal effects, with an emphasis on self-reported negative affect. Early smoking withdrawal symptoms may, therefore, provide a useful gauge of cessation outcome and guide tobacco interventions. For instance, smokers who experience particularly severe early withdrawal may benefit from withdrawal regulation training during the early hours of abstinence (Baker, Japuntich, Hogle, & Curtin, 2006) or

Table 2. Correlations (τ) of at Least .40 Between Early Withdrawal Effect Slopes and Smoking Abstinence, Cigarettes Smoked in the Past 24 Hours, and Self-reported Withdrawal Symptoms at Weeks 1 and 12 Follow-up

Early withdrawal effect slope		Abstinence	Cigarettes	1	2	3	4	5	6	Sleep disturbance
1. Anger	Week 1	—	—	.43	—	—	—	—	—	—
	Week 12	—	—	.51	—	.56	—	—	—	—
2. Anxiety	Week 1	-.60	.52	—	—	—	.41	—	.45	—
	Week 12	-.42	.51	.77	.53	.60	—	—	.58	.51
3. Concentration difficulty	Week 1	—	—	—	—	.40	.53	—	—	—
	Week 12	—	—	—	—	—	—	—	—	—
4. Craving	Week 1	.46	-.41	—	—	—	—	—	—	—
	Week 12	—	—	—	—	-.49	—	—	—	—
5. Hunger	Week 1	—	-.43	—	—	—	.49	—	-.53	—
	Week 12	—	—	—	—	—	—	.59	—	—
6. Sadness	Week 1	—	—	—	—	.54	—	—	—	—
	Week 12	—	—	—	—	—	.52	—	—	.41
RVIP reaction time	Week 1	—	—	—	—	—	.60	—	—	—
	Week 12	—	—	—	—	—	—	—	—	—
Heart rate decrease	Week 1	—	—	—	—	—	—	—	—	—
	Week 12	-.42	.41	—	—	—	.67	—	—	—

Note. Early withdrawal effect slope values were computed from 9 ratings assessed at baseline and during the first 4 hr of abstinence at 30-min intervals. Anger, Anxiety, Concentration difficulty, Craving, Hunger, Sadness, and Sleep disturbance are scales of the Wisconsin Smoking Withdrawal Scale. RVIP = Rapid Visual Information Processing task; Abstinence = biochemically confirmed 7-day point prevalence smoking abstinence; Cigarettes = cigarettes smoked in the past 24 hr. Findings in bold are significant ($p < .05$).

precessation nicotine replacement therapy (Rose, Herskovic, Behm, & Westman, 2009).

Greater NMR was associated with a faster increase in anxiety but a slower increase in craving during early withdrawal. Greater NMR also was related to greater cigarette consumption and more severe withdrawal symptoms at follow-up assessments, which is consistent with prior research (West et al., 2011). Thus, the effect of the rate of nicotine metabolism on smoking cessation outcomes may be mediated by its impact on the rates of change of anxiety and craving during early withdrawal. Future research should examine this mechanism further.

Findings should be considered in light of certain limitations. The sample was small, which limits the robustness of findings. We also conducted several tests without applying a significance criterion, which increases the likelihood of Type I error. Finally, the sample size necessitated somewhat simplistic analyses that could not account for the range of possible covariates or trajectory parameters such as volatility (Javitz et al., 2012). Though the strength of relationships and consistent pattern of results should somewhat offset these concerns, it should be noted that the goal of this preliminary study was to shed light on relationships for future scrutiny. Results should thus be interpreted with caution. Nonetheless, the current results are promising and suggest that additional study is warranted.

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DECLARATION OF INTERESTS

NLB has served as a consultant to several pharmaceutical companies that market medications to aid smoking cessation and has served as a paid expert witness in litigation against tobacco companies. SMH has a material grant from Pfizer Pharmaceuticals and serves as a consultant to Gilead.

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