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Comparison of three nicotine treatments: initial reactions and preferences with guided use

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Abstract *Rationale:* Misuse or dislike of nicotine replacement treatments (NRTs) undermines their effectiveness. Brief testing among NRTs could allow tailoring by preference to improve outcome. *Objective:* To test initial reactions/preferences to NRTs in a single session crossover design with guided use. *Methods:* Smokers were offered two doses of three NRTs: gum (2 and 4 mg), inhaler, and nasal spray (NNS) in a 5-h test with proper use enforced. Subjects *rated* each NRT and *ranked* among NRTs on use variables and preferences. *Results:* Gum was ranked over inhaler and NNS for “ease of use,” “safety” and “prefer in public.” Four-milligram gum was rated higher than 2 mg on several variables. With experience, “ease of use” and “liking” improved for gum. Both inhaler and NNS ranked low on considering “use >3 months” vs gum. Dislike of NRT was reflected in refusal of second doses. For those testing all doses ($n=9$), inhaler ranked last on “relief of withdrawal,” “choose under stress,” and “choice to help quit.” Craving and withdrawal were relieved over time with any NRT use. *Conclusions:* Sampling of treatments can identify reactions key to initial compliance with these NRTs.

Keywords Nicotine replacement treatments · Preferences · Tailoring · Nicotine gum · Nicotine nasal spray · Nicotine inhaler · Pharmacotherapy · Dependence

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Introduction

Nicotine replacement treatments (NRTs) still dominate pharmacotherapy for smoking and include moderately fast-acting systems (gum, inhaler, nasal spray, lozenges, and tablets) and slow-acting patches (Foulds et al. 2004). While efficacy is established for active drugs over placebo, absolute rates are low (~10–30%; Foulds et al. 2004; Shiffman et al. 2003; Silagy et al. 2004). Rates are even lower in practice: overall success was ~7% at 6 months for usage of gum and patches (Hughes et al. 2003). With any of these clinically established systems, it should be possible to improve outcome.

What is wrong? Low success rates with *acute* NRTs may be due to misuse of the drug or negative reactions to route of administration. Preference testing among five NRTs (Schneider et al. 2004) showed that systems are differentially liked/disliked, feared, perceived as easy/not easy to use, etc. Preference testing in a smoking reduction trial showed smokers may benefit from testing NRTs and choosing one they prefer (Fagerstrom et al. 1997). Preference rankings did not affect outcome in West et al. (2001); however, subjects ranked NRTs based on video presentations. Direct experience with the acute NRTs changed expectations with these drugs in Schneider et al. (2004). Sampling treatments could eliminate purchasing an NRT that is instantly rejected. The misuse or dislike of otherwise effective systems is a waste of their potential and of a smoker's attempt to quit. With multiple NRTs available, we could identify reactions and preferences (e.g., sensory, ritual, pharmacologic) that affect compliance and test tailoring by preference as one means of improving outcome.

In this trial, we wanted to test reactions when *use is guided*. Preferences among NRTs with guided use may differ from preferences with *ad lib* use (Schneider et al. 2004): inhalers may be liked less with puffing enforced to extract nicotine, nicotine nasal spray (NNS) may be better accepted with assurance of safety as in clinical trials (Schneider et al. 1996), and proper chewing of gum may mitigate dislike by controlling side effects.

Subjects were tested in a single-session crossover with monitored use of two doses of three NRTs: gum (2 and 4 mg), inhaler, and NNS. They rated use variables and preferences for each NRT (*ratings*) and among NRTs (*rankings*). Preferences were expected to differ among NRTs as a function of system elements (e.g., ease of use) and dosages of gum. Craving and withdrawal were assessed over the session (but not among NRTs as concentrations overlapped). Changes in expectations with testing NRTs were recorded.

Materials and methods

Subjects

Smokers of ≥ 20 cigarettes/day, 25–55 years of age, were recruited via print ads with a baseline carbon monoxide (CO) score of ≥ 15 parts per million (ppm) required for inclusion. Exclusion criteria included medical conditions, use of psychotropic drugs, substance abuse, pregnancy, and mouth, nose, or throat problems that preclude use of these NRTs. Subjects were paid \$120 for ~5 h of testing.

Treatments

NRTs “wean” smokers off nicotine by eliminating arterial “boli” and high venous blood nicotine concentrations of smoking. We tested three forms of NRT: gum (2 and 4 mg), inhalers and NNS. Lozenges were not available at the time of testing. These NRTs act within 7–40 min (Schneider et al. 2001; also see below). None produce the carcinogens and gases of burned tobacco.

For 2- and 4-mg gum, systemic delivery of nicotine is ~1 and 2 mg due to inactivation with swallowing and residual nicotine left in gum (Benowitz et al. 1987). Venous nicotine concentrations are $\sim 1/4$ – $1/3$ that of smoking for 2 mg and $\sim 1/2$ of smoking concentrations for 4-mg gum; both peak/plateau at ~ 30 – 40 min. The inhaler is “puffed” (but not lit) and delivers vaporized nicotine for oral absorption. Venous nicotine concentrations for inhaler are $\sim 1/4$ – $1/3$ of smoking and follow a course similar to 2-mg gum. NNS is delivered to nostrils via a pump, and a dose (1 mg) is made up of two squirts (0.5 mg per nostril). NNS venous concentrations peak at ~ 7 – 10 min and are $\sim 1/4$ – $1/3$ of the concentrations of smoking.

Careful instruction was instituted to control use problems and aid nicotine extraction. For NNS, subjects were shown how to prevent loss of nicotine from sneezing (place finger under nose, apply pressure), from a runny nose (hold nostril shut), and from active sniffing (also unpleasant on the back of the throat). For inhaler, subjects were to puff shallowly to prevent coughing and gagging; frequent puffing was enforced to insure sufficient intake of nicotine. For gum, we guided subjects in the “chew-and-park” method to control nausea and improve extraction of nicotine. The treatment regimen is under [Procedures](#).

Procedures

The study was approved by VA/UCLA institutional review boards and performed in accord with ethical standards of the 1964 Declaration of Helsinki. At entry, subjects gave informed consent, CO, vital signs, had an electrocardiogram (EKG) and had a brief physical examination to determine eligibility. We took saliva for cotinine (estimates nicotine), smoking/NRT histories, the Fagerstrom Test of Nicotine Dependence (FTND; Heatherton et al. 1991), and craving/withdrawal measures. The latter included a 20-item Smoker Anchored Withdrawal Grid (W-Grid) with a 10-point “anchored” scale where subjects see all prior responses. Responses were rated 1 (“definitely not experiencing”) to 10 (“experiencing all the time”). Total range was 20–200. Items covered included craving, urges, missing a cigarette, anxious, restless, mood fluctuation, irritable, easily annoyed, frustrated, hostile, depressed, lightheaded, panicky, disoriented, difficulty concentrating, slowed down, drowsy, hunger, trouble sleeping, and weight concern (the latter two are not relevant to this testing). This scale is easily administered pre–post each dose of NRT.

Abstinence was required from arising to arrival on test day. Order of drug was randomized for three NRTs. Table 1 shows the timetable for testing.

Subjects were instructed in use and monitored during doses. For the NNS, a dose takes ~ 1 – 3 min and the two doses were given $\sim 1/2$ h apart. For inhaler, subjects took ~ 80 puffs over 20 min, stopped 20 min, and puffed again for 20 min. For gum, subjects chewed 2 mg for 20 min, waited 20 min, and chewed 4 mg for 20 min (order constant for gum). Two-milligram gum preceded 4-mg gum in an effort to minimize masking effects from the stronger dosage (Schneider 1986).

Craving and withdrawal were assessed at entry baseline, at arrival on test day (after overnight abstinence), and pre–post *each dose* of NRT. CO was taken at entry, arrival, and after each NRT. For preferences, subjects *rated* 14 variables (see [Results](#)) for each NRT using a 7-point Likert scale from 1 (“very definitely not”) to 7 (“very definitely”). They rated *overall satisfaction* on a 1–10 scale (1=least, 10=most). Ratings were taken after each gum (2 and 4 mg), NNS, and inhaler. Subjects could decline a second dose of NNS or inhaler but had to test both 2- and 4-mg gum to be included in analyses. After all drugs were tested, subjects *ranked* preferences among the three forms of NRT (forced choice: 1, 2, 3) on 12 items: ease of use,

Table 1 Timetable for test day^a

9:00–9:30	Arrive at lab (deprived)
9:30–10:30	Test two doses of first NRT
10:30–11:00	No drug
11:00–12:00	Test two doses of second NRT
12:00–12:30	No drug
12:30–1:30	Test two doses of third NRT
1:30–2:00	No drug

^aExample of an arrival at 9:00 A.M.

craving relief, withdrawal relief, choose under stress, best to prevent slips, nicotine, comfortable use >3 months, safest to use, side effects, prefer in public, most satisfying, and choice to help quit. Subjects also rated NRTs on changes in expectations (better, same, worse) for ease of use, liking of drug, and help in quitting.

Data analysis

Chi-squares were used to assess differences among rankings. Ratings and craving/withdrawal items were analyzed using repeated measures analysis of variance (ANOVAs) and analysis of covariance (ANCOVAs). Bonferroni corrections were applied to pairwise contrasts.

Results

Subjects

Twenty-four subjects were enrolled; three violated smoking criteria, one had stomach distress (4-mg gum), and one did not use 4-mg gum. Of 19 subjects, missing data resulted in an $n=16$ for *rankings* (subjects had to test at least one dose of NNS, inhaler and both dosages of gum); for *rating* each NRT, $n=13$ tested at least one dose as described. Table 2 shows demographics for $n=16$ (13 males/3 females; 9 African-Americans/5 Caucasians/2 Asians). Two subjects had tried gum (12.5%); one tried gum for several weeks 2 years earlier and another tried one piece 5 years earlier. None of the subjects had tried a patch, NNS, or inhaler. Overnight abstinence was confirmed by self-report and a lowered CO on test day; mean (SD) for CO on arrival was 9.7 ppm (4.7).

Craving/withdrawal data

For craving and withdrawal, ANOVAs (1×7) were significant for five variables ($p < 0.05$) for three craving items, anxiety, and total withdrawal. Contrasts (Bonferroni cor-

Table 2 Demographics ($n=16$)

Measure	Mean	SD
Age	40.4	9.0
Years smoking	23.4	9.7
Cigarettes per day	25.3	6.7
Baseline CO (parts per million)	19.1	4.7
Baseline cotinine (ng/ml)	260.5	113.7
FTND (0–10) ^a	6.6	2.0
Time to first cigarette (0–3) ^b	2.25	0.77
Want to quit smoking (1–10) ^c	6.94	2.62

^aRange 0 (least dependent)–10 (most dependent)

^bRange 0 (after 60 min), 1 (within 31–60 min), 2 (within 6–30 min), 3 (within 5 min); a high score=more dependence

^cRange 1 (not very much)–10 (very much)

rected) for baseline vs deprived were not significant. Despite trends to rise, baseline scores may have been elevated as some subjects reported not smoking at entry. Craving, urge to smoke, missing a cigarette, and total withdrawal all decreased over time with significant contrasts from “deprived” (at arrival) through after the last NRT was administered. For example (using the abbreviation Tx for treatment), craving means (SDs) were 5.9 (3.2) at baseline entry, 7.7 (2.2) for deprived at arrival (same as pre-Tx1), 5.4 (2.0) at post-Tx1, 4.8 (2.1) at pre-Tx2, 4.3 (2.1) at post-Tx2, 4.1 (2.7) at pre-Tx3, and 3.6 (2.2) at post-Tx3. Note: the post-Tx3 score was lower than baseline. The results follow the same pattern for urges to smoke, for missing a cigarette, and for total withdrawal. Anxiety increased at arrival (but not significantly) and decreased over time with the exception of nonsignificant rises at pre-Tx3 and post-Tx3.

ANCOVAs (baseline covaried) were not significant but contrasts showed reductions (Bonferroni corrected) from deprived to post-NRT use for “craving” and “urge to smoke” (all contrasts $p < 0.005$) and for “missing a cigarette” ($p < 0.05$ to $p < 0.002$). For total withdrawal, contrasts were significant at $p < 0.05$ or less. Contrasts for reductions in anxiety were significant at $p < 0.04$.

Control of use and side effects

Coughing with inhaler occurred with drawing deeply (38%); shallow puffing prevented it. With NNS, 75% had a “runny” nose with nicotine loss reduced by holding the nostrils shut; sneezing occurred in 44% despite some prevention by placing a finger under nostrils. For gum, enforced “chew-and-park” methods controlled nausea (0% 2 mg, 6.25% 4 mg). Many common side effects were not preventable: dislike of taste (73% 2-mg gum, 60% 4-mg gum, 37.5% inhaler), excess saliva (>80% gum), burning sensation in mouth (81% 2-mg gum, 93% 4-mg gum, 31% inhaler), mouth dry (34% inhaler), throat irritation (67% inhaler, 60% NNS), and nasal irritation (87.5% NNS). The relative risk of the NRTs depends partly on contraindications (throat/stomach problems preclude gum use, sinus/allergies preclude NNS use, and throat problems preclude inhaler use).

Comparative preference rankings

Figure 1 shows *rankings* for several items among the three forms of NRTs. For *first choice*, gum was ranked highest for “ease of use” [$\chi^2(2)=6.13$, $p < 0.05$], “safest to use” [$\chi^2(2)=18.1$, $p < 0.001$], and “prefer in public” [$\chi^2(2)=9.13$, $p < 0.01$]. Overall rankings for “choice to help quit” are shown but were not significant.

For “comfortable with use >3 months” (not shown), 50% ranked inhaler last, 50% ranked NNS last vs 0% ranking gum last [$\chi^2(2)=8.00$, $p < 0.02$].

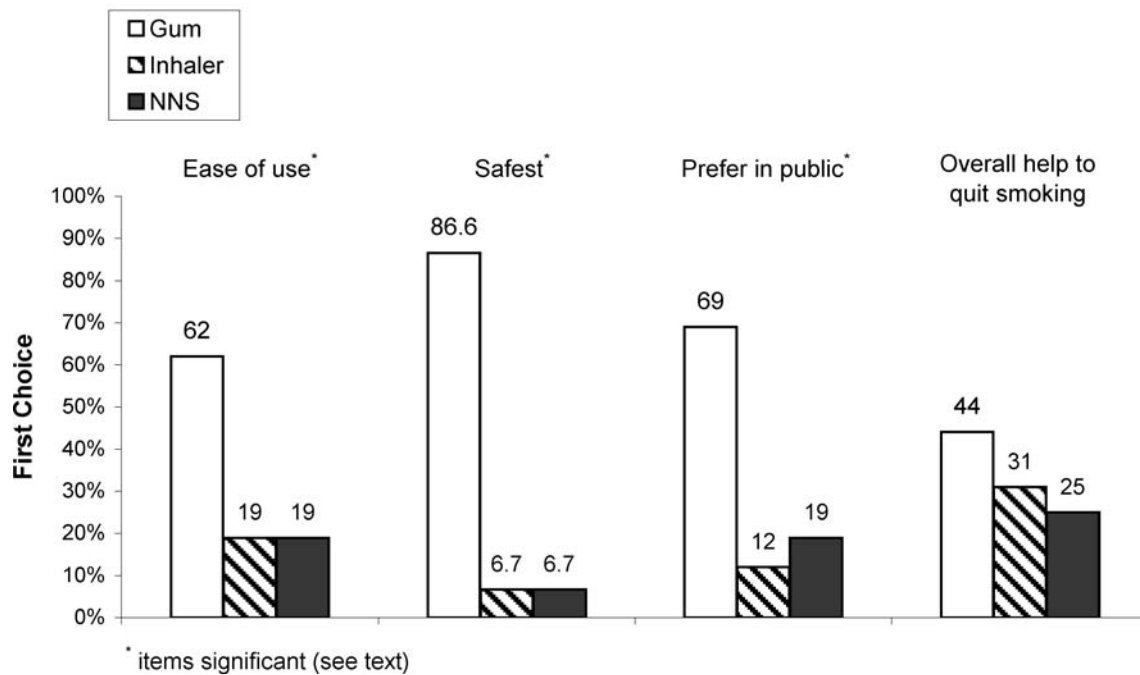


Fig. 1 Comparative rankings among NRTs

Refusal of second dose and preferences (n=9)

Of 16 subjects, 4 refused a second inhaler and 3 refused a second NNS (1 did not try 4-mg gum) due to dislike of drug or side effects. Overall, 6/16 said they would *never* use inhaler, 3 would *never* use NNS, and 1 would *never* use gum. For n=9, results were similar to n=16 for “safest to use,” “prefer in public,” and “use >3 months.” For rankings of last choice, three additional items differed with testing both doses (n=9): “relief of withdrawal,” “choose under stress,” and “choice to help quit” all showed inhaler ranked last (67%) vs NNS (33%) and gum (0%); for all items, $\chi^2(2)=6.00, p<0.05$.

Individual drug preference ratings (n=13)

Ratings show direct reactions to each variable (14 items) by drug (Table 3).

Differences were observed for “enough nicotine” [$F(3,36)=3.82, p<0.02$] and “uncomfortable using in public” [$F(3,36)=4.26, p<0.02$]. For dosage, a pairwise contrast (Bonferroni corrected) showed 4-mg gum rated higher than 2 mg on “enough nicotine” ($p<0.001$). For “In general, how satisfying was the (NRT),” 4 mg was rated more satisfying than 2 mg ($p<0.03$). For those who ranked gum first on “choice to help quit” (n=6), 4 mg rated higher than 2-mg gum on “excellent medication” ($t=2.91, p<$

Table 3 Ratings of treatments (n=13)

	Excellent medication overall	Effectiveness			Other positive elements			Nicotine levels			Negatives			
		Relief of withdrawal	Relief of urges	Not need cigs while using NRT	Liked sensory	Liked admin-istration	Liked how supplied	Ease of use	Enough nicotine	Too ^a much nicotine	Might ^a become dependent	Still ^b crave cigs	Side ^a effects bother-some	Uncom-fortable ^a using in public
INH	4.08	4.23	4.08	4.92	3.46	4.42	4.00	4.77	3.84	3.69	2.92	3.23	2.92	3.54
2 mg	4.15	4.38	4.08	4.38	3.54	4.12	4.31	5.31	3.54*	2.77	2.77	4.00	2.31	2.08
4 mg	4.77	5.00	5.00	4.85	3.54	4.92	4.62	5.62	5.15*	3.15	3.46	3.23	3.00	2.38
NNS	4.46	4.85	4.69	4.85	3.08	4.00	4.30	5.23	4.77	2.92	3.00	3.15	3.77	3.77
Tx Effect														
P values	ns	ns	ns	ns	ns	ns	ns	ns	.018	ns	ns	ns	ns	.011

Items in **bold** show significance of item; **bold** with asterisks indicate significance for the pairwise contrast

^aLow scores are desirable; all other items, high scores are desirable

^bAlso applies to effectiveness

0.04). Four-milligram gum rated highest on 8/14 items (one tie) but differences were not significant.

Expectations ($n=16$)

For changes in expectations with experience, attitudes toward gum improved for “ease of use” (63% better, 31% same, 6% worse), $\chi^2(2)=7.63$, $p<0.03$ and for “liking of drug” (69% better, 19% same, 13% worse), $\chi^2(2)=9.13$, $p<0.01$. The significance and direction of findings were similar with two people who had previously tried gum excluded ($n=14$). Trends were observed for inhaler and NNS: inhaler rated worse for “liking of drug” (50%) and NNS rated better on “liking of drug” (50%) and “help in quitting” (56%) but differences were not significant.

Discussion

Differences among three NRTs were observed for several rankings of use variables, for changes in expectations (gum), and between gum dosages. Craving/urges/missing cigarettes (and total withdrawal) were reduced with use of NRTs over time (a possible cumulative effect of the NRTs). The small sample size may have resulted in a number of false negatives (for any comparison as well as for tests between 2- and 4-mg dosages). Prior experience with gum ($n=2$) could have influenced some of the findings as people may come in to a trial with negative expectations due to any prior use (West et al. 2001; see below).

Use variables and preference

Gum was preferred over inhaler and NNS on “ease of use,” “safety,” and “prefer in public.” Expectations improved with gum experience for “liking” and “ease of use.” In West et al. (2001), subjects with prior exposure to gum rated it least preferred of four NRTs after viewing a video (no testing of drugs); however, liking for all NRTs increased when used to quit smoking. With a greater increase in liking for gum users, there were no differences in preference among NRTs by the end of 1 week. In the trial reported here, rankings and ratings were taken *after* guided use so prior experience may not have influenced those findings. For changes in expectations (likely to be sensitive to prior exposure), the results stayed the same when analyzed without the two subjects.

The 4-mg gum rated higher than 2 mg on “overall satisfaction,” “excellent medication,” and “enough nicotine.” As 4-mg gum always followed 2-mg gum, it is possible an order effect led to a superior rating of 4-mg gum, i.e., experience allowed a second dosage to be perceived as better *per se*. However, in prior testing using a partial latin square for order, 4-mg gum was preferred over 2 mg overall and on several variables (Schneider et al. 2004) and for action/strength/taste in a clinic (Schneider 1986). Dosage can be key as dislike of a lower dosage

(2 mg) may prevent a smoker from trying a higher, more acceptable dosage (4 mg) or vice versa. In practice, 2-mg gum is recommended for smokers using <25 cigarettes/day and 4 mg for ≥ 25 cigarettes/day. However, a higher dosage of NRT may be helpful for *any* smoker in the *initial* weaning from high concentrations of nicotine in smoke. Providing both dosages of gum at the start of cessation for *ad lib* use was very effective in a clinic setting (Schneider 1986).

Current formulations of gum allow choice of dosages and flavors, and a faster-acting gum is in development (Niaura et al. *in press*). We suggest the opportunity to “sample” gums and choose dosage can make this decades-old preparation more efficacious in practice.

The inhaler ranked lower than gum on “ease of use,” “safest,” and “prefer in public.” Four subjects refused a second dose and 6/16 would *never* use it. For subjects testing all doses ($n=9$), inhaler also ranked lowest for “choose under stress,” “relief of withdrawal,” and “choice to help quit.” In Fagerstrom et al. (1997), inhalers produced the least reduction in smoking of five NRTs. By contrast, in Schneider et al. (2004), inhalers were preferred with *ad lib*, 1/2-day use (puffing uncontrolled). The difference may lie in *ad lib* vs enforced, frequent puffing as the latter can be unpleasant. Inhalers may be better used in combination with patches (steady nicotine) where less puffing would be required (Bohadana et al. 2000). If high nicotine concentrations are essential to the user, the inhaler may be less effective as a stand-alone treatment.

For NNS, we expected to find acceptance with guided use similar to clinical trials where there are instructions and assurance about safety (Schneider et al. 1996). In clinical trials, NNS odds ratios for efficacy are similar to other NRTs (Silagy et al. 2004). Moreover, in a craving/withdrawal study, NNS (the fastest-acting NRT) provided better, immediate relief at 5–10 min than 4-mg gum (Hurt et al. 1998). Still, safety concerns, side effects, or dislike of a nasal system may trump any advantages of NNS even with guided use. It is relevant that in NNS clinical trials subjects self-select for use of a nasally administered drug. With that in mind and with NNS viable in clinical testing, one aim would be to identify smokers who do not mind or fear nasal administration for success with this preparation.

Note: since this trial, nicotine lozenges (2 and 4 mg) have become available with side effects similar to gum (Shiffman et al. 2002). While the lozenges bypass chewing problems, there are dislikes with dissolve time and taste (Schneider, unpublished data); lozenges will need to be included in preference testing along with newer systems.

Preferences and “sampling” among treatments

There are few trials of NRT choice by route. Leischow et al. (1997) noted that patches were preferred to 2-mg gum in a withdrawal study (2-day crossover), but that may have been a dose effect as few gums were used. Fagerstrom et al. (1997) tested five NRTs (2-week crossover) and found

greater reduction in cigarette use with free choice vs assigned drug. West et al. (2001) showed video descriptions of four NRTs before randomizing subjects to 15-week treatment. They found differences in expectations based on descriptions but no differences in outcome for choice vs assigned NRT. West et al. (2001) acknowledge that their findings may be due to sign-up (knowing which drugs will be used) and participating in a trial (subjects “came to like” assigned treatment) and not generalizable to over-the-counter experience. Changes in expectations for gum with *actual* use in this trial and for NRTs in Schneider et al. (2004) suggest descriptions alone may be insufficient for anticipating reactions to an NRT in “real world” settings.

What can be done? Why not allow smokers, in practice, to test several NRTs so compliance is not undermined by improper use, unnecessary fears, or simple dislike of route. *Sampling* NRTs (in physicians’ offices, in clinics) could solve a number of problems.

Developing better NRTs, encouraging consistent and sufficient dosing, and combining treatments (e.g., patch for steady nicotine + acute NRT *ad lib*) could also improve outcome. While all NRTs are considered first line therapies (Fiore et al. 2000; Sachs 2005), use of a *preferred* single NRT or combination patch + *preferred* acute NRT may be better “first line” approaches. Identifying preferences among the acute NRTs would probably benefit most current techniques used in this area (single treatment, combination treatment, harm reduction, “rescue” use for relapse prevention).

In conclusion, smokers can have reactions to an NRT that leads to instant rejection of the drug. Efficacy with acute NRTs may be enhanced with better awareness of those reactions and with sampling for choice of treatment. Though trials comparing multiple NRTs are difficult to do, more research on preferences and tailoring by choice is needed.

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References

- Benowitz NL, Jacob P II, Savanapridi C (1987) Determinants of nicotine intake while chewing nicotine polacrilex gum. *Clin Pharmacol Ther* 41:467–473
- Bohadana A, Nilsson F, Rasmussen T et al (2000) Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind controlled trial. *Arch Intern Med* 160(20):3128–3134
- Fagerstrom KO, Tejdning R, Westin A, Lunell E (1997) Aiding reduction of smoking with nicotine replacement medications: hope for the recalcitrant smoker? *Tob Control* 6(4):311–316
- Fiore MC, Bailey WC, Cohen SJ et al (2000) Treating tobacco use and dependence (clinical practice guideline). U.S. Department of Health and Human Services, Public Health Service, Rockville, MD
- Foulds J, Burke M, Steinberg M et al (2004) Advances in pharmacotherapy for tobacco dependence. *Expert Opin Emerg Drugs* 9(1):39–53
- Heatherton TF, Koslowski LT, Frecker RC, Fagerstrom KO (1991) The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict* 86:1119–1127
- Hughes JR, Shiffman S, Callas P, Zhang J (2003) A meta-analysis of the efficacy of over-the-counter nicotine replacement. *Tob Control* 12:21–27
- Hurt RD, Offord KP, Croghan IT et al (1998) Temporal effects of nicotine nasal spray and gum on nicotine withdrawal symptoms. *Psychopharmacology (Berl)* 140(1):98–104
- Leischow SJ, Valente SN, Hill AL et al (1997) Effects of nicotine dose and administration method on withdrawal symptoms and side effects during short-term smoking abstinence. *Exp Clin Psychopharmacol* 5(1):54–64
- Niaura R, Sayette M, Shiffman S et al (in press) Comparative efficacy of rapid-release nicotine gum versus nicotine polacrilex gum in relieving smoking cue-provoked craving. *Addiction*
- Sachs DPL (2005) California Thoracic Society. Position paper. Medical management for Tobacco Dependence. <http://www.thoracic.org/chapters/california/publications.asp>
- Schneider NG (1986) Use of 2 mg and 4 mg nicotine gum in an individual treatment trial. In: Ockene JK (ed) *Pharmacologic treatment of tobacco dependence: proceedings of the World Congress, 4–5 November 1985*. Institute for the Study of Smoking Behavior and Policy, Cambridge, MA, pp 233–248
- Schneider NG, Lunell E, Olmstead RE, Fagerstrom KO (1996) Clinical pharmacokinetics of nasal nicotine delivery: a review and comparison to other nicotine systems. *Clin Pharmacokinet* 31(1):65–80
- Schneider NG, Olmstead RE, Franzone MA et al (2001) The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. *Clin Pharmacokinet* 40(9):661–684
- Schneider NG, Olmstead RE, Nides M et al (2004) Comparative testing of 5 nicotine systems: initial use and preferences. *Am J Health Behav* 28(1):72–86
- Shiffman S, Dresler CM, Hajek P et al (2002) Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 162:1267–1276
- Shiffman S, Fant RV, Gitchell JG et al (2003) Nicotine delivery systems: how far has technology come? *Am J Drug Deliv* 1(2):113–124
- Silagy C, Lancaster T, Stead L et al (2004) Nicotine replacement therapy for smoking cessation. The cochrane database of systematic reviews 2004, Issue 3. Art. No.: CD000146.pub2. DOI: 10.1002/14651858.CD000146.pub2. Cited 19 July 2004
- West R, Hajek P, Nilsson F et al (2001) Individual differences in preference for and responses to four nicotine replacement products. *Psychopharmacology* 153:225–230