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Complementing the Standard Multicomponent Treatment for Smokers With Denicotinized Cigarettes: A Randomized Trial

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Abstract

Introduction: Standard treatments (STs) for smoking cessation typically combine pharmacotherapy and behavioral support but do not address the sensory and behavioral aspects of smoking which may play a role in maintaining smoking behavior. Replacing such sensations temporarily after cessation may enhance treatment efficacy. We hypothesized that denicotinized cigarettes (DNCs), which have a very low nicotine content but provide these sensory and behavioral stimuli, could help alleviate urges to smoke and tobacco withdrawal symptoms and in turn enhance the efficacy of ST.

Methods: Two hundred smokers seeking treatment received nine weekly behavioral support sessions and pharmacotherapy (100 used varenicline, 100 used nicotine replacement therapy). They were randomized on the target quit day to receive 280 DNCs (used *ad libitum* over 2 weeks in addition to ST) or ST alone.

Results: Urge-to-smoke frequency (2.61 vs. 2.96, $P = .03$) but not strength (2.85 vs. 3.10, $P = .20$) in the first week of abstinence was significantly lower in DNC users versus ST alone. There were no differences in composite withdrawal scores between groups. Abstinence was significantly higher among DNC users versus ST alone at 1 (OR = 2.07; 95% CI: 1.63% to 3.70%) and 4 weeks (OR = 1.83; 95% CI: 1.05% to 3.21%), but not at 12 weeks (OR = 1.42; 95% CI: 0.79% to 2.55%). DNC use was a significant predictor of abstinence at 1 and 4 weeks (OR = 2.63; 95% CI: 1.40% to 4.93% and OR = 2.38; 95% CI: 1.26% to 4.46%), but not at 12 weeks.

Conclusions: Adding DNCs to ST has the potential to assist smokers early in their quit attempt, but research is needed to determine how best to utilize DNCs in treatment.

Introduction

Current smoking cessation treatments typically combine pharmacotherapy (nicotine replacement therapy [NRT], varenicline, or bupropion) and multisession behavioral support. This is recommended in various smoking cessation guidelines.[1] Although this treatment package substantially increases the chance of long-term success, there remains considerable scope for improvement. Only about half of the patients starting treatment achieve abstinence at 4 weeks, and in general fewer than 20% achieve long-term success.[2]

While there is no doubt that people become dependent on tobacco and find it difficult to stop smoking, primarily because of nicotine and its actions on the mesolimbic dopamine system,[3] there are other factors that contribute to tobacco dependence.[4] Sensory and behavioral cues (eg, the sensory effects of smoke in the mouth and throat and the action

of puffing on a cigarette) appear to provide additional reinforcement of smoking behavior.[5,6] Other pharmacologically active ingredients in tobacco smoke, such as monoamine oxidase inhibitors and acetaldehyde, may also accentuate the rewarding effects of nicotine.[7–9]

Denicotinized cigarettes (DNCs) have a very low nicotine content (machine yield of 0.08 vs. 0.8 mg in most conventional cigarettes[10]) which has negligible or no central effects.[4] They provide many of the sensory-motor stimuli associated with smoking and can thus replace the behavioral and sensory aspects of smoking, which many smokers say they miss when they stop, without supplying nicotine. By divorcing the pairing of behavioral and sensory components of smoking with rapid nicotine delivery which makes them rewarding, it may be possible to disrupt the reinforcing properties of smoking and assist in smoking cessation. Such a process can be further enhanced if withdrawal symptoms are managed with appropriate medications.

There is evidence to support such assertions. DNCs have been shown to be satisfying over the initial few days of abstinence from smoking.[4,11,12] They were also shown to reduce tobacco withdrawal symptoms, including urges to smoke and low mood.[4,13–15] Three small studies have investigated the effect of DNCs combined with NRT prior to the quit day, on short-term outcome.[16–18] One study reported significantly higher abstinence at 4 weeks in those using DNCs with the nicotine patch versus controls (32.8% vs. 21.9%, $P < .05$),[18] though the other trials failed to find an effect at either 4 weeks[16] or 3 and 6 months.[17] In a trial that randomized smokers to receive either standard quitline treatment plus a 6-week supply of DNCs, or standard treatment (ST) alone, use of DNCs was associated with significantly higher 6-month continuous abstinence rates (23% vs. 15%, RR = 1.50, $P < .001$).[19]

Despite these encouraging results, the progress in exploring the role of DNCs in smoking cessation has been slow. This may be due to the reluctance to utilize a tobacco product that remains harmful to health. However, using DNCs for a short-time period, if this would assist smoking cessation in lifetime habitual smokers, should pose minimal health risk.

We wanted to explore the efficacy and the mechanism of action of DNCs when combined with a standard NHS Stop Smoking Service (NHS SSS) program. Our hypothesis was that complementing current NHS SSS treatments with DNCs, to address the nonnicotine factors associated with smoking, and to help extinguish smoking behavior, would result in lower urges to smoke than ST alone. We were also interested to see if DNCs could improve short-term cessation outcomes and if the effects of DNCs were different in patients using NRT versus those using varenicline. Our primary objective was to compare urges to smoke in the first week of abstinence between participants who receive DNCs alongside standard NHS SSS treatment (DNC+ST) with those who receive standard NHS SSS treatment (ST) alone. Secondary objectives were to (1) compare severity of tobacco withdrawal symptoms between the DNC+ST and ST groups; (2) compare continuous validated abstinence at weeks 1, 4, 6, and 12 post-target quit day (TQD) between the DNC+ST and ST groups; (3) compare standard NHS SSS smoking cessation outcomes (continuous validated abstinence from weeks 2 to 4 post-TQD) between the DNC+ST and ST groups; and (4) examine baseline predictors of abstinence.

Methods

Study Design

Participants attended nine weekly sessions (two prior to the TQD, one on the TQD, and six post-TQD) and were followed up at 3 months post-TQD. They were randomized (1:1 within pharmacotherapy group) on their TQD to either the intervention group, where they received standard NHS SSS treatment and a 2-week supply of DNCs (DNC+ST), or the control group (ST). Participants were recruited until 100 patients were randomized who opted for NRT and 100 who selected varenicline. Thus, the study employed a 2 (pharmacotherapy: NRT vs. varenicline) × 2 (DNC: yes vs. no) between subjects design.

Participants

Two hundred smokers seeking treatment were recruited from a stop-smoking clinic in London, United Kingdom, and through advertisements in local newspapers from July 2011 to March 2012. Participants were able to choose NRT or varenicline for use as their stop-smoking medication. Participants were eligible if they were over 18 years of age, were not pregnant or breastfeeding, and had no acute psychiatric illness.

Procedures

Participants attended treatment sessions at baseline (2 weeks pre-TQD), 1 week before the TQD, on the TQD, and then weekly for 4 weeks (weeks 1–4 post-TQD), as per normal NHS SSS treatment. Participants attended two additional study sessions at weeks 5 and 6 post-TQD, and a follow-up visit at 12 weeks post-TQD. Study enrolment, treatment sessions, and randomization were conducted by experienced research health psychologists. Written informed consent was collected at the baseline session. Participants were asked to smoke *ad libitum* until their TQD. As per NHS SSS practice, at the baseline session, participants were offered a range of NRTs (patch, gum, inhalator, lozenge, mini lozenge, microtabs, nasal spray, and mouth spray, including combination NRT), or varenicline, to use for up to 12 weeks on prescription. Medication choice was patient-driven. Those choosing to use varenicline were instructed to start taking their medication 1 week prior to the TQD, and those choosing NRT on the TQD, as per standard practice. Prescriptions for NRT and varenicline were provided fortnightly. Participants were randomized on the TQD and were sequentially allocated (via a concealed envelope) to receive either DNC+ST or ST, using a computer-generated randomization list generated by a researcher independent to the study. Within each medication group (NRT or varenicline), 50 people were randomly allocated to either DNC+ST or ST. Participants and study staff were not blinded to treatment allocation. Those randomized to DNC+ST were given 140 DNCs and instructed to use these *ad libitum*. Six participants smoked 40 cigarettes per day at baseline and as such were provided with 280 DNCs. If required, participants were able to request more DNCs the following week. DNCs were used for 2 weeks post-TQD and any remaining DNCs were returned.

All participants were contacted at 12 weeks post-TQD, and those who self-reported abstinence were invited to attend the clinic for verification (end-expired carbon monoxide [CO] reading of <10 ppm). Participants received £10 per visit for transport costs associated with the three visits additional to standard NHS SSS treatment (weeks 5, 6, and 12 post-TQD).

Ethical approval for the study was obtained from the English NHS National Research Ethics Service Committee (approval reference: 11/H0711/2).

Denicotinized Cigarettes

We purchased XODUS brand DNCs manufactured by 22nd Century Group Inc (Clarence, NY). These DNCs contain about 1 mg nicotine per gram of filler, which is about 95% lower than most US cigarette

brands. The machine yields of nicotine under ISO smoking conditions are approximately 0.088 mg nicotine/cigarette (M. Moynihan, 22nd Century Group Inc, personal communication, August 31, 2010). At this level, systemic absorption of nicotine and the central effects are negligible.[20]

Measures

The primary (urges to smoke in the first week of abstinence) and secondary outcomes (severity of withdrawal symptoms in the first week of abstinence) were measured with the Mood and Physical Symptoms Scale.[21] This was administered weekly to capture the frequency (6-point scale from 1 [not at all] to 6 [all of the time]) and strength (1 [no urges] to 6 [extremely strong]) of urges to smoke over the previous week; and the occurrence of withdrawal symptoms (depression, irritability, restlessness, poor concentration, hunger, sleep disturbance) on a 5-point scale (from 1 [not at all] to 5 [extremely]).

Secondary outcomes included comparison of continuous abstinence at weeks 1, 4, 6, and 12 post-TQD (not a single puff, and CO validated at weeks 4–12) and comparison of standard NHS SSS smoking cessation outcomes (not a single puff from weeks 2–4 post-TQD, CO validated) between DNC+ST and ST groups; changes in composite withdrawal from baseline to 4 weeks post-TQD; medication adherence; DNC user ratings; and baseline predictors of abstinence. CO readings were collected weekly using a Bedfont CO monitor to verify abstinence. Excluding the first 2 weeks post-TQD when participants were using DNCs, a reading of less than 10 ppm was used to verify self-reported abstinence. Smoking status ("Have you smoked any normal cigarettes since your last visit?") was recorded at each visit: responses were "no, not a single puff"; "yes, just a few puffs"; "yes, between 1 and 5 cigarettes"; or "yes, more than 5 cigarettes." Participants in the DNC+ST group were also asked: "how many Xodus cigarettes per day have you smoked over the past week?," to rate the usefulness of DNCs in helping them to stop smoking, how likely they would be to buy them and how likely they would be to recommend them to others (rated from 1 = not at all to 4 = very much so; adapted from previous work[22]) and to report any adverse events. For assessment of baseline predictors of abstinence, a baseline questionnaire was completed prior to quitting, which included demographic details, health status, smoking history, and the Fagerström Test for Nicotine Dependence (FTND).[23]

Sample Size

The primary outcome concerned urges to smoke in the first week of abstinence, measured using the Mood and Physical Symptoms Scale. The Mood and Physical Symptoms Scale is a rating scale sensitive to tobacco withdrawal and to both pharmacological[24] and behavioral[25] treatment effects. Effective treatments typically generate a difference in ratings over the first week of abstinence of at least 0.7 compared to control procedures, for example, 1.8 (SD = 1) compared to 2.5 (SD = 1). As, in this case, the advantage of the combination over the first week of abstinence may be subtle and even a difference of 0.5 would be worth detecting, 69 participants would be needed in each treatment group ($P < .05$, two-tailed test, power = 0.90). To account for participant attrition between the TQD and 1 week post-TQD, estimated at 30%, a sample of 200 participants was required. We included an equal number of people using NRT and varenicline to examine differences between DNC+ST and ST by medication type.

Data Analysis

Differences between the study arms were assessed by analysis of variance for continuous variables and chi-square for categorical variables. We also tested pharmacotherapy (varenicline vs. NRT) × group (DNC+ST vs. ST) interactions. The relationship between prequit variables and postquit endpoints was assessed using regression modeling: univariate analyses were used to identify baseline variables which differed significantly between abstainers and nonabstainers at 1, 4, and 12 weeks post-TQD. These variables were then entered into a logistic regression model. Differences in urges to smoke at 1 week post-TQD were compared using one-way analysis of variance. Changes in withdrawal symptom ratings from TQD to 1 week post-TQD, and from baseline to 4 weeks post-TQD, were assessed using repeated measures analysis of variance. Analyses of withdrawal symptoms and urges to smoke were conducted only on those participants who had abstained from smoking. All tests were two-tailed. Mean DNC use in the first and second week is reported, along with the frequency of participants rating DNCs as useful, and likelihood of buying and recommending DNCs to others.

The primary cessation outcome was defined as the standard NHS SSS outcomes, that is, continuous CO-validated abstinence from weeks 2 to 4 post-TQD.[26] This is the standard outcome used to monitor short-term outcomes of the NHS SSS in England. Continuous abstinence from regular cigarettes (not a single puff) was used to measure smoking cessation outcomes at weeks 1, 4, 6, and 12 post-TQD. Those who were lost to follow-up at any stage were considered to be smoking.

We also report on secondary cessation outcomes pertaining to the difference between urges to smoke and 4-week continuous abstinence rates from the time when participants were not allowed to smoke either regular cigarettes or DNCs. We therefore compared urges to smoke at 1 week post-TQD for the ST group versus 3 weeks post-TQD for the DNC+ST group; and abstinence rates at 4 weeks post-TQD for the ST group versus 6 weeks post-TQD for the DNC+ST group.

Results

Sample Characteristics

A total of 200 volunteers were enrolled and randomized. Figure 1 shows the flow of participants through the trial. Table 1 shows the baseline characteristics of the participants and their choice of stop-smoking medication. There were no significant differences between the two study arms, except that significantly more participants in the DNC+ST group chose to use nicotine mouth spray. There were also no significant differences in baseline characteristics between participants choosing varenicline versus NRT (see Table 2).

Effect of DNCs on Urges to Smoke and Withdrawal Symptoms

Mean ratings of urges to smoke in the first week of abstinence are shown in Table 3. In the total sample, DNC+ST and ST differed significantly in frequency of urges to smoke (2.61 in DNC+ST vs. 2.96 in ST, $P = .03$) but not their strength (2.85 DNC+ST vs. 3.10 ST, $P = .20$). Within the NRT and varenicline groups, the observed differences in frequency of urges to smoke were similar, but not statistically significant.

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brands. The machine yields of nicotine under ISO smoking conditions are approximately 0.088 mg nicotine/cigarette (M. Moynihan, 22nd Century Group Inc, personal communication, August 31, 2010). At this level, systemic absorption of nicotine and the central effects are negligible.[20]

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Differences between the study arms were assessed by analysis of variance for continuous variables and chi-square for categorical variables. We also tested pharmacotherapy (varenicline vs. NRT) × group (DNC+ST vs. ST) interactions. The relationship between prequit variables and postquit endpoints was assessed using regression modeling: univariate analyses were used to identify baseline variables which differed significantly between abstainers and nonabstainers at 1, 4, and 12 weeks post-TQD. These variables were then entered into a logistic regression model. Differences in urges to smoke at 1 week post-TQD were compared using one-way analysis of variance. Changes in withdrawal symptom ratings from TQD to 1 week post-TQD, and from baseline to 4 weeks post-TQD, were assessed using repeated measures analysis of variance. Analyses of withdrawal symptoms and urges to smoke were conducted only on those participants who had abstained from smoking. All tests were two-tailed. Mean DNC use in the first and second week is reported, along with the frequency of participants rating DNCs as useful, and likelihood of buying and recommending DNCs to others.

The primary cessation outcome was defined as the standard NHS SSS outcomes, that is, continuous CO-validated abstinence from weeks 2 to 4 post-TQD.[25] This is the standard outcome used to monitor short-term outcomes of the NHS SSS in England. Continuous abstinence from regular cigarettes (not a single puff) was used to measure smoking cessation outcomes at weeks 1, 4, 6, and 12 post-TQD. Those who were lost to follow-up at any stage were considered to be smoking.

We also report on secondary cessation outcomes pertaining to the difference between urges to smoke and 4-week continuous abstinence rates from the time when participants were not allowed to smoke either regular cigarettes or DNCs. We therefore compared urges to smoke at 1 week post-TQD for the ST group versus 3 weeks post-TQD for the DNC+ST group; and abstinence rates at 4 weeks post-TQD for the ST group versus 6 weeks post-TQD for the DNC+ST group.

Results

Sample Characteristics

A total of 200 volunteers were enrolled and randomized. Figure 1 shows the flow of participants through the trial. Table 1 shows the baseline characteristics of the participants and their choice of stop-smoking medication. There were no significant differences between the two study arms, except that significantly more participants in the DNC+ST group chose to use nicotine mouth spray. There were also no significant differences in baseline characteristics between participants choosing varenicline versus NRT (see Table 2).

Effect of DNCs on Urges to Smoke and Withdrawal Symptoms

Mean ratings of urges to smoke in the first week of abstinence are shown in Table 3. In the total sample, DNC+ST and ST differed significantly in frequency of urges to smoke (2.61 in DNC+ST vs. 2.96 in ST, $P = .03$) but not their strength (2.85 DNC+ST vs. 3.10 ST, $P = .20$). Within the NRT and varenicline groups, the observed differences in frequency of urges to smoke were similar, but not statistically significant.

There was no difference in the first week of abstinence in change from baseline of composite withdrawal symptom ratings

group were significantly more likely to be abstinent from conventional cigarettes than patch or DNC alone.

DNCs had no significant effect on tobacco withdrawal symptoms other than craving. All participants were taking standard smoking cessation treatments, so any additional effect of DNC use may have been masked.

We purposely recruited an equal number of participants on varenicline and NRT, and randomized to DNC+ST or ST within these medication groups, to explore if there was any differential effect. We hypothesized that varenicline users may be more likely to benefit from the behavioral replacement provided by DNCs, as oral NRT products may already provide a degree of behavioral replacement in that smokers are instructed to use these products as regularly as they would smoke cigarettes. The results, however, did not support this hypothesis.

The main limitation of the study was the relatively small sample size. To detect smaller effects expected at longer follow-ups, larger studies are needed. We limited use of DNCs to the first 2 weeks of quitting as it is during this time that smokers trying to quit struggle most with urges to smoke and withdrawal symptoms. It is possible that participants who did not return all their DNCs at the end of the 2 weeks continued using the DNCs. Future studies may wish to consider providing DNCs for a longer period of time, and providing a stronger encouragement for their ongoing use, especially in crises and lapse situations. We also did not collect data on participants who smoked mentholated cigarettes, and all participants in the DNC+ST group received nonmentholated DNCs regardless of their preference. There are also limits to the generalizability of our results. Participants were highly dependent smokers seeking treatment, and treatment consisted of intensive behavioral support. However, our findings are consistent with those of Walker et al.,[19] which examined the use of DNCs in combination with telephone support and NRT.

It is not clear how best to utilize DNCs in treatment. The most pragmatic approach may be to offer an ongoing supply of DNCs to those who want to continue using them. There is unlikely to be any risk of long-term DNC use as their appeal seems to diminish quickly as the behavior is not accompanied by pharmacological reinforcement. The availability of DNCs may however limit any clinical translation. Although once commercially marketed in the United States, DNCs are currently distributed for research only.

Electronic cigarettes, which also offer some sensory and behavioral input but without tobacco, may be a safer and more acceptable behavioral replacement than DNCs. There is already some evidence to suggest that even without nicotine, these devices can acutely reduce urges to smoke.[22,23] How these compare to DNCs as a behavioral replacement is not known. The close proximity of DNCs to real smoking, and other properties of tobacco smoke which may in themselves be reinforcing,[4] may confer added benefit over electronic cigarettes.

The finding that DNCs reduce the frequency of urges to smoke suggests that they may have potential as a relapse prevention tool. Indeed, the most commonly reported aspect that participants most liked about DNCs was as a replacement for smoking regular cigarettes. This effect of using DNCs has also been reported by others.[19] The role of DNCs in preventing relapse needs to be examined in an adequately designed trial.

In conclusion, we found that supplementing standard smoking cessation treatment with DNCs for 2 weeks, approximately doubled the odds of quitting smoking at 4 weeks, although the effect diminished by 12 weeks.

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Declaration of Interests

HM has received research funding from and provided consultancy to manufacturers of smoking cessation medications. All other authors have no conflicts of interest to disclose.

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