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Original Investigation

Withdrawal in adolescent light smokers following 24-hour abstinence

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Abstract

Introduction: Withdrawal is one of the most important symptoms of nicotine addiction. We examined the extent to which adolescent light smokers experienced withdrawal symptoms when deprived of nicotine for a 24-hr period.

Methods: A total of 20 adolescents aged 13–17 years who smoked 1–5 cigarettes/day (CPD) refrained from smoking for a 24-hr period. Withdrawal scales were administered, and heart rate was measured at baseline, 12, and 24 hr. Neuropsychological testing was performed at baseline and 24 hr. Participants were divided into two groups: very light smokers (1–3 CPD) and light smokers (4–5 CPD).

Results: At 12 hr, very light smokers experienced a decrease in withdrawal symptoms versus light smokers, who reported an increase in symptoms (−2.9 vs. 2.8, $p = .02$). Similarly, at 24 hr, very light smokers experienced a mean decrease in withdrawal score compared with a mean increase for the light smoker group (–2.2 vs. 5.8, $p = .04$). We did not find a significant change in heart rate or any differences in participants' scores on the memory or concentration tasks.

Discussion: Based on our findings in this controlled laboratory experiment, adolescent very light smokers did not appear to have significant withdrawal symptoms following abstinence from nicotine. Adolescent light smokers who smoke 4–5 CPD experienced subjective withdrawal symptoms but did not have objective signs of nicotine withdrawal. The stage of smoking in which adolescents are smoking 5 CPD or fewer appears to be a crucial time for studying development of nicotine addiction in teens as they may be transitioning from social smoking to early addiction.

Introduction

Studies have well documented the social influences on adolescent smoking initiation and that smoking levels increase over time, as physiological addiction takes hold (Landrine, Richardson, Klonoff, & Flay, 1994; O'Neill, Glasgow, & McCaul, 1983). This transition from social to pharmacological smoking is central to the addiction process (Benowitz & Henningfield, 1994) but is not well understood in adolescents primarily because no consensus exists as to what constitutes nicotine addiction during adolescence (Benowitz, 1996; Dozois, Farrow, & Miser, 1995; O'Loughlin et al., 2003; Stanton, 1995). For adult smokers, addiction is defined by daily smoking of cigarettes, difficulty in not smoking every day, and a high likelihood of withdrawal symptoms after cessation of smoking (Centers for Disease Control and Prevention [CDC], 1989). Benowitz and Henningfield (1994) estimated, based on measurements of nicotine metabolite levels in nonaddicted smokers (smokers of 5 cigarettes/day [CPD] or fewer), that 5 mg of nicotine per day (roughly corresponding to 5 CPD) is a reasonable threshold for establishing nicotine addiction in adults.

Defining nicotine addiction in adolescents is particularly difficult because, unlike most adult smokers, adolescents are often inconsistent in their smoking (CDC, 2005). Additionally, most daily adolescent smokers report smoking fewer than 5 CPD (CDC, 2005). However, despite their low level of cigarette consumption, most adolescent smokers who are daily smokers want to quit but are unable to do so (CDC, 1994). One of the primary reasons given by adolescents for not quitting is the experience of withdrawal symptoms (Biglan & Lichtenstein, 1984).

Understanding whether or not adolescent light smokers experience withdrawal symptoms following abstinence and to what extent they experience symptoms is essential to our understanding the development of addiction as adolescents transition from social to pharmacological smoking. Findings from several studies have suggested that adolescents may become addicted to nicotine at lower levels of smoking (e.g., fewer cigarettes and/or less frequent) than do adults (DiFranza et al., 2000; O'Loughlin et al., 2003). Both DiFranza et al. and O'Loughlin et al. reported that many adolescents describe withdrawal symptoms prior to becoming daily smokers. However, these studies relied on

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retrospective, self-reported symptoms of withdrawal. In addition to the potential recall bias introduced by retrospective questionnaires, self-report is problematic because expectancies concerning withdrawal symptoms may influence perceptions of withdrawal (Killen et al., 2001). Illustrating this possibility are findings from Killen et al. (2001), in which adolescents blinded to whether they had an active or a "placebo" nicotine patch still complained of withdrawal symptoms despite wearing an active nicotine patch. This could represent a placebo-like effect whereby adolescents who expect to have withdrawal symptoms feel that they are experiencing them regardless of the physiological probability of this occurring.

The use of biological markers in studies can circumvent the use of subjective reported symptoms. One of the more commonly used markers is heart rate. Nicotine activates the sympathetic nervous system (Wonnacott, Russell, & Stolerman, 1990), and withdrawal from nicotine results in a decrease in heart rate (Hughes & Hatsukami, 2003). This finding of decreased heart rate following nicotine deprivation has been demonstrated in studies of adolescent heavy smokers (e.g., smoking at least 10 CPD; Killen et al., 2001). Another objective marker for nicotine withdrawal is impairment of cognitive function. Research demonstrates that adolescent heavy smokers experience a significant decline in cognitive function as defined by impairment of both memory and concentration following abstinence (Jacobsen et al., 2005).

To date, no study has prospectively investigated the presence of objective withdrawal signs in adolescent light smokers. The purpose of this study was to prospectively examine the extent to which adolescent light smokers, defined as smoking 1–5 CPD, experience withdrawal signs and symptoms when deprived of nicotine for a period of 24 hr in a laboratory-controlled setting. In particular, we sought to examine both objective markers of nicotine withdrawal such as decrease in heart rate and cognitive impairment and self-reported withdrawal symptoms in a cohort of adolescent light smokers. We also examined the effect of adolescents' expectations of experiencing withdrawal symptoms on actual withdrawal symptoms.

Methods

Subjects

Adolescent smokers were recruited from several San Francisco Bay area schools and pediatric clinics area using fliers and posters from 2006 to 2007. Participants had to be aged 13–17 years and smoke 1–5 cigarettes daily for at least 6 months. Adolescents who were using or had used nicotine replacement in the prior week were excluded. Current use of bupropion or use within the past 30 days also was grounds for exclusion.

Informed consent

The research design and procedures were reviewed and approved by the University of California Institutional Review Board. Informed written assent from the adolescent subject and consent from one parent were obtained prior to data collection.

Procedures

Prospective participants were screened by telephone. Those who passed the phone screen were instructed to present to the Pediatric Clinical Research Center (PCRC) at approximately 8 a.m. They were told that they could smoke their last cigarette prior to 8 a.m. but must refrain from additional smoking from that point on for the duration of the study. Participants underwent a brief physical examination and had blood collected for baseline cotinine measurement. Participants then completed a baseline questionnaire, which included questions about demographics and smoking behavior (e.g., frequency, quantity). Withdrawal scales were administered, and heart rate was measured at baseline (e.g., pre-nicotine deprivation), 12 hr after baseline, and 24 hr after baseline. Participants also were asked to complete the Minnesota Nicotine Withdrawal Scale at baseline (pre-cessation) based on how they *thought* they would feel at 24 hr (e.g., after 24 hr of nicotine deprivation). Neuropsychological testing was performed at baseline and 24 hr after baseline.

Participants were monitored closely in the PCRC during the 24 hr of abstinence. They were provided with a selection of movies, games, and books to help reduce boredom. In addition, all participants received a cash incentive of US$125 for their participation.

Measures

Subjective withdrawal. The Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 2003) was used to measure subjective withdrawal.

Heart rate. Heart rate was measured at 12-hr intervals using an automated DINAMAP machine.

Self-reported smoking. Participants were asked about the frequency and quantity of cigarette smoking. Number of cigarettes smoked each day was calculated by averaging the reported number of cigarettes smoked for each day of the last week during which they smoked.

Addiction. Nicotine addiction was measured using the modified Fagerström Tolerance Questionnaire (mFTQ; Prokhorov et al., 2000), which has been validated for use in adolescent smokers. A score of 6 or greater is the classification for highly nicotine dependent (Fagerström & Schneider, 1989). Participants also were asked to rate how addicted to nicotine they felt using a scale from 0 = "not at all addicted" to 100 = "extremely addicted."

Memory and concentration. Since no standard memory or concentration test spans 13- to 17-year-olds, we used a combination of age-validated tests. We used the numbers subtest of the Children's Memory Scale (CMS; Cohen, 1997) for subjects younger than 16 years and the digit span of the Wechsler Memory Scale, 3rd edition (WMS-III; Wechsler, 1997), for subjects aged 16–17 years. To assess concentration, attention, and reaction/response time, we used a series of tests: the sequences subtest of the CMS for subjects younger than 16 years, the mental control subtest of the WMS-III for subjects aged 16–17 years, the trail making test of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001), and the sorting and tower subtests of the D-KEFS.

Cotinine. Blood was collected from all participants at baseline for cotinine measurement. Cotinine was measured using liquid chromatography–tandem mass spectrometry (Dietrich et al., 2003).

Data analyses

Descriptive univariate analyses of all the variables were performed, and means and standard deviations were calculated. Wilcoxon analyses were conducted to determine the differences in self-reported withdrawal scores from baseline to 12 and 24 hr after baseline. Correlation coefficients were then calculated using the Pearson method to determine the associations between addiction, baseline cotinine, and changes in withdrawal score from baseline to 12 and 24 hr after baseline. Based on our sample size of 20, we had 80% power to detect a minimum correlation of $r = .60$ between markers using a two-sided alpha of .05. We would require roughly 50 participants to achieve the same power to detect a correlation of $r = .40$. The Wilcoxon test was used to compare participants' *actual* mean withdrawal score at 24 hr after baseline with their *anticipate*d 24-hr withdrawal score. Regression analyses were then performed to determine if anticipated withdrawal was predictive of actual withdrawal at 24 hr.

Wilcoxon tests were conducted to determine the differences in heart rate from baseline to 12 and 24 hr after baseline. Regression analyses were then performed to determine the effect of withdrawal symptoms on the differences in heart rate from baseline to 12 and 24 hr after baseline while controlling for hours since last cigarette at baseline. Next we performed regression analyses to determine if participants' withdrawal symptoms at 24 hr affected the change in scores on the memory or concentration tests from baseline to 24 hr while controlling for hours since last cigarette at baseline.

Finally, we performed a post-hoc analysis of withdrawal symptoms after dividing the group into very light smokers (i.e., participants who reported smoking more than 1 CPD but fewer than 4 CPD) and light smokers (i.e., participants who reported smoking 4–5 CPD). Unfortunately, the literature on adolescent light smokers is scarce, and no consistent definition exists for a light smoker among adolescents. However, our previous research (Rubinstein, Thompson, Benowitz, Shiffman, & Moscicki, 2007) showed that salivary cotinine levels among adolescents begin to plateau after 5 CPD, suggesting that fewer than 6 CPD represents light or inconsistent smoking.

Results

Baseline

Twenty adolescents aged 13–17 years ($M = 16.6$, $SD = 0.90$) were consented. The sample was racially diverse (40% White, 35% mixed race, and 25% Hispanic), and 50% were female. Participants reported mean levels of smoking at baseline of 4.1 CPD ($SD = 2.3$) with a mean duration of daily smoking of 2.5 years ($SD = 1.2$). Although all participants reported on average smoking at least one cigarette daily, three participants reported no cigarettes for 1 of the 7 days in the week before entry. However, all participants smoked at least one cigarette within 24 hr of the trial. Participants reported a mean of 7.8 hr ($SD = 5.1$) since smoking their last cigarette. Mean cotinine was 60.5 ng/ml (range = 1.7–232.3, $SD = 57.4$). Participants' mean score on the mFTQ was 3.4 (range = 0.83–5.3, $SD = 1.4$), and their self-rated level of addiction on a scale of 0–100 was 62.8 ($SD = 24.0$). Self-rated addiction was highly correlated with the mFTQ ($r = .84$, $p < .001$) but not with cotinine ($r = .25$, $p = .32$). A total of 10 participants (50%) reported at least one unsuccessful attempt to quit smoking.

Withdrawal

After controlling for the time since last cigarette smoked, we found no difference in the self-reported withdrawal score from baseline to 12 hr. Although the withdrawal score was slightly higher at 24 hr, this finding was not significant (Table 1). Neither the self-reported addiction nor the mFTQ score was correlated with the change in withdrawal score from baseline to 12 hr after baseline ($r = -.20$, $p = .55$ and $r = .14$, $p = .94$, respectively). Similarly, we found no correlation between self-reported addiction or mFTQ score and the change in withdrawal from baseline to 24 hr after baseline ($r = .28$, $p = .39$ and $r = -.43$, $p = .84$, respectively). Baseline cotinine was not correlated with change in withdrawal at either 12 or 24 hr after baseline ($r = .09$, $p = .74$ and $r = .00$, $p = .99$, respectively).

The *actual* mean withdrawal score at 24 hr after cessation was higher than participants *predicted* their 24-hr withdrawal score would be when asked to do so at baseline (e.g., 15.2 vs. 11.5, $p = .07$). Furthermore, anticipated withdrawal was not predicative of actual withdrawal at 24 hr ($F = 0.08$, $p = .93$). We found no significant changes in heart rate over the 24-hr period of abstinence (p values ranged from .33 to .90; see Table 1). Additionally, withdrawal was not predictive of heart rate changes over the 24-hr period (F values ranged from 0.04 to 1.67; p values ranged from .22 to .79).

Memory and concentration

After controlling for the time since last cigarette smoked, we failed to find any significant association between withdrawal and the change in participants' scores on any of the memory or concentration tasks from baseline to 24 hr after baseline (F values ranged from 0.16 to 3.18; p values ranged from .08 to .86).

Post-hoc analysis

When the sample was divided into two groups—light smokers (those who reported smoking 4–5 CPD; $n = 8$) and very light smokers (those who reported smoking 1–3 CPD; $n = 12$)—we

Table 1. Withdrawal signs and symptoms at baseline and at 12- and 24-hr postbaseline.

	Baseline	12 hr	*p* value[a]	24 hr	*p* value[b]
Mean heart rate (*SD*)	74.8 (11.5)	77.1 (13.4)	.43	76.9 (16.1)	.57
Mean Minnesota Nicotine Withdrawal Scale score (*SD*)	14.0 (5.5)	13.5 (7.0)	.86	15.2 (9.0)	.33

Note. [a]Wilcoxon test comparing results at 12 hr with baseline.
[b]Wilcoxon test comparing results at 24 hr with baseline.

found a significant difference in subjective withdrawal symptoms. At 12 hr after baseline, very light smokers experienced a decrease in withdrawal score; by contrast, light smokers reported an increase ($M = 15.1$ [$SD = 6.6$] to 12.1 [$SD = 8.2$] vs. $M = 12.5$ [$SD = 3.3$] to 15.6 [$SD = 4.6$]; $p = .02$). Similarly, at 24 hr after baseline, the mean withdrawal score had decreased among very light smokers; by contrast, the mean withdrawal score had increased among light smokers ($M = 15.1$ [$SD = 6.6$] to 12.7 [$SD = 10.8$] vs. $M = 12.5$ [$SD = 3.3$] to 18.9 [$SD = 3.8$]; $p = .04$). We did not find a significant change in heart rate after dividing the group into light and very light smokers (p values ranged from .49 to .64). We also failed to find a change in memory and concentration when dividing the group into light and very light smokers as described above.

Discussion

The low baseline mFTQ scores (none were 6 or greater) suggest that these adolescent light smokers were not "heavily addicted" by adult standards. However, our study shows that participants who smoked 4–5 CPD experienced an increase in subjective withdrawal symptoms compared with a relative decrease in symptoms among participants who reported smoking fewer than 4 CPD. Neither group experienced a significant change in heart rate nor a decline in memory or concentration from baseline at either the 12- or 24-hr follow-up. This finding suggests that among adolescent light smokers, the very light smokers are not yet physically dependent on nicotine. However, those who smoke 4–5 CPD may be experiencing physical dependence as evidenced by subjective symptoms of withdrawal. The lack of significant objective markers of withdrawal in some of our participants may suggest that it is not necessarily physical dependence on nicotine that drives the adolescent to smoke as much as the social and behavioral influences associated with smoking in adolescence (Adelman, 2004). In addition, adolescents may experience positive reinforcement from nicotine without experiencing physical dependence. On the other hand, changes in heart rate and memory or concentration during withdrawal may occur at a later stage of addiction, in which case we are simply capturing adolescent smokers prior to the onset of these physiological changes. It is also possible that we did not use a long enough duration of abstinence to capture the specific physiological outcomes we were measuring (e.g., changes in heart rate). However, Killen et al. (2001) found a significant decrease in heart rate along with an increase in withdrawal symptoms in only 8 hr of abstinence. Similarly, Jacobsen et al. (2005) found impairments in memory after only 24 hr of abstinence among adolescent smokers. Participants in the Killen and Jacobsen studies were, on average, heavier smokers that the participants in our study. Finally, given the moderately strong associations found, the lack of significant differences between self-reported addiction and changes in withdrawal symptoms could have been due to power issues resulting from the small sample size.

Although we studied a relatively small number of subjects, this is the first study to prospectively examine adolescent light smokers for physiological evidence of addiction in a controlled experiment. Based on our findings in this controlled laboratory experiment, adolescent very light smokers did not appear to have significant withdrawal symptoms following abstinence from nicotine. Adolescent light smokers who smoked 4–5 CPD experienced subjective withdrawal symptoms but did not have objective signs of nicotine withdrawal. The period during which adolescents are smoking 5 CPD or fewer appears to be a crucial time for studying development of nicotine addiction in teens as they may be transitioning from social smoking to physical dependence.

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Declaration of Interests

Dr. Benowitz has been a paid expert in litigation against tobacco companies, including providing testimony of tobacco addiction in adolescents. None of the other authors have competing interests to report.

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