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Rapid absorption of nicotine from new nicotine gum formulations

Saul Shiffman [a], Edward J. Cone [b,c], August R. Buchhalter [b,*], Jack E. Henningfield [b,c], Jeffrey M. Rohay [a], Joe G. Gitchell [b], John M. Pinney [b], Tommy Chau [d]

[a] Pinney Associates, 201 North Craig Street, Suite 320, Pittsburgh, PA 15213, United States
[b] Pinney Associates, 3 Bethesda Metro Center, Suite 1400, Bethesda, MD 20814, United States
[c] Department of Psychiatry and Behavioral Sciences, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Baltimore, Maryland 21287, United States
[d] Nutravail Technologies Inc., 14790 Flint Lee Road, Chantilly, VA 20151, United States

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ABSTRACT

Rationale: A clinically limiting feature of currently-available nicotine gum is its slow rate of nicotine delivery and consequently slow onset of therapeutic effects. Previous research suggested that a nicotine hydrogen tartrate gum (NHTG1) that delivered nicotine more rapidly provided more effective craving relief. A subsequent gum formulation (NTHG2) was developed to further increase speed of delivery.
Objective: Compare the plasma nicotine absorption and clinical tolerability of NHTG2 to NHTG1 and Nicorette® FreshMint™.
Methods: A single-dose, randomized, crossover study evaluated the early kinetics of nicotine absorption and tolerability of 4 mg NHTG2 compared to NHTG1 and Nicorette.
Results: NHTG2 gum reached higher C_{max} ($p=0.059$ versus Nicorette; $p=0.006$ versus NHTG1) and delivered significantly more nicotine than Nicorette or NHTG1 within the first 10–30 min of chewing ($AUCs_{0-10,\ 0-30}$) and overall (AUC_{0-180}). NHT gums and Nicorette were well tolerated, with little difference in their AE profiles.
Conclusions: Study results indicate that NHTG2 gum provided more rapid uptake of nicotine in blood without notable decreases in tolerability. To the extent that rate of delivery and onset of therapeutic effects are related, these gums would be expected to provide more rapid therapeutic effects.

1. Introduction

Nicotine gum is one of several nicotine replacement therapies (NRTs) recognized as a safe and effective treatment for tobacco dependence and withdrawal (Stead et al., 2008). NRT use has been shown to approximately double cigarette smokers' odds of quitting, compared to placebo (Fiore, 2000; Fiore et al., 2008). Among NRTs, nicotine gum has gained broad acceptance world wide, in part because of its safety, user control, and peoples' familiarity with chewing gum. Since its introduction, nearly 28 years ago in Europe and 24 years ago in the United States (Henningfield et al., 2005), nicotine gum has not changed substantively, with the exception of improved organoleptic features (e.g., flavors, textures). These changes may increase product satisfaction, but they do not directly address or enhance the clinical benefits of the product (e.g., craving reduction, relapse prevention, cessation).

A clinically limiting feature of commercially available nicotine gum is its slow rate of nicotine absorption leading to its slow onset of therapeutic effects. While nicotine gum is labeled for use at regular intervals, to reduce overall levels of craving and withdrawal, it can also be used to respond to acute "breakthrough" cravings that are provoked by situational stimuli (Bliss et al., 1989; Niaura et al., 1988; Shiffman et al., 1996, 2003). In this application, the speed of onset for craving relief is critical. Nicotine gum's craving-relief effects have an onset of approximately 15 to 20 min (Shiffman et al., 2003), while acute craving often leads to relapse within 10 min (Shiffman et al., 1996). This suggests that there is a need for a nicotine gum that provides more rapid uptake of nicotine and faster onset of craving relief. A nicotine gum that delivers nicotine more rapidly may provide more effective craving relief and thus greater clinical benefits.

Two rapid-release, nicotine hydrogen tartrate gums (NHTG2 and, its predecessor, NHTG1; Nutravail Technologies, 14790 Flint Lee Road, Chantilly, Virginia 20150) have been formulated to provide biphasic nicotine delivery, starting with accelerated delivery to promote rapid craving relief and then leveling off to avoid overdosing (Chau et al., 2008; Cherukuri et al., 2002; Pinney et al., 2002, 2005). This has been accomplished through use of a unique gum base that allows a combination of rapid initial nicotine release and with buffering to increase pH to facilitate rapid absorption through the oral mucosa (Chau et al., 2008; Cherukuri et al., 2002; Pinney et al., 2002, 2005). Also as part of its formulation, the gums' organoleptic qualities have been improved to provide a chewing experience that is very similar to confectionary chewing gums (Niaura et al., 2005). An initial study of a 2-mg NHTG prototype (similar to the NHTG1 formulation) validated the principle that more rapid nicotine delivery would result in more rapid and

* Corresponding author. Tel.: +1 301 718 8440; fax: +1 301 718 0034.
E-mail address: abuchhalter@pinneyassociates.com (A.R. Buchhalter).

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effective craving relief: NHTG1 was found to provide significantly faster and more effective relief than nicotine polacrilex (i.e., Nicorette® [mint flavor]) in reducing craving for a cigarette following exposure to a provocative cue (Niaura et al., 2005).

In some applications, even faster nicotine delivery might be desirable, for example, to provide faster craving relief during efforts to quit smoking. Accordingly, NHTG2 was developed with the objective of providing even higher levels of nicotine in the first 10 min after initiation of dosing. The current study compared the kinetics of NHTG2 to NHTG1 and a conventional nicotine polacrilex product, Nicorette® Fresh Mint™, marketed in the United States and elsewhere. NHTG2 gum was tested to determine if it provided incrementally faster absorption and higher initial nicotine levels than either NHTG1 or Nicorette over the first 10 min of chewing.

2. Methods

2.1. Subjects

Nine male and five female healthy, adult volunteer smokers, who were not intending to quit smoking within the next 30 days completed this study. On average, subjects were 29.8 years old (SD = 10.7) and smoked 11.6 cigarettes per day (SD = 6.2) for the past 9.1 years (SD = 7.9).

Subjects were included if they were between 18 and 60 years old; smoked their first cigarette within 30 min of waking up (an indicator of nicotine dependence (Heatherton et al., 1991); judged to be healthy and free of illicit drugs based on a physical examination, medical history, and urine and blood tests at screening; had normal blood pressure at screening; had a Body Mass Index in the range of 19 to 30 kg/m^2; provided a breath sample ≥10 ppm carbon monoxide at screening (indicating active smoking); and provided written informed consent prior to participation.

Subjects were excluded if they had dentures, dental bridges, missing molars or dental work or disease that precluded the use of nicotine chewing gum; a history of temporomandibular joint disease or pain; a known or suspected hypersensitivity to nicotine; admitted abusing alcohol or drugs within 3 months of study enrollment; an active history of xerostomia (dry mouth); and were currently enrolled in another clinical trial or used any investigational drug within 30 days. Female subjects were excluded if they were nursing or pregnant or were not using birth control. A complete medical history, physical examination, and an electrocardiogram (had to be deemed normal for study enrollment) were performed at screening to confirm eligibility.

Participants were paid for their involvement and provided informed consent. The study was approved by the National Institutional Review Board for Bioanalytical Systems, Inc. Clinical Research Unit (1103 Harriton Road, Baltimore, MD 21210).

2.2. Nicotine gum

Nicotine polacrilex (Nicorette® FreshMint™; product used in the study was manufactured by Pfizer Health AB, Helsingborg, Sweden for GlaxoSmithKline Consumer Healthcare, L.P., Moon Township, PA), 4 mg was purchased from commercial sources. Two nicotine tartrate gum formulations (NHTG2 and NHTG1) were manufactured for human use at Nutravail Technologies (Chantilly, Virginia) according to a patented and patent pending procedure (Chau et al., 2008; Cherukuri et al., 2002; Pinney et al., 2002, 2005). Both gum products contained nicotine hydrogen tartrate providing the equivalent of 4 mg of nicotine base. The gums contained a potassium carbonate buffer.

2.3. Protocol

Each subject participated in three sessions; each session was separated by a minimum of a twenty-hour washout period. Subjects were allowed to smoke as usual between sessions, but were not allowed to smoke or use tobacco within 12 h prior to dosing (confirmed by an exhaled carbon monoxide [CO] sample equal to or less than 10 ppm), or eat or drink (except for water) 1 h prior to dosing. Additionally, subjects were not allowed to use tobacco during the confinement periods of the study.

The study was designed as a single-dose, randomized, crossover study of 4 mg NHTG2 in comparison to 4 mg NHTG1 and 4 mg Nicorette. Subjects received a single dose of each of the three nicotine gums, provided in individually sealed foiled pouches. Subjects and investigators were blind to the NHTG2 and NHTG1 treatment conditions. Due to the fact that Nicorette® FreshMint™ is a coated gum, and NHT gums were uncoated, subjects and investigators were potentially unblinded to those conditions. During each session, subjects chewed a single piece of gum for 30 min. A two-second chew rate (30 chews per minute) was dictated by a metronome for all gum products. The rationale to use a structured chew rate was to standardize dosing across products, a practice commonly implemented in pharmacokinetic studies of oral nicotine products (Choi et al., 2003; Molander and Lunell, 2001). Session order was randomized per Williams square design to counterbalance for all preceding conditions.

Because the pharmacokinetics of absorbed nicotine have been well studied (Benowitz, 1996), the present study was not designed to assess the full elimination phase of nicotine. Rather, the emphasis was on the early rise in plasma levels and therefore blood sampling was taken frequently after placement of gum in the mouth and following chewing. The primary end-point of the study was the AUC nicotine over the first 10 min of chewing.

Blood samples (10 mL) were obtained via an indwelling venous catheter at −5 min (pre-dose), and at 2, 4, 6, 8, 10, 15, 30, 45, 60, 90, and 180 min timed from start of gum chewing. Following plasma harvesting, specimens were frozen for subsequent analysis.

Subjects were asked in a systematic but non-specific way, "Have you felt unwell or experienced any unusual symptoms since chewing the gum?," about possible adverse events (AEs) at the end of chewing (30 min) and at 180 min post dosing.

2.4. Plasma analysis

Plasma samples were assayed for nicotine concentrations by a validated gas chromatographic method (Advanced Bioanalytical Service Laboratories Ltd., Wardalls Grove, London) (Feyerabend and Russell, 1990). The lower limit of nicotine quantitation in plasma was 0.5 ng/mL; no sample values fell below this limit.

2.5. Pharmacokinetic analysis

Plasma nicotine levels were adjusted to baseline because of pre-existing nicotine levels (−5-minute specimen) by the following equation:

$$\mathrm{CT(adj.)} = \mathrm{CT} - C_0 e^{-Kt}$$

where CT(adj) = adjusted plasma concentration, CT = observed plasma concentration, C_0 = baseline plasma concentration at time zero, K = nicotine elimination rate, and t = time. K was derived from an average half-life of 120 min (Benowitz et al., 2006) from the equation $K = 0.693/T_{1/2}$. Individual subject-specific half-lives for nicotine in the baseline adjustment procedure might have been preferred, but the individual half-lives could not be estimated from the 3 h of data available. C_0 was derived from the equation $C_0 = C_{-5}e^{-K5}$.

Of the 14 subjects who completed the study, two were excluded from pharmacokinetic analysis, one because of a missed-baseline specimen and another for three missing sequential blood specimens. Two additional subjects had a total of three missing specimens. The missing values for these subjects were estimated by interpolation. (Analysis of the data with and without interpolation of the 3 missing values made no difference to the statistical outcome). Area under the

Table 1
Mean (±SD) pharmacokinetic parameter estimates and *p*-values — baseline-adjusted plasma nicotine concentrations ($N=12$)

Measure	NHTG2	NHTG1	Nicorette	NHTG2 versus NHTG1	NHTG2 versus Nicorette	NHTG1 versus Nicorette
AUC_{0-10}, min ng/mL	25.9 (19.5)	14.3 (12.7)	6.6 (5.0)	$p=0.015$	$p=0.000$	$p=0.070$
AUC_{0-30}, min ng/mL	206.8 (75.5)	141.1 (80.4)	118.6 (51.3)	$p=0.017$	$p=0.002$	$p=0.387$
AUC_{0-180}, min ng/mL	1967.8 (709.8)	1467.5 (460.5)	1583.0 (430.6)	$p=0.001$	$p=0.009$	$p=0.402$
C_{max}, ng/mL	14.9 (4.9)	11.4 (4.0)	12.6 (2.7)	$p=0.006$	$p=0.059$	$p=0.319$
T_{max}, min	53.8 (16.3)	51.3 (17.5)	56.3 (14.5)	$p=0.718$	$p=0.718$	$p=0.472$

Note: Evaluation of AUC_{0-10} was based on a directional significance level (1-tailed, $\alpha=0.05$ level).
Evaluation of all remaining PK parameter estimates was based on a non-directional significance level (2-tailed, $\alpha=0.05$ level).
Both C_{max} and T_{max} were determined by visual inspection of the data. It should be noted that both measures are influenced by the timing of specimen collection.

response–time curve (AUC) values were calculated by the trapezoidal rule (Rowland and Tozer, 1989). C_{max} and T_{max} were determined by data inspection.

2.6. Adverse event analysis

Adverse event (AE) data were recorded for all subjects. Treatment-emergent AEs were summarized and tabulated by COSTART system organ class and preferred term, by severity (mild, moderate, or severe), and by relationship to study medication (not related, unlikely, possible, probable, or not assessable), which was determined by study site medical personnel. Multiple reports of an AE were counted only once for the tabulation of AE rates, with the most severe intensity being used. The denominator for the calculation of AE rates frequencies included all subjects who received study medication. No inferential statistics were performed.

2.7. Data analysis and statistics

Analysis of variance (ANOVA) was used to compare AUCs, C_{max}, and T_{max}. The ANOVA model tested the within-subjects factor of gum condition (NHTG2, NHTG1, and Nicorette). All estimates were based on baseline-adjusted measures. A priori contrasts were used to compare mean differences of the treatment groups. Statistical significance was determined at the 0.05 level, with no formal adjustment for multiplicity. Evaluation of $AUC_{(0-10)}$ and individual time-points was based on a directional significance level (1-tailed, $\alpha=0.05$), based on product design, prior data, and hypothesized differences. The study was powered to detect expected differences in AUC_{0-10} between NHTG2 versus NHTG1 or Nicorette based on a 1-tailed test in the hypothesized direction. Evaluation of remaining $AUCs_{(0-30,\ 0-180)}$, C_{max}, and T_{max} was based on a non-directional significance level (2-tailed, $\alpha=0.05$), because these pharmacokinetic (PK) parameters were not necessarily hypothesized to differ between products.

Pairwise contrast tests were used to compare group differences in plasma nicotine concentrations at 4, 6, 8, and 10 min (2 min was considered too soon to see differences in nicotine absorption). Lastly, plasma nicotine concentrations at 2, 4, 6, 8, and 10 min were tested to see when significant rises first became evident for each product.

3. Results

3.1. Pharmacokinetics

Table 1 shows the PK and statistical parameters calculated for the initial rise in nicotine (AUC_{0-10}) and AUCs measured during chewing (AUC_{0-30}) and over the entire three-hour period of sampling (AUC_{0-180}). The absorption of nicotine into the bloodstream occurred at a more rapid rate for NHTG2 compared to both NHTG1 and Nicorette during the first 10 min of gum chewing (Fig. 1). The AUC_{0-10} for NHTG2 was significantly higher than the AUC_{0-10} compared to both NHTG1 ($p<0.02$) and Nicorette ($p<0.0005$). Further, the AUCs for NHTG2 were significantly higher than those for NHTG1 and Nicorette over all time intervals ($ps<0.02$; Table 1). AUCs for NHTG1 were numerically higher than Nicorette over the first 30 min, but trended lower and were not significantly distinguished at the end of the sampling period.

Nicotine plasma elevations were significantly detectable as rising above baseline after chewing NHTG2 for 4 min ($p<0.002$), NHTG1 for 6 min ($p<0.02$), and Nicorette for 8 min ($p<0.03$). As shown in Fig. 1, nicotine plasma concentrations achieved by NHTG2 were higher than those for Nicorette after 4, 6, 8, and 10 min of chewing, and higher than NHTG1 after 6, 8, and 10 min of chewing (and marginally higher after 4 min). NHTG1 produced levels higher than Nicorette only after 8 min of chewing.

The PK profile of all three products over 180 min is shown in Fig. 2. As shown in Table 1, the C_{max} for NHTG2 gum was significantly higher compared to NHTG1, but only trended higher in comparison to Nicorette. NHTG1 did not differ significantly from Nicorette. No significant differences were seen in T_{max} among the three gums.

3.2. Adverse events

Twelve of the 14 subjects (85.7%) reported one or more AEs. A total of 39 AEs were reported and all were rated as mild. As shown in

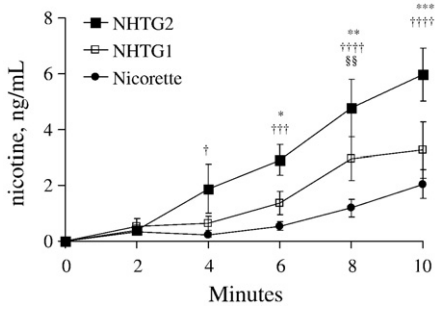

Fig. 1. Mean (±SEM) baseline-adjusted plasma nicotine concentrations during the first 10 min of gum chewing ($N=12$). Dagger (†) denotes significant differences between NHTG2 and Nicorette. Asterisk (*) denotes significant differences between NHTG2 and NHTG1. Section sign (§) denotes significant differences between NHTG1 and Nicorette. One symbol = $p<0.05$, two symbols = $p<0.01$, three symbols = $p<0.001$, and four symbols = $p<0.0001$.

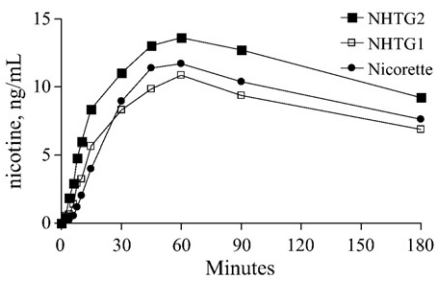

Fig. 2. Mean baseline-adjusted plasma nicotine concentrations across experimental session ($N=12$).

Table 2
Number of adverse events, intensity, and relationship to study medication by treatment group ($N=14$)

Treatment	Number of subjects[a]	Number of (%) subjects with ≥1 AE	Number of AEs[b]	Probably treatment related	Possibly treatment related	Unlikely treatment related
NHTG2	14	10 (71.4%, [41.9%, 91.6%])	17	47.1%	35.3%	17.6%
NHTG1	14	9 (64.3%, [35.1%, 87.2%])	10	70.0%	30.0%	0.0%
Nicorette	14	10 (71.4%, [41.9%, 91.6%])	12	75.0%	25.0%	0.0%

Percentage of AEs reported not related to study medication or not assessable were zero.
[a] Includes 2 subjects who were not included in the PK analyses.
[b] Out of 39 total adverse events. All recorded AEs were classified as mild.

Table 2, the number of subjects who reported at least one AE was approximately equal across all gum conditions. The number of AEs was slightly greater for NHGT2, but those AEs were less likely to be attributed to the product. As shown in Table 3, the most common AEs across all groups, accounting for 80% of AEs, were pharyngitis ($n=13$, 33.3% of the total AEs), numbness or tingling around the mouth ($n=10$, 25.6%), dizziness ($n=4$, 10.3%), and headache ($n=4$, 10.3%).

4. Discussion

Nicotine gum is an established dosage form for the treatment of nicotine withdrawal and as a tobacco cessation aid. However, formulation limitations, namely its slow rate of nicotine delivery and subsequent slow onset of therapeutic effects, may diminish the performance of currently-available nicotine gums.

As part of a continuing development effort, we tested the speed of nicotine delivery of an enhanced rapid-delivery gum, NHTG2 against the performance of a predecessor formulation NHTG1 and against commercial Nicorette nicotine gum. The study was not powered to detect differences between NHTG1 and Nicorette, but previous PK studies have demonstrated such differences (see Niaura et al., 2005). The results of this study demonstrated that NHTG2 provided increased absorption during the first 10 min of chewing, compared to Nicorette nicotine gum, as well as to NHTG1, which had earlier demonstrated superior craving relief compared to Nicorette (Niaura et al., 2005). The more aggressive nicotine delivery was accomplished without altering overall nicotine content or diminishing tolerability and with only a moderate increase (i.e., 24–34%) in total nicotine delivery (AUC_{0-180}) compared to Nicorette and NHTG1. The mechanisms by which nicotine delivery is controlled in the new gums involve an interaction between the gum base, nicotine hydrogen tartrate, and the buffering system (Chau et al., 2008; Cherukuri et al., 2002; Pinney et al., 2002, 2005). The delivered dose, by design, is partly under the control of the user's pattern of chewing, which is considered clinically desirable.

A clinical benefit of the conventional nicotine gum platform, generally, and the newly formulated prototypes, specifically, is their potential to serve as a rescue medication when smokers face threats to abstinence. Nicotine gum, as an acute dosing form, offers the user some degree of control over the timing of dosing in anticipation of or in response to situations that can trigger cravings and relapse. Studies of smoking cessation show that relapse is often acutely triggered by exposure to provocative stimuli that lead to intensive craving, which can escalate to smoking within 10 min of provocation (Shiffman et al., 1996, 2003). A study of an early 2-mg prototype of NHTG1 compared to Nicorette demonstrated that its faster nicotine delivery was associated with more effective and faster craving relief following exposure to a provocative stimulus (Niaura et al., 2005). This suggests that NHTG2, which was designed and demonstrated to yield even faster initial increases in nicotine plasma levels, may provide more effective relief of acute craving, with potential benefits for relapse prevention.

In addition to their use in traditional smoking cessation approaches, more aggressive nicotine dosing products such as this may be useful for helping smokers switch from smoking to safer forms of nicotine use. Public health advocates have argued that smokers who are unable to quit smoking and nicotine use altogether should be provided with alternative sources of nicotine that do not carry the enormous health risks of smoking (Foulds et al., 2003; Royal College of Physicians, 2007; Sumner, 2005). These authors have argued that use of NRT instead of smoking would offer substantial health benefits, but have criticized the nicotine delivery profile of current NRT formulations as too low and too slow to be useful for this purpose (Royal College of Physicians, 2007). The data presented here suggest the potential for novel oral-delivery formulations to meet this need.

Adverse events data suggested that NHT gums and Nicorette were all well tolerated, with little difference in their AE profiles. Moreover, all the AEs reported were considered mild, and all were consistent with the inconsequential AE profile associated with the clinical use of commercial nicotine gum (Fiore et al., 2008). These results are also consistent with those of Niaura et al. (2005), and suggest that NHT gums are tolerated comparably to commercially available nicotine gums, despite their more aggressive initial nicotine delivery.

In addition to their faster delivery of nicotine and faster onset of craving relief, NHT gums have been designed to overcome other product limitations characteristic of commercially available nicotine gums including elaborate chewing instructions and a sensitivity to acidic beverages (Henningfield et al., 1990; Henningfield, 1995; Sachs, 2000). These limitations may diminish consumer acceptance and compliance, and product performance. Unlike conventional nicotine gums, NHT formulations have simple chewing directions, ("chew as you would normal gum"; see Niaura et al., 2005), and are less likely to be affected by consumption of acidic beverages, which has been shown to substantially impair nicotine absorption (Henningfield et al., 1990). The sensory appeal of nicotine gums also limit their use and therefore their effectiveness. The development of NHT gums has also aimed to improve their sensory appeal, with promising preliminary results, but evaluation of the gums' sensory properties was not a focus of this study. Overcoming the limitations of current gum formulations may enhance consumer acceptance and thus increase compliance, which is related to clinical efficacy (Shiffman et al., 2002).

Current formulations of nicotine gum have been shown to have very little abuse potential, particularly in comparison to cigarettes or intravenous nicotine (Henningfield and Keenan, 1993; Henningfield and Slade, 1998; Stitzer and De Wit, 1998). The NHT gum was designed to provide faster and more palatable nicotine delivery while still remaining far slower and producing lower typical plasma nicotine levels than cigarettes, but this study did not evaluate its abuse liability.

While this study tested nicotine gums, it is possible that other nicotine delivery forms or formulations may also be able to achieve

Table 3
Listing of adverse events and frequency by treatment group ($N=14$)

Adverse event	NHTG2 n	NHTG1 n	Nicorette n	Total n (% of the total AEs)
Pharyngitis	5	3	5	13 (33.3%)
Circumoral paresthesia	2	4	4	10 (25.6%)
Headache	3	1	0	4 (10.3%)
Dizziness	0	1	3	4 (10.3%)
Tooth disorder	0	1	0	1 (2.6%)
Vomiting	1	0	0	1 (2.6%)
Lacrimation disorder	1	0	0	1 (2.6%)
Rhinitis	1	0	0	1 (2.6%)
Stomatitis	1	0	0	1 (2.6%)
Eructation	1	0	0	1 (2.6%)
Hiccup	1	0	0	1 (2.6%)
Dyspepsia	1	0	0	1 (2.6%)
Total	17	10	12	39

rapid nicotine delivery. Current oral NRT products (inhaler, lozenge) are roughly on par with Nicorette gum (Choi et al., 2003; Schneider et al., 2001), which was evaluated here, but reformulations such as NHT have the potential for performance improvements. Nicotine nasal spray achieves a C_{max} (ng mL^{-1}) of 6.0 and a T_{max} (h) of 0.28 (Lunell et al., 1995) and can produce effects characteristic of those of abusable drugs (Schuh et al., 1997). However, this mode of delivery is often aversive and irritating (Rose, 2006; Schuh et al., 1997), leading to frequent consumer non-compliance: the nasal spray is used in only <3% of quit efforts in the US (Centers for Disease Control and Prevention, 2000). This illustrates the importance of balancing pharmacokinetic and sensory characteristics of nicotine medications to promote compliance and appropriate use.

The current study was based on a single-dose analysis with a small sample of smokers who were not quitting smoking, and was not powered to detect differences between NHTG1 and Nicorette. The analysis also included multiple tests, which may increase the overall alpha error rate. These limitations not withstanding, the results confirmed the expectation that NTHG2 would yield faster nicotine delivery.

In summary, compared to commercially available nicotine gums and to an earlier NHTG1 formulation, NHTG2 gum was shown to deliver more nicotine within the first 10 min of chewing, while remaining well tolerated. The use of NHT gums to provide rapid craving relief, when a rescue medication is needed, could forestall relapse and thus enhance clinical efficacy. Products with more aggressive nicotine delivery profiles may also be useful for smokers who are unable to give up all nicotine intake, but need to stop or reduce smoking to reduce their health risk. To assess their clinical potential fully, these gums merit further study in appropriate clinical trials.

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