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Brief Report

Randomized crossover trial of the acceptability of snus, nicotine gum, and Zonnic therapy for smoking reduction in heavy smokers

Brent Caldwell, Carl Burgess, & Julian Crane

Abstract

Introduction: Novel approaches to nicotine replacement therapy (NRT) are needed to improve the modest long-term quit rate of 10%. Snus (Swedish tobacco) and Zonnic (oral nicotine sachet) rapidly deliver nicotine via buccal absorption and have potential as NRTs. As a prelude to formal evaluation of either product as a smoking cessation therapy, it is necessary to determine their acceptability and the willingness of smokers to use them in populations with no history of access to oral tobacco products.

Methods: An open-label crossover study of *ad libitum* snus, Zonnic, and nicotine gum among 63 smokers for 2 weeks each, and smoking reduction if the subjects did not feel the desire to smoke. Diary cards recorded use of products and cigarettes; formal and ad hoc scales measured urges to smoke, withdrawal symptoms, and the sensory quality of the products.

Results: Subjects preferred snus and Zonnic over gum. Snus and Zonnic were superior to gum in reducing urges to smoke and caused fewer side effects. All three products suppressed withdrawal symptoms. Subjects reduced their smoking by *Ms* of 33%, 37%, and 42% during the gum, snus, and Zonnic fortnights, respectively.

Discussion: Most subjects reported a strong desire to use Zonnic or snus to quit smoking. Subjects preferred snus and Zonnic, which both had significantly fewer gastrointestinal side effects than gum and resulted in greater reductions in smoking. Snus and Zonnic are effective in suppressing desires to smoke and reducing smoking, and further studies are warranted to investigate their effect on long-term quit rates.

Introduction

Novel approaches to nicotine replacement therapy (NRT) are needed to improve the modest long-term quit rate of 10% at 12 months (Institute of Medicine, 2001). Snus (Swedish oral tobacco) and Zonnic (oral nicotine sachet) rapidly deliver nicotine via buccal absorption and have potential as NRTs. As a prelude to formal evaluation of either product as a smoking cessation therapy, it is necessary to determine their acceptability and the willingness of smokers to use them in populations with no history of access to oral tobacco products.

Zonnic is a small sachet of peppermint-favored nicotine bound to microcrystalline cellulose beads and is placed between the upper lip and gum. Zonnic has a time to maximal venous concentration (T_{max}) of 29 min and maximal venous concentration (C_{max}) of 7.8 ng/ml (Skrtic, 2008). In a small clinical trial, Zonnic was well tolerated and was nonsignifcantly twice as effective at reducing cravings compared with Nicorette gum ($p = .14$) and significantly three times as effective as placebo ($p < .01$; Thornley et al., 2009).

Snus is an oral tobacco which has a long tradition of use in Sweden and may have potential to act as an NRT. Its health risks are lower than the risks associated with continued smoking because it lacks toxicants associated with combustion and has a low-nitrosamine content (Broadstock, 2007; Fagerström & Schildt, 2003; Foulds, Ramström, Burke, & Fagerström, 2003). Snus has a T_{max} of 30 min and a C_{max} of 15 ng/ml, which is 2–2.5 times higher than that with 2 mg Nicorette gum (Foulds et al.; Lunell & Lunell, 2005).

Zonnic may be an ideal nontobacco alternative to snus. We report data from a pilot study of the acceptability of snus and Zonnic, compared with nicotine gum, in a population with no

Brent Caldwell, M.B.Ch.B., *University of Otago, Department of Medicine, Wellington, New Zealand*
Carl Burgess, F.R.C.P., *University of Otago, Department of Medicine, Wellington, New Zealand*
Julian Crane, F.R.C.P., *University of Otago, Department of Medicine, Wellington, New Zealand*

Corresponding Author:
Brent Caldwell, M.B.Ch.B., *University of Otago, PO Box 7343, Wellington, New Zealand. Telephone: +64-4-918-6041; Fax:+64-4-389-5427; E-mail: brent.caldwell@otago.ac.nz*

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tradition of or access to oral tobacco products and report the effects of these three products on cigarette consumption among smokers who were not asked to quit smoking.

Methods

An open-label, randomized crossover study of *ad libitum* snus, Zonnic, and nicotine gum for 2 weeks each, and ad libitum smoking reduction if the subjects did not feel an urge to smoke.

Participants

Adult smokers were eligible who smoked 15 or more cigarettes per day (CPD) with a Fagerström Test for Nicotine Dependence (FTND) score of ≥3 (Heatherton, Kozlowski, Frecker, & Fagerström, 1991). Exclusion criteria were history of cardiovascular disease or serious medical conditions and breastfeeding or risk for pregnancy in women. Ethical approval was obtained from the Central Ethics Committee; subjects received no compensation.

Medications

Snus (Swedish Match, Stockholm, Sweden) is an oral low-nitrosamine tobacco. We used 0.4 g portions (8 mg nicotine/gram of tobacco) in three favors: general, cassis, and eucalyptus. Zonnic (Niconovum AB, Helsingborg, Sweden) is a small pouch containing peppermint favored 4 mg of nicotine bound to microcrystalline beads. Habitrol contains 4 mg of nicotine per piece of mint- or fruit-favored gum. Supplies of each were pur - chased from their respective manufacturers. Subjects were not asked to quit but were requested to use each product when they would usually have had a cigarette and only smoke if they continued to feel the desire.

Procedure

Subjects attended the clinic for informed consent and baseline assessments and were given a diary card to record daily smoking for 1 week. Researchers met subjects 1 week later to collect lead-in diary cards, readminister questionnaires, and provide the NRT, diary cards, and questionnaires for the rest of the trial. The order in which subjects used the products was block randomized. Subjects were telephoned at the end of each treatment fortnight to collect data from diary cards and psychological batteries. Subjects were seen at the conclusion of the study to collect paper copies of the data.

Outcome measures

The acceptability of the products was assessed by the modifed Cigarette Evaluation Scale (mCES; Cappelleri et al., 2007). The following side effects were rated on an ad hoc 5-point Likert scale from 1 = *not at all* to 5 = *extremely*: indigestion, heartburn, acid reflux, hiccup, burp, hurt mouth, and bad taste. The brief Questionnaire on Smoking Urges (QSU) (Cox, Tiffany, & Christen, 2001) and Minnesota Nicotine Withdrawal Scale (MNWS) (Cappelleri et al., 2005) were administered at baseline, the end of the lead-in week, and the end of the three treatment fortnights. The QSU evaluates the desire to smoke with 10 questions on a 6-point Likert scale, from 1 = *negative* to 6 = *positive*. The MNWS assessed withdrawal symptoms over the past 24 hr on a scale from 0 = *not at all* to 4 = *extreme*. Smoking reduction and use of the products were recorded daily on diary cards.

Data analysis

We included subjects who completed at least one treatment period. Reductions in CPD and psychological scores were calculated as a proportion of the lead-in levels. Total side-effect scores were the sum of each subject's side-effect scores. Normally distributed data are reported as means and standard deviations, and Student's t test calculated p values. Nonnormally distributed data are reported as medians and interquartile range (IQR), Mann–Whitney–Wilcoxon rank sum and signed rank tests calculated p values, and Friedman's chi-square test calculated correlations. No adjustment has been made for multiple comparisons.

Results

Flow of participants

Seventy-nine applicants were screened, 72 enrolled, 68 completed baseline evaluations, 63 completed the lead-in week and were randomized, and 50 completed at least one treatment fortnight. Forty-one, 38, and 42 subjects completed the snus, gum, and Zonnic fortnights, respectively. Thirty-two subjects completed all three products, 4 completed only snus and Zonnic, 3 completed only gum and Zonnic, 3 completed only gum, 3 completed only Zonnic, and 5 completed only snus. Reasons for discontinuing snus, gum, and Zonnic, respectively, included (number of subjects) altered personal circumstances (3, 1, and 1), gastrointestinal symptoms (1, 2, and 1), bad taste/texture (2, 1, and 0), other (2, 3, and 3), and loss to follow-up (14, 18, and 16).

Characteristics of subjects

Subjects had a mean age of 43 years, 54% were women, 67% were European, and 18% Maori. At screening, subjects' mean self-reported cigarette smoking was 23 CPD (*SD* 7.68). The mean age they started smoking regularly was 16 years. Seventy-four percent smoked regular tobacco, 10% smoked mentholated tobacco, 10% smoked mild, and 5% extra mild. Almost half the subjects (48%) had attempted to quit, 30% had tried once, 9% had tried twice, and 9% had tried to quit between three and eight times. One third of those who tried to quit had used NRT, 48% used nicotine gum, and 43% nicotine patches.

At baseline, 48% of subjects rated their desire to quit as "a lot," while 63% rated their desire to reduce smoking as a lot. Their mean FTND was 7.02 (*SD* 1.86). In the lead-in week, subjects smoked an *M* of 19.85 CPD (*SD* 6.01).

Subjects who were lost to follow-up had a mean FTND of 6.23 and smoked an *M* of 20 CPD in the lead-in week.

Acceptability of the products

Subjects scored Zonnic and snus more highly than gum for four of the fve reward domains of the mCES, which was signifcant for the item "satisfying" (Table 1). However, Zonnic and snus also scored highly on the off-putting sensations that make up the aversion score.

Side effects were uncommon for all three products. Seventy-fve percent of subjects gave scores of less than 3 for all side effects except "tasted bad," for which snus had the worst

Table 1. Cigarette Evaluation Scale median, mean (interquartile range)

	Snus	Gum	Zonnic™
Satisfaction	4.50, 4.60	4.00, 4.27	5.00, 4.95
(score out of 10)	(3.00–6.00)	(2.00–5.00)	(3.50–6.00)
Satisfying	3.00, 2.60	2.00, 2.13	3.00, 2.70
(score out of 5)	(2.00–3.00)[a]	(1.00–3.00)	(2.00–4.00)[b]
Tasted good	2.00, 2.00	2.00, 2.11	2.00, 2.26
(score out of 5)	(1.00–3.00)	(1.00–3.00)	(1.00–3.00)
Psychological reward	11.00, 10.57	9.50, 9.71	12.00, 11.21
(score out of 25)	(7.00–13.75)	(6.00–13.00)	(7.50–14.50)
Enjoyment	1.00, 1.57	1.00, 1.41	1.00, 1.61
(score out of 5)	(1.00–2.00)	(1.00–1.00)	(1.00–2.00)
Craving reduction	3.00, 3.05	3.00, 2.54	3.00, 2.98
(score out of 5)	(2.00–4.00)	(1.00–3.50)	(2.00–4.00)
Aversion	3.00, 3.50	3.00, 3.31	3.00, 3.67
(score out of 10)	(2.00–4.75)	(2.00–4.00)	(2.00–5.00)
Dizzy	1.00, 1.64	1.00, 1.56	1.00, 1.61
(score out of 5)	(1.00–2.00)	(1.00–2.00)	(1.00–2.00)
Nausea	1.50, 1.86	1.00, 1.74	2.00, 2.07
(score out of 5)	(1.00–2.75)	(1.00–2.00)	(1.00–3.00)

Note. [a]$p = .036$ Compared with gum;
[b]$p = .026$ compared with gum; p values were $> .05$ for all other comparisons among products.

median score of 4, followed by gum 3, and Zonnic 2. Gum had a statistically signifcant ($p < .05$) higher median total gastrointestinal side-effects score of 7 compared with 5 for snus and Zonnic.

The mean numbers of pieces of product used per day (*SD*) were 4.78 (3.25), 4.22 (3.59), and 5.06 (3.60) for snus, gum, and Zonnic, respectively (no signifcant differences).

The mean, median (IQR) reductions in QSU total craving score as percent of the lead-in score for the three products were (negative numbers are an increase) snus 3.6, 13.2 (−19.4 to 40.3); gum −8.9, 3.6 (−32.1 to 37.3); and Zonnic 4.5, 7.9 (−18.6 to 45.0), $p > .05$ for all three products.

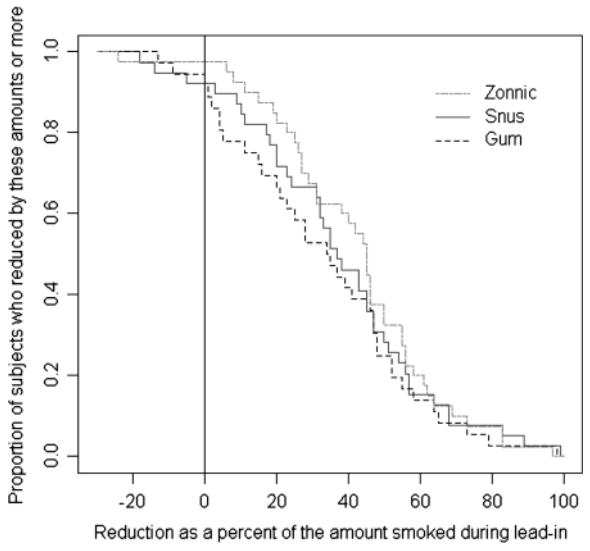

Figure 1. Kaplan–Meier curve of cumulative proportion of subjects who achieved reductions in cigarettes per day (CPD) as a percent of lead-in CPD.

Compared with baseline and lead-in, there was a statistically signifcant ($p < .01$) absolute reduction in the craving subscale of the MNWS with all three products. The mean, median (IQR) reductions in craving were 0.60, 1.00 (0.00–1.00) with snus, 0.58, 1.00 (0.00–1.00) with gum, and 0.93, 1.00 (0.00–1.25) with Zonnic (no signifcant differences among products).

The Kaplan–Meier curve (Figure 1) illustrates that all three products enabled subjects to reduce their smoking signifcantly compared with the lead-in week ($p < .01$). The mean (*SD*) reductions were 42% (24) with Zonnic, 37% (26) with snus, and 33% (26) with gum (comparisons among products were nonsignifcant). Eight percent of subjects in - creased the amount they smoked during the snus and gum fortnights compared with 2% with Zonnic. No one stopped smoking. The percents of subjects who reduced their smoking by half or more during the snus, gum, and Zonnic fortnights were 28.2%, 25.0%, and 32.5%, respectively. Of the subjects who reduced by ≥50% CPD, 23.3% did so with snus and with gum, 20.6% with snus and Zonnic, 15.2% with gum and Zonnic, and 16.7% with all three products. However, although Zonnic assisted more people to reduce their smoking, the 2% of subjects who increased their smoking with Zonnic did so by a greater magnitude (≥20%) than those who increased their smoking during the snus and gum fortnights (≥10%).

The mean CPDs smoked during the first, second, and third fortnights were 13.91, 11.73, and 10.71, respectively. Subjects smoked signifcantly less in the second fortnight ($p = .03$) and third fortnight ($p < .01$) compared with the first fortnight. Differences between second and third fortnights were not significant.

At the end of each fortnight, subjects were asked to rank their preferred purpose for using the products if they could use them long term. Subject could choose among the following

three uses for the products: "short-term to quit smoking," "to reduce smoking," and "long-term instead of smoking," which were ranked on a Likert scale from 1 = *not at all* to 5 = *extremely*. For snus, the median values were as follows: "to quit": 3.0, "to reduce": 4.0, and "instead of": 2.5. For gum, the median values were as follows: to quit: 2.0, to reduce: 2.0, and instead of: 2.0. For Zonnic, the median values were as follows: to quit: 3.0, to reduce: 4.0, and instead of: 2.0. The highest ratings were for snus, then Zonnic, followed by gum for using the products to quit or to reduce. Snus and Zonnic rated higher than gum to quit (Friedman chi-squared = 11.0097, $df = 2$, $p < .01$) and to reduce (Friedman chi-squared = 9.20, $df = 2$, $p = .01$); the ratings for "instead of" among products were not significant.

At the conclusion of the study, subjects were asked to rank the three products in order of overall preference. For their frst choice, an equal number (40%) chose snus or Zonnic, while 20% chose gum (differences in preferences were not signifcant, Friedman chi-squared = 2.21, $df = 2$, $p = .33$).

The only significant differences in the results between genders were in the median scores for two subscales of the mCES: "Craving Reduction" with gum (females = 3, males = 2, $p = .015$) and "Enjoyment" with Zonnic (females = 1, males = 2, $p = .047$).

Discussion

Both snus and Zonnic have demonstrated potential as NRTs. Snus and Zonnic showed a nonsignificantly greater effect than gum in controlling urges to smoke and withdrawal symptoms, which are the key therapeutic requirements of effective NRTs. All three products had similar scores on the 5 subscales of the mCES, although snus and Zonnic had significantly higher scores than gum for the satisfying item of the satisfaction subscale. In addition, and perhaps surprisingly, Zonnic and snus had significantly less side effects than gum.

Subjects gave similar scores to snus and Zonnic and lower scores to gum for their intention to use the products to quit, reduce, or use long term instead of smoking. Likewise, subjects had greater preference for snus and Zonnic than for gum, which may in part be due to its gastrointestinal side effects. Notably, the higher scores for Zonnic and snus for intention to quit were statistically signifcant.

There were large variations in the fairly small number of pieces of products used, which refects the diversity in how sub - jects managed the balance among each product's satisfaction of their craving on the one hand and the adverse sensory effects and side effects on the other hand. Subjects used more Zonnic than gum or snus, which may explain the large reduction in smoking with Zonnic therapy.

All three products must have provided subjects with suff - cient substitution of nicotine to cause the statistically signif - cant reductions in the craving subscale of the MNWS and nonsignifcant reductions in QSU scores. This enabled subjects to spontaneously reduce their smoking. During all three fortnights of product use, the amount smoked was statistically signifcantly different from the lead-in week ($p < .01$), although there were no statistically signifcant differences in the mean reduction in CPD achieved with one product compared with the others.

The present study was a small preliminary study of the acceptability of snus and Zonnic, and hence, the conclusions that can be drawn from it are limited. Snus and Zonnic were acceptable and well tolerated among New Zealand smokers, and further research is warranted to assess their efficacy as NRTs.

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Declaration of Interests

None declared.

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