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EVALUATING THE EFFECTS OF VARENICLINE ON CRAVING, WITHDRAWAL AND AFFECT IN A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL OF VARENICLINE FOR SMOKELESS TOBACCO DEPENDENCE IN INDIA

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Abstract

This study examined changes in tobacco craving, withdrawal and affect as correlates of efficacy in a phase 2 clinical trial of varenicline for smokeless tobacco dependence in India. Smokeless tobacco users (N = 237) at the All India Institute of Medical Sciences were randomized to placebo or varenicline. Abstinence was defined as cotinine-verified 7-day point prevalence cessation at end of treatment (EOT). General Linear Model repeated measures assessed the effects of treatment condition, time, abstinence state and interaction effects on changes in craving, withdrawal, positive (PA) and negative affect (NA) from baseline to EOT. All participants showed a significant reduction in withdrawal ($p < .001$), total craving ($p < .001$), positive reinforcement (PR) craving ($p < .001$), and NA ($p = .02$), and an increase in PA ($p = .04$) from baseline to EOT. However, there were no differences between placebo and varenicline participants in measures of withdrawal, craving, or affect from baseline to week 3 or at EOT. Significant interactions between time and abstinence state were found for total craving ($p = .008$), PR craving ($p < .001$), and withdrawal ($p = .001$), indicating reductions in these processes among those abstinent vs. those still chewing smokeless tobacco. Additional research is needed concerning the effects of varenicline on craving, withdrawal, and affect among smokeless tobacco users.

Keywords

Varenicline; Smokeless tobacco; Treatment; Intervention

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The Global Adult Tobacco Survey conducted in India from 2009–2010 revealed that tobacco use prevalence is staggeringly high with an estimated 275 million users. More than one-third (35%) of adults in India use tobacco in some form and among them 21% of adults use only smokeless tobacco (Global Adult Tobacco Survey, 2009). Thus, there is a clear predominance of smokeless tobacco use in India in relation to other forms of tobacco use and the nation has one of the highest rates of oral cancer in the world, partly attributed to high prevalence of tobacco chewing (Vora, Yeoman, & Hayter 1997; Franceschi, Bidoli, Herrero, & Munoz N, 2000; Moore, Johnson, Pierce, & Wilson, 2000; Dikshit & Kanhere, 2000) with a strong dose-response effect in terms of duration of use and amount consumed (Sapkota et al., 2007; Znaor et al. 2003). Studies in India show that use of smokeless tobacco is responsible for approximately 10,000 deaths each year from oral cancer (Critchley and Unal, 2003). Thus, intervention trials for smokeless tobacco users in India should be a priority.

Varenicline is a selective nicotinic receptor partial agonist with specificity for the $\alpha 4\beta 2$ nicotine acetylcholine receptor (nAChR) that is efficacious for increasing long-term tobacco abstinence rates in cigarette smokers (Gonzales et al., 2006; Jorenby et al., 2006; Tonstad et al., 2006). By partially activating $\alpha 4\beta 2$ nAChRs, varenicline produces a moderate amount of dopamine release, replacing some of nicotine's effects (Foulds, Steinberg, Williams, & Ziedonis, 2006). Indeed, varenicline has been shown to increase tobacco abstinence rates among Scandinavian snus users (Fagerström, Gilljam, Metcalfe, Tonstad, & Messig, 2010). However, little is known about the mechanisms by which it facilitates abstinence in smokeless tobacco users. Nicotine withdrawal leads to cravings and a continued desire to smoke (West, Ussher, Evans, & Rashid, 2006; Hughes, 2007) and a strong relation between severity of withdrawal symptoms and relapse has been shown in some studies (McCarthy, Piasecki, Fiore, & Baker, 2006; West, 2005). Varenicline's agonist function is thought to minimize nicotine craving and withdrawal, while its antagonist properties are expected to attenuate the reinforcing effects of nicotine, thereby reducing pleasure from a "slip" cigarette and the likelihood of relapse (Foulds et al. 2006; Patterson et al., 2009). Thus, the role of craving and withdrawal may be important in the efficacy of varenicline.

This study used data from the first double blind placebo controlled trial of varenicline for smokeless tobacco dependence in India which showed that when controlling for covariates including treatment adherence, varenicline increased cessation rates from smokeless tobacco (Jain et al; 2014). The present study examined changes in tobacco craving, withdrawal, and negative and positive affect as potential correlates of varenicline efficacy in smokeless tobacco use cessation. This is of interest as there are few published studies of the mechanisms that play a role in smokeless tobacco cessation treatment effects.

METHODS

Participants

The study was conducted at the National Drug Dependence Treatment Centre (NDDTC), All India Institute of Medical Sciences (AIIMS), New Delhi, India. Participants (N = 237) were recruited from the Centre for Dental Education and Research (CDER) at AIIMS. Participant

inclusion and exclusion criteria and study procedures can be found in the published clinical trial results (Jain et al., 2014). The present study examined the effects of treatment condition (placebo vs. varenicline), time, and abstinence state (abstinence vs. relapsed), and interaction effects on changes in craving, withdrawal, and negative and positive affect from baseline to EOT for N = 173 completers.

Procedures

The study procedures were approved by the University of Pennsylvania Institutional Review Board, the AIIMS Ethics Committee, Drug Controller General India, and the Indian Council for Medical Research. Treatment was initiated at baseline (week 0). Medication (varenicline or matching placebo) was taken for 12 weeks: 0.5mg each day for days 1–3, 2 × 0.5mg each day for days 4–7, and 2 × 1.0mg each day for 11 weeks. Counseling was provided at weeks 0, 1, 3, 5, 7, and 9 in-person. A target quit-date was established for week 1. Assessments were conducted at baseline (week 0) and at weeks 1, 3, 5, 7, and 9 and 12 (EOT). Participants reporting abstinence at EOT (week 12) were asked to attend AIIMS to provide a urine sample for cotinine assessment.

Measures

Covariates—At baseline, demographic parameters and smokeless tobacco use (e.g., rate, years of use) data were collected. The smokeless tobacco version of the Fagerström Test for Nicotine Dependence ([FTND-ST]; (Ebbert, Patten, & Schroeder, 2006) was completed.

Correlates—Assessments for the following correlates were conducted at baseline (week 0) and at weeks 1, 3, 5, 7, and 9 and 12 (EOT).

Affect—The Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988), a 20-item Likert-format self-report measure, was used to assess positive (PA; 10 items, e.g., enthusiastic) and negative (NA; 10 items, e.g., distressed) affect. PA and NA was assessed using a 1-week reference. Measuring affect using this approach has been validated across several countries, including Southeast Asia (Oishi, Diener, Napa Scollon, & Biswas-Diener, 2004).

Withdrawal—The Minnesota Nicotine Withdrawal Scale was used to measure withdrawal symptoms related to smokeless tobacco cessation (Hughes & Hatsukami 1986). Withdrawal was assessed using a 1-week time frame. This measure has been validated with Southeast Asian populations (Kim Glick, Kim, & Seo, 2007).

Craving—The questionnaire on smoking urges, modified for smokeless tobacco, was used (Cox, Tiffany, & Christen, 2001; Killen & Fortmann 1997). The QSU contains 2 subscales (anticipation of reward, relief from negative affect). Craving was assessed using a 1-week time frame. This scale was chosen since it has received cross-cultural validation (Araujo, Oliveira, & Mansur, 2006; Guillin et al., 2000) and was used in varenicline clinical trials (Jorenby et al., 2006).

Tobacco Cessation—Self-reported 7-day point prevalence abstinence was assessed at EOT and participants who indicated abstinence were asked to attend clinic for biochemical confirmation of smokeless tobacco cessation with urinary cotinine (cut-off for abstinence 50 ng/ml; Benowitz et al., 2002) and absence of tobacco smoking using breath CO (>10ppm).

Statistical Analysis—General Linear Model repeated measures assessed the main effects of time, treatment condition (placebo vs. varenicline), and abstinence state (abstinence vs. relapsed), and interaction effects on changes in craving, withdrawal, and negative and positive affect from baseline to EOT (with N = 173 completers)

RESULTS

Sample Characteristics

Most participants were hindu males, married and chronic users of smokeless tobacco with a high FTND-ST score (Table 1). There were no significant differences in these characteristics across the treatment arms (p 's >0.05; Table 1). 173 participants completed the study, and 165 provided a urine sample for biochemical assessment at EOT. There were no significant differences in these tobacco use and socio-demographic characteristics between participants who completed the study and those who did not (all p 's > .05). The main results from the trial concerning treatment arm effects on smokeless tobacco cessation showed that, at week 12, more participants treated with varenicline self-reported abstinence from smokeless tobacco use, compared to participants treated with placebo (42.9% vs. 30.5%; unadjusted OR = 1.7, 95% CI: 1.001–2.92, p = .05; adjusted OR = 2.6, 95% CI: 1.2–4.2, p = 0.009). Quit rates were higher for varenicline vs. placebo among those who adhered to treatment, but the comparison using biochemically-confirmed abstinence was not statistically different (Jain R et al, 2014).

All participants who completed this study(N=173) had a significant reduction in withdrawal (p <.001), total craving (p <.001), positive reinforcement craving (p <.001), and negative affect (p =.02), and an increase in positive affect (p =.04) from baseline to EOT (Table 2). However, there were no significant interaction effects in these processes for treatment arm (varenicline vs placebo) (Table 4). Since treatment effects on these variables may have been confined to the first few weeks following treatment initiation, we repeated these analyses using measures collected at week 3 of the trial. As reported above, there were no differences between placebo and varenicline participants in terms of changes in measures of withdrawal, craving, or affect from baseline to week 3.

Significant interaction effects were also seen between time and abstinence state for total craving (p =.008), positive reinforcement craving (p <.001), and withdrawal (p =.001) (Table 3). Reduction in these variables was significantly greater among those confirmed abstinent at EOT vs. those still chewing smokeless tobacco.

DISCUSSION

Nicotine addiction is a chronic condition (Fiore et al,2000). Rates of relapse to tobacco use remain high despite provision of treatment and escalation of withdrawal symptoms, craving, and smoking urges during a quit attempt may contribute to relapse (Allen, Bade, Hatsukami, & Center, 2010). In terms of the efficacy of varenicline for treating smokeless tobacco dependence, our original study showed higher quit rates when assessed using self-report and also among participants who showed higher levels of adherence (Jain et al., 2014). Here, we explored potential correlates of these effects.

This study showed no differences between placebo and varenicline participants in terms of changes in measures of withdrawal, craving, or affect from baseline to early stage of treatment(week 3) or end of treatment. However, participants who were able to achieve cessation from smokeless tobacco dependence were significantly more likely to show a decrease in nicotine craving (total and positive reinforcement), withdrawal, and negative affect, and an increase in positive affect, vs. participants who relapsed to tobacco use. However, these beneficial effects of the treatment program were evident for those treated with both placebo or varenicline suggesting that these changes were not attributable to treatment arm allocation. Significant interaction effects between time and abstinence state were found for total craving, positive reinforcement craving, and withdrawal, indicating significant reductions in these processes among those abstinent at EOT vs. those still chewing smokeless tobacco in this study. These findings are different from some of the previous smoking cessation studies with varenicline which showed that varenicline decreases tobacco craving and significantly lowers urge to smoke, negative affect, and restlessness on measures of withdrawal, vs. placebo (Gonzales et al., 2006; Jorenby et al., 2006). A pilot study of the efficacy of varenicline for the treatment of smokeless tobacco in the United States reported that varenicline was associated with significantly less craving compared with placebo (Ebbert, Croghan, Severson, Schroeder, & Hays, 2011). However, varenicline's impact on other withdrawal symptoms (i.e., restlessness, negative affect) was not discernible in smokeless tobacco users in this study.

It is possible that behavioral counseling for smokeless tobacco dependence, which was received by all participants in the study, may have affected the findings. The behavioural intervention was designed to enhance awareness of the harmful effects of smokeless tobacco, assist the person in developing skills to quit (including how to manage craving and withdrawal), avoid relapse, and instruct the participant on medication use. In previous studies, behavioral interventions for smokeless tobacco users have been shown to be effective (Ebbert et al., 2007; Severson, 2003) and a large control group effect, as in this study, has been attributed to the frequency and intensity of the behavioral counselling delivered to both study and control groups. (Boyle, 1992; Dale et al, 2007; Hatsukami, Jensen, Allen, Grillo, & Bliss, 1996; Hatsukami et al., 2000). Indeed, behavioural counseling has been previously demonstrated to be useful in the treatment of smokeless tobacco dependence in India also: a 5-five year evaluation of tobacco cessation clinics in India set up by Government of India in collaboration with the World Health Organization (WHO) showed that among 23,320 registered cases, behavioural forms of intervention,

which included health education, simple tips for quitting and counseling to improve motivation and prevent relapse, yielded a 14% quit rate after 6-weeks (Murthy, 2009).

Another possible reason why varenicline may have failed to show significant decrease in craving and withdrawal is that, relative to other clinical trials of varenicline for smokeless tobacco dependence, the present study showed that adherence to medication use is low in this population and there were high rate of false self-reported abstinence (36%). However there were no significant differences across treatment arms (varenicline vs placebo) in the rate of medication adherence or false self-reported abstinence.

Thus, the present study contrasts with previous results on cigarette smokers that have shown that varenicline reduced craving and withdrawal symptoms consistent with the proposed agonist/antagonist effects of varenicline. Future studies are needed to better understand the potential correlates of action underlying varenicline's potential therapeutic benefits for smokeless tobacco cessation. The present study is limited by low rates of medication adherence among participants and the low statistical power to detect small, yet clinically meaningful, differences. Given these weaknesses, and the inclusion/exclusion criteria that is typical of a clinical trial such as this, the generalizability of the present findings may be limited and additional studies may be needed to clarify the effects of varenicline on craving, withdrawal, and affect among smokeless tobacco users utilizing varenicline.

Overall craving, positive reinforcement craving, withdrawal effects are appropriate targets for smokeless tobacco intervention but do not appear to be unique factors underlying varenicline's effects on smokeless tobacco dependence. The current study illustrates the need for further studies to clarify mechanisms through which varenicline may influence the likelihood of cessation from smokeless tobacco use.

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Table 1

Participant Characteristics by Treatment Arm Assignment

<u>Characteristic</u>	Placebo (n = 118)	Varenicline (n = 119)	Overall (n = 237)
Sex (% Male)	96.6	97.5	<u>97</u>
Age (Years; Mean, SD)	34.7 (9.9)	33.8 (8.4)	34.2 (9.2)
Marital Status (% Married)	78	77.3	77.6
Education (% Primary School)	29.7	34.5	<u>32.1</u>
Religion (% Hindu)	83.1	79.8	81.4
Income (% < 1 lakh or < \$1,782 US dollars, annually)	77.1	75.6	76.4
FTND (Mean, SD)	7.1 (1.7)	7.0 (2.0)	7.0 (1.9)
Years of Smokeless Tobacco Use (Mean, SD)	11.4 (7.6)	10.9 (7.6)	11.2 (7.6)

Table 2

Change in Craving, Withdrawal, and Affect over Time

Mean Scores of Craving, Withdrawal and Affect at Baseline and EOT			
Measures	Baseline (n=237) Mean (SD)	EOT (n=173) Mean (SD)	F (DF)
Craving Total	122.6 (3.3)	57.6 (2.3)	295.9 (1,171)
Craving PR	64.7 (1.5)	30.0 (1.3)	363.4 (1, 171)
Craving NR	32.7 (1.4)	15.9 (0.67)	129.2 (1, 171)
Withdrawal	2.39 (0.14)	0.47 (0.05)	37.4 (1, 171)
Negative Affect	10.4 (0.12)	10.1 (0.03)	5.4 (1, 171)
Positive Affect	29.5 (0.24)	28.9 (0.22)	4.1 (1, 171)

Table 3

Change in Craving, Withdrawal, and Affect over Time by Abstinence State

Mean Scores of Craving, Withdrawal and Affect at Baseline and EOT (in abstinent vs non-abstinent smokeless tobacco users)						
Measures	Abstinent at EOT (N=53)	Non-Abstinent at EOT (N = 120)	F (DF)	p		
	Baseline M (SD)	EOT M (SD)	Baseline M (SD)	EOT M (SD)		
Craving Total	113.1 (5.4)	38.0 (3.8)	132.0 (3.6)	77.1 (2.5)	7.1 (1, 171)	0.008
Craving PR	61.5 (2.4)	18.8 (2.1)	67.8 (1.6)	41.3 (1.4)	20.0 (1, 171)	< .001
Craving NR	28.1 (2.3)	11.7 (1.1)	37.3 (1.5)	20.2 (0.75)	0.1 (1, 171)	0.8
Withdrawal	2.58 (0.24)	0.13 (0.08)	2.20 (0.16)	0.80 (0.05)	12.4 (1, 171)	0.001
Negative Affect	10.4 (0.19)	10.1 (0.06)	10.3 (0.13)	10.1 (0.04)	0.4 (1, 171)	0.55
Positive Affect	29.6 (0.40)	29.4 (0.36)	29.5 (0.26)	28.3 (0.24)	2.2 (1, 171)	0.14