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Original Investigation

A single-blind, randomized, crossover trial of the effects of a nicotine pouch on the relief of tobacco withdrawal symptoms and user satisfaction

Simon Thornley, Hayden McRobbie, Ruey-Bin Lin, Chris Bullen, Peter Hajek, Murray Laugesen, Hugh Senior, & Robyn Whittaker

Abstract

Introduction: We compared the effects of a 4-mg oral nicotine pouch (Zonnic pouch), with nicotine chewing gum and placebo pouch, on withdrawal discomfort after overnight tobacco abstinence. We also assessed participants' preferences, satisfaction, and consumption patterns.

Methods: This was a randomized, placebo-controlled, three-way crossover study of 30 adult smokers. After overnight tobacco abstinence, subjects reported on a Visual Analog Scale (VAS; 0–100) tobacco withdrawal symptoms (craving, irritability, difficulty concentrating, and restlessness) before use and during the first hour after first product use. They then used the product throughout the study day and in the evening reported product usefulness, temporary abstinence success, and satisfaction.

Results: In a multivariate analysis, area under the curve (craving vs. time) was reduced by 23 points 60 min after taking the study medication in the nicotine pouch group, compared with 15- and 8-point decreases in the gum and placebo groups, respectively. The difference in craving ratings between the pouch and placebo was significant ($p = .002$). Nicotine pouch reduced irritability more than gum (difference = 9.86; $p = .01$). For pouch users, the odds ratio for temporary tobacco abstinence (21.5 hr) during study days (compared with gum) was 2.8 (95% *CI* = 0.8–8.1). Compared with the gum, the pouch was rated as significantly more "helpful to stop smoking" (difference = 20.6; 95% *CI* = 2.4–38.9) and "pleasant to use" (difference = 17.3; 95% *CI* = 2.6–32.0).

Discussion: The Zonnic pouch appears to be as effective at relieving craving as nicotine gum and was subjectively favored over the gum. These results suggest that the pouch will be a helpful addition to the range of existing nicotine replacement treatments.

Introduction

Nicotine withdrawal symptoms, especially craving, contribute to smoking relapse during quit attempts (Killen & Fortmann, 1997). Better relief of craving and other withdrawal symptoms may help smokers to abstain. This rationale underpins the use of nicotine replacement therapy (NRT) for smoking cessation.

Six different NRT products available on the world market are currently licensed for smoking cessation: transdermal patch, gum, sublingual tablet, lozenge, inhaler, and nasal spray. These products differ in their delivery of nicotine, ease of use, and the element of substitution for smoking behavior they provide but all nearly double the chances of long-term abstinence, compared with placebo (Stead, Perera, Bullen, Mant, & Lancaster, 2008).

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The transdermal patch is considered the easiest NRT product to use and one of the most widely purchased over the counter. However, because of its slow delivery of nicotine, it does not provide quick relief of urges to smoke or other withdrawal symptoms (Rose, Herskovic, Trilling, & Jarvik, 1985). The other NRT products provide faster craving relief but require more instruction on correct use and can be unpleasant to use initially. Nicotine gum, for example, requires a specific technique (chew–park–chew) for optimal absorption of nicotine and to limit adverse effects (e.g., unpleasant taste and hiccups), and nicotine nasal spray is often associated with sneezing, coughing, and watering eyes (Demazieres et al., 2006; GlaxoSmithKline, 2002; Sutherland, Russell, Stapleton, Feyerabend, & Ferno, 1992). Ideally, in addition to providing fast delivery of nicotine, NRT products should be simple to use with few unpleasant side effects.

The nicotine oral pouch (Zonnic pouch) is a new product developed by NicoNovum AB that contains nicotine granules in a small sack of nonwoven paper to be stored under the upper lip for 30 min, with passive pressure from the lip maintaining the product adjacent to the oral mucosa. It thus provides a discrete means of delivering nicotine, which does not require chewing, and the pouch nicotine pH of 8.5 ensures rapid absorption across the oral mucosa. A preliminary pharmacokinetic study of four healthy volunteers showed that the 4-mg pouch delivered a shorter time to peak concentration than 4-mg Nicorette™ gum (30 vs. 45 min, respectively; NicoNovum AB, 2007).

We conducted a randomized, placebo-controlled, three-way crossover within-participant study (a) to compare the effects of the nicotine pouch on craving and withdrawal discomfort after overnight tobacco abstinence with placebo pouch and with 4-mg Nicorette™ chewing gum and (b) to assess participants' preferences for, satisfaction with, and consumption patterns for the three products.

Methods

Recruitment and inclusion and exclusion criteria

Recruitment was undertaken in conjunction with another similar study (Figure 1). The other study had identical selection criteria. If eligible, participants were given a choice to participate in either study based on the study timetable that was most suitable for them.

A total of 30 participants were recruited from advertisements in local newspapers and by posters in the local community that invited them to call a local number. On calling, applicants were given a brief explanation of the study and their eligibility to participate was assessed. Smokers were eligible if they were aged 18–70 years, smoked 15 or more cigarettes per day for at least the past year, smoked their first cigarette within 30 minutes of waking, were in good health (verified by medical history at the screening visit), and were able to read and write English and give written consent. Smokers were ineligible if they had any of the following: recent (within the previous 6 months) myocardial infarction, angina pectoris, diabetes mellitus, or other serious medical condition; previous severe allergic reaction; current chemical dependence other than nicotine; current psychiatric disorder; chronic oral disorder that would prevent them from using oral NRT products; pregnant or breast feeding; weight less than 45 kg or more than 120 kg; blood pressure greater than 180 mmHg systolic or 100 mmHg diastolic; current use of nicotine products other than cigarettes; current use of psychotropic drugs; or unwillingness to abstain from smoking prior to and during the study day. Participants who wanted to stop smoking had to agree to smoke as normal between study days. At the end of the study, cessation services were provided.

Procedures

Medications. The Zonnic 4-mg nicotine pouch contains nicotine granules in a buccal pouch made of nonwoven paper. The pouch is kept under the upper lip for 30 min to release about 3 mg of nicotine. The placebo pouch used in this study was manufactured in the same way as the Zonnic 4-mg pouch but without nicotine. To mimic the flavor and irritation of nicotine, the placebo contained a small amount of capsaicin. The placebo was otherwise identical to the active product. The active and placebo pouches were supplied sealed in foil bags of 15. Nicotine chewing gum (4-mg Nicorette™) was purchased commercially.

Participants were randomly allocated to one of three predetermined sequences (according to the Latin square method) of drug–placebo administration. Participants were assigned to a sequence of randomization codes on arrival at the first study day. Randomization codes were prepared in advance by the study statistician (RL). On each study day, the subject was assigned the medication indicated by the randomization code.

Participants were instructed to use one pouch or piece of gum every hour. All participants used each study medication for approximately 9 hours (8:30 a.m. to 5:30 p.m.).

Screening. All participants attended a screening visit before the start of the study. They provided written informed consent and completed a short questionnaire that included demographic data and smoking history: Fagerström Test for Nicotine Dependence (FTND; Fagerström & Schneider, 1989), cigarette consumption, previous quit attempts, and age at onset of smoking. All participants underwent a brief medical history and physical examination (blood pressure, heart rate, and urine dipstick for protein and glucose).

Test sessions. Participants who met the inclusion criteria were provided with the dates of the study days and asked to abstain from smoking and alcohol from 8 p.m. on the evening prior to each of three study days. They were instructed to have their normal breakfast but abstain from caffeine and food for 1 hr prior to the test session at the study center.

On each study day, participants first underwent an expired-air carbon monoxide (CO) test using a Smokerlyzer CO Monitor (Bedfont Scientific Ltd., Rochester, England; Low, Ong, & Tan, 2004). If their CO level was 15 parts per million (ppm) or less, they received their assigned medication for the day according to the medication allocation log. If participants self-reported smoking during the previous 12 hr or had a CO level greater than 15 ppm, they were rescheduled to a subsequent session. Participants were seated at desks in a large room and provided two baseline ratings of withdrawal symptoms at 15 and 5 min before taking the study medication. They then rinsed their mouth with water (to equalize oral pH) and received the first dose of their allocated treatment at 8:30 a.m.

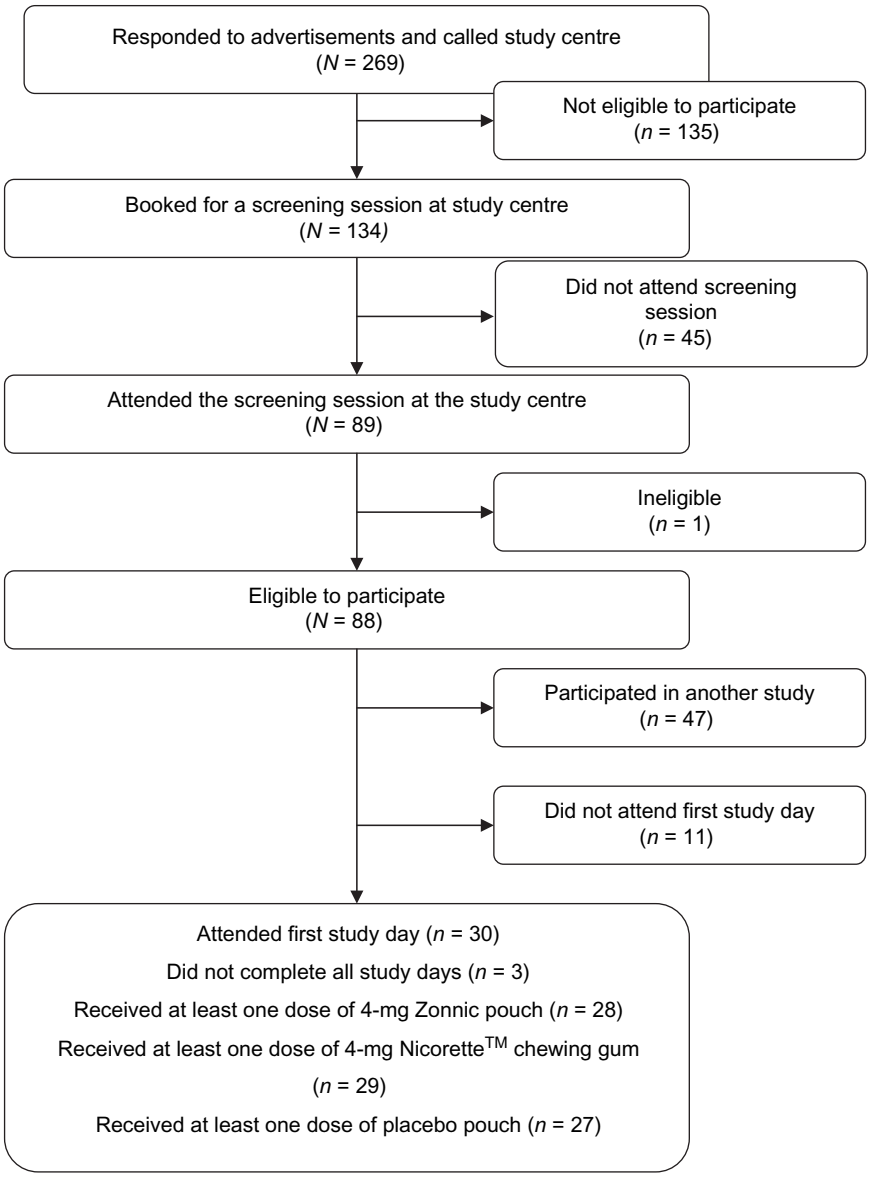

Figure 1. Participant flowchart.

Next, they rated withdrawal symptoms at 5, 10, 15, 20, 25, 30, 40, 50, and 60 min after medication use. After administration of the second medication dose at 9:30 a.m., participants left the study center with instructions to take the allocated treatment hourly and *ad libitum*, to record each dose on a log sheet, and to abstain from smoking until they returned at 5:30 p.m. that same day.

Each study day was separated by three days. Participants were asked to smoke as usual during these days.

Measures

Withdrawal was assessed using the Minnesota Nicotine Withdrawal Scale (Hughes & Hatsukami, 1986, 1998). Participants were asked to indicate on a 100-mm line (VAS), their feelings of irritability, restlessness, difficulty concentrating, and craving. We asked an additional question ("Would you say that the product is having an effect on how you feel?") to ascertain the subjective effect of the medication.

Satisfaction and helpfulness of the products were measured at the end of each study day using an adapted five-item questionnaire (Hajek, Jarvis, Belcher, Sutherland, & Feyerabend, 1989) that asked how satisfying they found the study medication compared with their usual cigarettes (0 = less satisfying; 100 = more satisfying), whether it kept them from smoking (0 = not at all; 100 = extremely), how unpleasant (0 = very unpleasant) or pleasant (100 = very pleasant) it was, how embarrassing it was to use in company (0 = not at all; 100 = extremely), whether they would use it to aid a quit attempt, and whether they would recommend it to a friend who wanted to stop (0 = definitely not; 100 = definitely).

Side effects were measured by participants rating the frequency (never, often, and sometimes) and strength (weak,

moderate, and strong) of a range of possible reactions (mouth and throat irritation, aching jaws, feeling sick, vomiting, flatulence/belching, stomachache, heartburn, diarrhea, hiccups, feeling high, feeling dizzy, headache, palpitations, sweatiness, and cold hands/feet; Hajek et al., 1989). Free text entries also were permitted.

Data analyses

We calculated that a sample of 30 participants would give 90% power at a two-sided 5% significance level to detect a treatment difference of 13 points in craving scores measured at 20 min for the comparison between nicotine pouch and placebo, assuming that the within-participant *SD* of the response variable on a 100-point VAS is 15. This calculation was based on a similar study comparing fast-acting nicotine gum to placebo (Demazieres et al., 2006). Analyses were undertaken using SAS version 9.1.3 according to the assigned sequence group regardless of participant compliance or withdrawal. All statistical tests were two-tailed with a 5% significance level.

The primary outcome (the difference between self-reported craving scores more than 60 min after taking the study medications) was analyzed using the area under the curve (AUC) method. AUC refers to the area under the curve of withdrawal (measured using the Minnesota Nicotine Withdrawal Scale) versus time after product use and was used to compare the average effect of the treatment on such symptoms over 60 minutes. Area of treatment effect was calculated as the total AUC minus the baseline AUC. To derive the treatment effect, area of treatment effect was divided by 60 min to convert the unit from VAS minutes to VAS. Hence, the treatment effect is the average VAS change in 60 min after taking the medication and was considered the dependent variable in multivariate analyses. Normality assumptions were checked and skewed data transformed before analysis.

Analysis of covariance was used with participants as a random effect in the crossover trial analysis. Treatment effect was adjusted for baseline craving score (average of craving score at 5 and 15 min before medication) and period. Period effect also was tested. If data were missing, the last value was carried forward. Adjustment for multiple comparisons was made using the Tukey–Kramer method. We calculated *p* values and 95% *CI* for the three treatment comparisons.

The study was approved by the New Zealand Ministry of Health's Northern Y Ethics Committee.

Results

Baseline characteristics

A total of 30 participants (17 males and 13 females) was randomized. The majority (63%) were of New Zealand European origin and 20% identified as Maori (indigenous New Zealanders). The mean age was 50 years (*SD* = 13), and two thirds were married. Participants smoked a mean of 23 cigarettes/day (*SD* = 8) and had a mean FTND score of 6.0 (*SD* = 1.8). Some 23% of the sample smoked hand-rolled cigarettes, using a mean of 64 g of loose tobacco per week. Most had used nicotine patches (77%) or gum (60%) in the past, and 73% of these participants had found such treatment to be at least moderately helpful.

Table 1. Multivariate treatment effect area under the curve: change in craving from baseline to 60 min after taking the study medication[a]

Medication	*M* (*SE*)
Active pouch	−23.1 (3.2)
Gum	−15.4 (3.2)
Placebo pouch	−8.7 (3.3)

Note. [a]Adjusted for treatment period, baseline craving, participant as random effect, and multiple comparisons using Tukey's method.

Three participants did not abstain over night or had CO readings of 15 ppm or greater (two on day 2, one assigned to gum and the other to pouch, and one on day 3 assigned to gum) and could not be rescheduled on each of the three study days. Analyses of change in craving and other withdrawal symptoms were undertaken with these participants included (intention-to-treat) and excluded.

Change in craving, other withdrawal symptoms, and treatment effect

Mean ratings of craving were lower in the nicotine pouch group (−24) compared with gum (−17) and placebo pouch (−10) 60 min after taking the study medication. From the multivariate AUC analysis (Table 1), craving reduced by 23 VAS points in the nicotine pouch group compared with 15- and 8-point decreases in the gum and placebo groups, respectively. Between-product AUC comparisons (Table 2) showed that the nicotine pouch reduced craving more than placebo (difference = 14.4; $p = .002$), and subjects experienced a greater effect of treatment from pouch use than placebo (difference = 17.0; $p = .01$). Nicotine pouch reduced irritability more than gum (difference = 9.86; $p = .01$). No significant between-medication differences were detected for reductions in restlessness and difficulty concentrating. The AUC of effect of medication (pouch = 50 points, gum = 41 points, placebo pouch = 33 points) corresponded to change in craving. The predicted difference was significant for the comparison between nicotine and placebo pouch only (adjusted $p = .01$).

AUC over the first 30 min showed that the treatment effect of the nicotine pouch, compared with placebo, was significantly stronger at all time points: 5, 10, 15, 20, 25, and 30 min (Figure 2). No such pairwise comparisons were significantly different between either the active pouch and gum or the gum and placebo pouch groups. A sensitivity analysis that excluded data from participants who did not abstain during the compulsory abstinence period produced similar results to the intention-to-treat analysis.

Compliance with temporary abstinence and medication

Only 41% of participants (11/27) managed to abstain completely from smoking when using the placebo, compared with the 52% (15/29) and 75% (21/28) who abstained when using the gum and nicotine pouch, respectively. The odds ratio (*OR*) for

Table 2. Multivariate comparisons of treatment effect area under the curve: change in craving from baseline to 60 min after taking study medication[a]

Treatment effect	Mean difference (95% *CI*)	Adjusted *p* value
Active pouch–gum	−7.7 (−17.3 to 1.9)	.14
Active pouch–placebo	−14.4 (−24.1 to −4.8)	.002
Gum–placebo pouch	−6.7 (−16.4 to 2.9)	.22

Note. [a]Adjusted for treatment period, baseline craving, participant as random effect, and multiple comparisons using Tukey's method.

abstinence using the pouch compared with the gum was 2.8 (95% *CI* = 0.8–8.6). Both active products compared favorably to placebo, with the gum–placebo comparison (*OR* = 1.6, 95% *CI* = 0.5–4.5) more modest than the pouch–placebo comparison (*OR* = 4.4, 95% *CI* = 1.4–13.8).

Those who did not abstain smoked a mean of two cigarettes during the study day, with no difference between the treatment groups. Participants in the two active treatment groups used similar quantities of medication (seven and six pieces for pouch and gum, respectively). Mean duration of use for the nicotine pouch, gum, and placebo, respectively, was 46, 34, and 29 min. The majority of participants (range = 60%–67%) used the product when they felt they needed it rather than using it hourly.

Product satisfaction and helpfulness

Ratings of satisfaction and helpfulness favored the nicotine pouch over the gum and placebo in some domains (Table 3). Nicotine pouch was superior to the gum in the domains of "helpful in abstaining from cigarettes" (difference = 20.6; $p = .02$), "pleasant to use" (difference = 17.3; $p = .02$), and "would recommend to others" (difference = 28.0; $p = .005$; Table 4). All products scored low on satisfaction compared with smoking normal cigarettes, although the pouch was the most highly rated product (cigarettes = 50 points, pouch = 47 points, gum = 34 points, and placebo = 27 points).

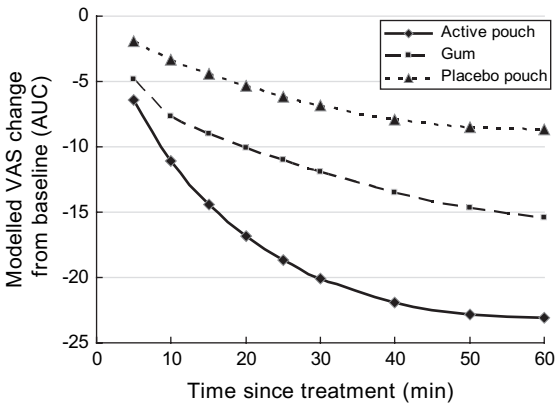

Figure 2. Comparison of area under the curve product change in Visual Analog Scale score for craving during the first hour after product use.

Table 3. Participants' ratings of satisfaction and helpfulness for individual products

Endpoint	Medication	*M* (*SE*)
Satisfaction compared with normal cigarette	Nicotine pouch	47.1 (4.7)
	Gum	33.6 (4.7)
	Placebo	27.3 (4.8)
Helpfulness in abstaining from cigarettes	Nicotine pouch	69.4 (5.6)
	Gum	48.8 (5.6)
	Placebo	35. 1 (5.7)
Pleasant to use	Nicotine pouch	60.9 (4.8)
	Gum	43.6 (4.8)
	Placebo	44.8 (4.9)
Embarrassing to use	Nicotine pouch	8.5 (3.4)
	Gum	18.3 (3.4)
	Placebo	5.4 (3.6)
Use to aid smoking cessation	Nicotine pouch	76.0 (7.1)
	Gum	54.1 (7.0)
	Placebo	49.8 (7.1)
Would recommend to others	Nicotine pouch	81.5 (6.6)
	Gum	53.6 (6.6)
	Placebo	49.8 (6.7)

Note. A higher rating indicates a greater likelihood of endorsing each of the endpoints.

Adverse effects

Participants reported similar frequencies of adverse effects when using the nicotine pouch and gum (Table 5). Mouth irritation and throat irritation were the most common effects. Among less frequently reported effects, nausea was less than half as common for the nicotine pouch ($n = 4$; 13%) than for gum ($n = 10$; 33%), but this difference was not significant ($p = .23$). The majority of adverse effects reported were rated as weak or moderate.

Discussion

This study showed that the Zonnic 4-mg nicotine pouch was more effective than placebo for relief of craving. Although the pouch produced greater craving relief than the gum, the difference was not significant. The nicotine pouch was superior to the gum in reducing irritability. For other withdrawal symptoms, no difference was detected.

Improved success with temporary abstinence was noted with the pouch over gum, although this finding was not significant. This trend may be due to improved withdrawal relief with the pouch, given the within-participant comparisons. The pouch was preferred to the gum in a number of domains (a) to aid abstinence, (b) it was more pleasant to use, and (c) participants were more likely to recommend the pouch to others to aid a quit attempt.

This study had several limitations. First, participants used the products for only 9-hour sessions. This does not mimic real-life use, and withdrawal relief and user satisfaction may differ with longer use. It also could be argued that 9 hours of use may not have been long enough for some adverse effects to appear. However, given that these products deliver similar doses of nicotine

Table 4. Between-product comparisons of product helpfulness and satisfaction

Endpoint	Treatment effect	Mean difference (95% *CI*)	Adjusted *p* value[a]
Satisfaction compared with normal cigarette	Pouch vs. gum	13.5 (−1.1 to 28.0)	.07
	Pouch vs. placebo	19.8 (5.1–34.5)	.01
	Gum vs. placebo	6.3 (−8.4 to 21.0)	.56
Helpfulness in abstaining from cigarettes	Pouch vs. gum	20.6 (2.4–38.9)	.02
	Pouch vs. placebo	34.4 (16.0–52.8)	.0001
	Gum vs. placebo	13.8 (−4.6 to 32.1)	.18
Pleasant to use	Pouch vs. gum	17.3 (2.6–32.0)	.02
	Pouch vs. placebo	16.1 (1.4–30.9)	.03
	Gum vs. placebo	−1.2 (−15.9 to 13.6)	.98
Embarrassing to use	Pouch vs. gum	−9.8 (−20.5 to 1.0)	.08
	Pouch vs. placebo	3.1 (−7.8 to 14.1)	.77
	Gum vs. placebo	12.9 (2.0–23.8)	.02
Use to aid smoking cessation	Pouch vs. gum	21.8 (0.3–43.4)	.05
	Pouch vs. placebo	26.1 (4.4–47.9)	.01
	Gum vs. placebo	4.3 (−17.2 to 25.8)	.88
Would recommend to others	Pouch vs. gum	28.0 (7.7–48.2)	.005
	Pouch vs. placebo	31.7 (11.3–52.2)	.001
	Gum vs. placebo	3.8 (−16.6 to 24.2)	.90

Note. A higher rating indicates a greater likelihood of endorsing each of the endpoints.
[a]Adjusted for treatment period, baseline craving, participant as random effect, and multiple comparisons using Tukey's method.

by the same route as existing oral NRTs (the buccal mucosa), we consider it unlikely that new adverse effects would emerge with prolonged product use.

Second, because this study was conducted in a group of smokers who were not actively attempting to quit, the findings may not be generalizable to smokers trying to quit. However, evidence of an effect of NRT on relief of withdrawal symptoms has been observed in such individuals in other studies (Perkins, Grobe, Stiller, Fonte, & Goettler, 1992).

The superiority of the pouch over the gum in some ratings should be interpreted with caution given that 50%–60% of participants in this study had prior experience with nicotine gum in previous failed quit attempts. Their expectations of the new products might have been more positive than their expectation of the gum, which might have affected their ratings. However, a small ($n = 4$) study showed that the pouch delivers higher peak concentrations of plasma nicotine than nicotine chewing gum (NicoNovum AB, 2007); thus, at least some of the differences may be genuine, probably due to greater craving relief.

Finally, the study was powered to detect a difference in craving between the nicotine pouch and placebo and was not designed to determine a difference between the active pouch and gum. Nonetheless, we noted a trend toward a difference between the two.

Some participants did not comply with the study protocol, which might have affected the magnitude of comparison between products in both directions. For example, several participants ($n = 3$) who did not manage 12 hr of abstinence were included in the intention-to-treat analysis. Although we found no difference in the outcome of a sensitivity analysis, the inclusion of these subjects decreases the likelihood that a significant change in withdrawal ratings will be detected. Also, the number of people with low baseline craving ratings (VAS <30) was higher in the gum (38%; 11/29) group than in the pouch (25%; 7/28) and placebo (26%; 7/27) groups. We speculate that individuals with low baseline ratings are likely to have lower perception of craving relief from NRT administration, and such characteristics may have favored the pouch over the gum.

In summary, the Zonnic 4-mg nicotine pouch reduced craving for a cigarette after overnight abstinence. The pouch is likely to be at least as effective as nicotine gum in helping dependent smokers to quit. Whether our findings of improved short-term abstinence and user satisfaction with the pouch (compared with gum) translate into greater long-term efficacy than is found for existing products is as yet uncertain.

Table 5. Adverse effects

Symptom	Nicotine pouch ($N = 30$)	Gum ($N = 30$)	Placebo ($N = 30$)
Mouth irritation (%)	15 (50)	14 (47)	11 (37)
Throat irritation (%)	15 (50)	17 (57)	6 (20)
Aching jaws (%)	2 (7)	5 (17)	1 (3)
Feeling sick (%)	4 (13)	10 (33)	2 (7)
Vomiting (%)	2 (7)	0	0
Flatulence/belching (%)	5 (17)	4 (13)	1 (3)
Stomachache (%)	5 (17)	4 (13)	2 (7)
Heartburn (%)	5 (17)	2 (7)	0
Diarrhea (%)	2 (7)	3 (10)	0
Hiccups (%)	7 (23)	4 (13)	0
Feeling high (%)	10 (33)	8 (27)	3 (10)
Feeling dizzy (%)	8 (27)	6 (20)	7 (23)
Headache (%)	5 (17)	5 (17)	3 (10)
Sweatiness (%)	2 (7)	4 (13)	3 (10)
Cold hands/feet (%)	2 (7)	2 (7)	0

Note. All values are numbers of subjects with percentages.

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Declaration of Interests

HM has undertaken research and consultancy for, and received honoraria for speaking at meetings for, the manufacturers of smoking cessation medications. RW has undertaken consultancy for, and received honoraria for speaking at meetings for, the manufacturers of smoking cessation medications. PH has undertaken research and consultancy for, and received honoraria for speaking at meetings for the manufacturers of smoking cessation medications.

References

Demazieres, A., Luthringer, R., Coppel, E., Gilles, C., Fleury, C., Roegel, J. C., et al. (2006). Ability of a new oral nicotine substitute to reduce smoking urge in moderate smokers. *Addictive Behaviors*, *31*, 537–543.

Fagerström, K. O., & Schneider, N. G. (1989). Measuring nicotine dependence: A review of the Fagerström Tolerance Questionnaire. *Journal of Behavioral Medicine*, *12*, 159–182.

GlaxoSmithKline (2002). *NiQuitin CQ mint gum: Summary of product characteristics.* Brentford, Middlesex, England: GlaxoSmithKline Consumer Healthcare.

Hajek, P., Jarvis, M. J., Belcher, M., Sutherland, G., & Feyerabend, C. (1989). Effect of smoke-free cigarettes on 24 h cigarette withdrawal: A double-blind placebo-controlled study. *Psychopharmacology*, *97*, 99–102.

Hughes, J., & Hatsukami, D. K. (1998). Errors in using tobacco withdrawal scale. *Tobacco Control*, *7*, 92–93.

Hughes, J. R., & Hatsukami, D. (1986). Signs and symptoms of tobacco withdrawal. *Archives of General Psychiatry*, *43*, 289–294.

Killen, J. D., & Fortmann, S. P. (1997). Craving is associated with smoking relapse: Findings from three prospective studies. *Experimental and Clinical Psychopharmacology*, *5*, 137–142.

Low, E. C. T., Ong, M. C. C., & Tan, M. (2004). Breath carbon monoxide as an indication of smoking habit in the military setting. *Singapore Medical Journal*, *45*, 578–582.

NicoNovum AB (2007). *Investigator's brochure: NicoNovum nicotine sachets 5 mg*. Helsingborg, Sweden: Author.

Perkins, K. A., Grobe, J. E., Stiller, R. L., Fonte, C., & Goettler, J. E. (1992). Nasal spray nicotine replacement suppresses cigarette smoking desire and behavior. *Clinical Pharmacology and Therapeutics*, *52*, 627–634.

Rose, J. E., Herskovic, J. E., Trilling, Y., & Jarvik, M. E. (1985). Transdermal nicotine reduces cigarette craving and nicotine preference. *Clinical Pharmacology and Therapeutics*, *38*, 450–456.

Stead, L. F., Perera, R., Bullen, C., Mant, D., & Lancaster, T. (2008). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews, 1),* CD000146.

Sutherland, G., Russell, M. A., Stapleton, J., Feyerabend, C., & Ferno, O. (1992). Nasal nicotine spray: A rapid nicotine delivery system. *Psychopharmacology*, *108*, 512–518.