

Real-world efficacy of prescription and over-the-counter nicotine replacement therapy

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ABSTRACT

Aims To assess smoking cessation rates achieved with nicotine gum and patch in simulated over-the-counter (OTC) and actual prescription (Rx) settings.

Design Separate open-label studies with gum and patch in OTC and Rx settings.

Participants There were multiple samples: OTC gum: 2981 smokers; OTC patch: 2367; Rx gum: 324; Rx patch: 669.

Interventions All smokers received active nicotine replacement. In the OTC setting, smokers self-selected doses of nicotine gum (2 or 4 mg Nicorette[®]) or patch (21, 14 or 7 mg NicoDerm[®] CQ). No intervention was provided. In the Rx setting, smokers were prescribed gum or patch by their physician.

Measurements Biochemically verified continuous smoking abstinence was assessed at 6 weeks (28-day abstinence) and 6 months.

Findings OTC success rates were consistently higher than Rx rates: differences were significant at 6 weeks for both patch [OR = 1.45 (1.05–1.98)] and gum [OR = 2.92 (1.58–5.40)], and remained significant at 6 months for patch [OR = 3.63; (1.74–7.61)] but not gum [OR = 1.37; (0.73–2.58)]. Among OTC gum users, 16.1% were abstinent at 6 weeks and 8.4% at 6 months. For Rx gum users, abstinence rates were 7.7% at 6 weeks and 7.7% at 6 months. With OTC patch, 19.0% were abstinent at 6 weeks and 9.2% at 6 months. With Rx patch, abstinence rates were 16.0% at 6 weeks and 3.0% at 6 months.

Conclusions Smoking cessation rates achieved with nicotine gum and patch under OTC conditions were as good as those under real-world prescribing conditions.

KEYWORDS Cigarette smoking, nicotine gum, nicotine patch, nicotine replacement, over-the-counter, prescription, smoking cessation.

INTRODUCTION

Smoking is the greatest source of preventable morbidity and mortality, making smoking cessation a public health priority (US Department of Health & Human Services 2000). Accordingly, it is essential to promote smoking cessation. However, nicotine dependence makes quitting smoking difficult, and most quit attempts fail; without treatment, 97% of quit attempts end in failure (Garvey

et al. 1992). Pharmacological treatment improves success, as does behavioral treatment (Fiore *et al.* 2000). The most-studied and most-used medication is nicotine replacement therapy (NRT). Its effectiveness has been documented in numerous clinical trials (Silagy *et al.* 2000).

The public health impact of smoking cessation treatments—i.e. the number of smokers converted to non-smoking—depends on their effectiveness in actual use

and their utilization (Shiffman *et al.* 1997). Utilization of NRT is heavily influenced by its regulatory status, which may impose restrictions on access (Shiffman & Gitchell 2000). Until 1996, nicotine gum and patches were restricted for sale only by prescription (Rx) in the US. In 1996, gum and patch were approved for over-the-counter (OTC) sale (corresponding to 'General Sales' status elsewhere). As a result, utilization of gum and patch increased by over 150% (Shiffman *et al.* 1997; Burton, Gitchell & Shiffman 2000), probably resulting in the saving of approximately 3000 lives per year (Lawrence *et al.* 1998). Thus, OTC status has enhanced NRT utilization.

At the same time, there have been questions about the effectiveness of NRT under OTC conditions (Leischow *et al.* 1999; Walsh & Penman 2000). Most clinical trials of NRT evaluated efficacy in conjunction with substantial behavioral intervention (Lancaster *et al.* 2000; Silagy *et al.* 2000). Although meta-analyses have concluded that the effectiveness of NRT is independent of concomitant behavioral treatment (Hughes 1995; Silagy *et al.* 2000), most clinical trials provided some behavioral counseling, as well as instruction in NRT use, repeated medical visits, abstinence inquiries, carbon monoxide (CO) testing and/or group meetings. Thus, this literature has not evaluated NRT under OTC conditions.

Recent trials evaluating the efficacy of nicotine patches under OTC conditions (Davidson *et al.* 1998; Hays *et al.* 1999) concluded that they were effective [e.g. Shiffman *et al.* (2002) demonstrated a substantial effect of active patch versus placebo patch with no contact or intervention beyond the minimum necessary to enroll and assess participants].

Just as it does not capture OTC usage, the clinical trials literature does not represent the conditions of real-world prescribing. Clinical trials provide careful instruction, behavioral counseling and multiple visits, which are rarely provided in practice (Kottke *et al.* 1988). Thus, to assess the impact of switching NRT products from Rx to OTC status, one would need to assess the efficacy of NRT under real-world prescribing conditions as well as under OTC conditions. The US Food and Drug Administration (FDA) undertook an assessment of whether NRT efficacy under OTC conditions was comparable to that under real-world Rx conditions.

The objective of the present studies was to assess NRT efficacy under OTC conditions and to compare it to efficacy under real-world prescription practices. Assessing real-world outcomes is a substantial challenge. The traditional clinical trials approach, in which patients and physicians are prospectively enrolled in a study (Kottke *et al.* 1989), does not address real-world practices credibly. Physicians participating in such a study would be

expected to be on their best behavior and might not be representative of prescribing physicians. Accordingly, to assess real-world practice, we studied NRT use naturalistically in actual clinical practice, assessing patients who had already been prescribed NRT by their provider in the course of their normal care. Neither physicians nor patients knew in advance that smoking cessation outcomes would be evaluated.

To evaluate NRT outcomes in the OTC setting, the present studies (conducted prior to the OTC switch) simulated OTC usage in open-label usage trials. These trials allowed smokers to purchase active NRT and assessed outcomes as they quit on their own, with no instruction or intervention beyond the package label, and no visits beyond those required for enrollment and outcomes assessment.

We report the efficacy of nicotine gum and patch under real-world prescribing and simulated OTC conditions. Given the different demands of assessing the two dispensing conditions, the comparison groups were not randomized, but were recruited and assessed separately and differently.

METHODS

Overview

Parallel, independent studies were undertaken to assess usage and outcomes of nicotine gum (Nicorette®) and a nicotine patch (NicoDerm® CQ) in simulated OTC and real-world Rx settings. The gum and patch trials were completely independent, but very similar in design. We report the common methods, noting differences.

Simulated OTC usage was assessed by enrolling smokers in open-label trials that allowed them to purchase and use patch or gum with no provider instruction or intervention, while assessing smoking status at 6 weeks and 6 months. Real-world Rx abstinence rates were assessed by recruiting, through pharmacies, smokers who had already filled prescriptions for nicotine gum or nicotine patch, and assessing their current smoking status. Smoking status was assessed in people who had filled NRT prescriptions either 6 weeks or 6 months earlier.

Procedures

Simulated OTC studies

Two separate multi-center, open-label trials assessed OTC outcomes for nicotine gum (at 6 weeks, 12 weeks and 6 months) and nicotine patch (at 6 weeks, 10 weeks and 6 months). Callers responding to advertising were directed

to study sites. To enhance the OTC-ness of the study, the study used sites, such as pharmacies or mall storefronts, not usually associated with clinical research. At the site, study candidates completed screening and baseline questionnaires. Smokers who chose to enroll, met the inclusion/exclusion criteria, and signed an informed consent were considered study participants. The studies were approved by appropriate ethics committees.

Potential participants were presented with a simulated NRT retail product display. The labels showed product information, dosage, usage instructions and contraindications. In the nicotine gum study, both 2 mg and 4 mg doses were displayed. The 2 mg was labeled for smokers of ≤ 24 cigarettes a day; 4 mg was for those smoking >24 cigarettes a day. In the patch study, three doses were displayed: 21 mg, 14 mg and 7 mg. The labels listed contraindications such as heart disease, diabetes mellitus, active stomach ulcer, current use of asthma or depression medication, potential pregnancy and conditions relevant to the specific NRT product (e.g. patch: skin disease, rashes or allergy to adhesives; gum: temporal-mandibular joint disease).

To simulate an OTC purchase decision, potential participants reviewed the product labels and decided whether to purchase the product (and thus participate in the study) and what dose and quantity to purchase. They were permitted to return as needed to purchase additional product during the treatment period (12 weeks for gum and 10 weeks for patch). Gum was priced at \$35 for 96 pieces, and patches were priced at \$42 for 14 patches (purchase costs were later refunded, but participants were not aware of this at the time of purchase). Participants were given a written product label and directions, a user's guide and an audiotape with quitting tips. The label and user's guide described how to use the product. No other intervention was delivered. Site personnel provided no product instruction and no support or instruction in smoking cessation.

Follow-up visits were scheduled 6 weeks after enrollment and at the end of treatment (12 weeks for gum and 10 weeks for patch). A week before the scheduled visits, participants were mailed a reminder, noting that they would be reimbursed for visit-related travel expenses. At the visits, participants reported smoking status; those who claimed abstinence were tested using exhaled CO. Participants also reported their product use and occurrence of adverse experiences (AEs). In the patch study only, participants who reported AEs were asked how they managed the AEs, and physician investigators subsequently judged whether participants' self-management of each AE was medically appropriate (e.g. had they sought care when needed or stopped using NRT if appropriate). Participants who did not appear for the follow-up

visits were contacted and invited to the study site. No other contact or intervention was implemented.

Only participants who were abstinent (as verified by $CO \leq 10$ p.p.m.) at the end-of-treatment visit were asked to consent to follow-up at 6 months. In the nicotine gum study, the 6-month visit had not been anticipated at enrollment, so a new consent and enrollment were necessary, and 226 eligible (abstinent) participants declined to continue. They were treated as failures at 6 months. At 6 months, participants were interviewed by telephone regarding smoking abstinence; abstinence claims were tested at the study site using exhaled CO. Those who refused biochemical verification or failed to appear for verification were considered smokers.

Real-world Rx studies

The Rx studies aimed to assess cessation rates 6 weeks and 6 months after use of nicotine gum or patch prescribed by a physician in the course of normal health-care interactions. We studied smokers who had filled new prescriptions (refill prescriptions were not considered) for patch or gum either 6 weeks or 6 months earlier. Four separate samples were collected, for two time frames (6 weeks and 6 months) and two products (gum and patch). Patients were not followed prospectively, and the studies were not longitudinal; rather, point estimates of abstinence rates at each time were obtained from independent samples who had filled prescriptions 6 weeks and 6 months earlier, respectively.

Prescription NRT users were identified through prescription records of one of the largest national mass merchandising chains with pharmacies in the United States. This chain included over 2000 stores with locations in each of the 50 states. People who had filled new prescriptions for NRT either 6 weeks or 6 months prior were mailed a letter from the pharmacy that asked them to call a toll-free number to answer questions about pharmacy services in return for a \$20 payment. Patients were not identified to the research team; the mailing was handled by the pharmacy. The letter made no mention of smoking or smoking cessation. Candidates who called were interviewed about pharmacy services and screened to exclude those who were not primarily cigarette smokers, used other smoking cessation medications, denied having filled a prescription, or refused participation. Participants reported their current and recent smoking status, after being informed that abstinence would be biochemically verified using CO measurement (Jones & Sigall 1971).

Respondents were considered to be abstinent if they reported abstaining for the preceding 28 days at 6 weeks or for the past 6 months at the 6-month visit. Those who

reported abstinence were offered \$50 to provide a breath sample for biochemical verification, either by visiting a site in their area or through a home visit by study staff. Participants were considered abstinent only if they reported abstinence and had expired CO \leq 10 p.p.m. Those who did not appear for biochemical verification were considered to be smoking.

Participants

Simulated OTC studies

Smokers wishing to quit smoking were recruited via media advertisements into non-clinical sites within the United States. Volunteers were not offered payment. To qualify, smokers had to meet the following criteria: \geq 18 years of age; primary cigarette smokers; not involved in a study of NRT within the past year or any study within the previous 30 days; not pregnant or nursing; and provided written informed consent. Exclusionary criteria included a myocardial infarction within 3 months or uncontrolled cardiac arrhythmia. The product label cautioned against product use in cases of heart disease; high blood pressure; diabetes mellitus; active stomach ulcer; current use of asthma or depression medication; potential pregnancy; or skin disease, rashes, or allergy to adhesives (nicotine patch only).

Real-world Rx studies

There were four samples of Rx users: two for nicotine gum (followed at 6 weeks and 6 months) and two for nicotine patch (followed at 6 weeks and 6 months). To qualify, smokers had to meet the following criteria: \geq 18 years of age; a cigarette smoker (prior to NRT use); called within the 6-week/6 month interview window; and acknowledge receipt of the NRT prescription.

Nicotine replacement therapy

Nicotine patch

The Alza patch (NicoDerm[®] CQ in the United States, Nicabate[®] in Australia and New Zealand and NiQuitin[®] CQ in Brazil, Mexico and Europe; marketed by GlaxoSmithKline) was studied. In the Rx condition, physicians were free to prescribe as they deemed appropriate. The Rx labeling recommended daily 24-hour application of the 21 mg patch for 6 weeks, 14 mg patch for the following 2 weeks and 7 mg patch for the last 2 weeks. If the smoker had cardiovascular disease, weighed less than 100 pounds or smoked less than 10 cigarettes per day, the smoker was to start with the 14 mg patch for 6 weeks, followed by 7 mg for a final 2–4 weeks. In the OTC trial, the label prescribed 21 mg patches for the first 6 weeks, 14 mg for the following

2 weeks and 7 mg for the final 2 weeks. The same three-step program was indicated for all cigarette smokers. Subsequent to OTC approval of the nicotine patch, the indicated treatment for smokers of 10 cigarettes or less per day was reduced to a two-step program beginning with the 14 mg per day dose. OTC participants could apply the patch for either 24 or 16 hours per day.

Nicotine gum

The Rx labeling for nicotine gum recommended dose selection based on tobacco dependence: heavy smokers ($>$ 24 cigarettes per day) or those who were tobacco dependent [Fagerström Tolerance Questionnaire scores \geq 7 (Fagerström 1978)] were to use 4 mg gum; others were to use 2 mg gum. The label recommended 9–12 pieces of gum daily for 12 weeks, with tapering beginning after 12 weeks and completing by 6 months. The OTC label recommended dose selection based on smoking rate: 4 mg for heavy smokers ($>$ 24 cigarettes per day) and 2 mg for all others. After reviewing these instructions, subjects self-selected either the 2 mg or 4 mg dose. The label also described a schedule for gum use: one piece per 1–2 hours during the first 6 weeks, one piece per 2–4 hours during the following 3 weeks, and one piece per 4–8 hours during the final 3 weeks.

Outcome definitions

Smoking status

Smoking status was determined at the 6-week and 6-month follow-up visits, using criteria established by the FDA. Participants were considered abstinent if they reported smoking no cigarettes during the last 28 days at 6 weeks or during the last 26 weeks at 6 months, respectively, and had expired CO \leq 10 p.p.m. Participants who did not complete CO monitoring were counted as smokers. All enrolled participants were included in analyses of abstinence ('intent-to-treat'); non-respondents were considered treatment failures.

Safety

Participants in the simulated OTC studies were asked about the occurrence of any adverse experiences. Data on AEs deemed by the medical investigator to have any potential relation to NRT use (definitely, probably or possibly related) were tabulated.

Data analysis

Analyses were conducted separately for the gum and patch studies. OTC and Rx samples were compared on baseline characteristic using one-way analysis of

variance for continuous variables and χ^2 analyses for categorical variables. Efficacy in the two groups was compared using χ^2 analysis. Odds ratios (ORs) and 95% confidence intervals were calculated using the Cochran–Mantel–Haenszel procedure. Logistic regression analyses and ORs were adjusted for demographic and smoking variables. Two-tailed tests were used at ≤ 0.05 , using SAS version 8.0 for Windows.

RESULTS

Participant disposition

Table 1 shows participant characteristics in the OTC and Rx nicotine patch and gum samples. The two OTC studies were similar in reasons for disqualification and in 6-week and 6-month follow-up rates (see Table 2). Response rates to the recruitment mailing and enrollment rates were consistent among samples (see Table 3). As expected, because there were differences in inclusion/exclusion criteria (see above), some differences are apparent between rates and reasons for disqualification.

Efficacy analyses

Nicotine patch

Under simulated OTC conditions, smokers using nicotine patch achieved abstinence rates of 19.0% at 6 weeks and 9.2% at 6 months (Table 4). Real-world Rx users achieved abstinence rates of 16.0% at 6 weeks and 3.0% at 6 months. The OTC abstinence rates were higher, but not significantly so, at 6 weeks. At 6 months the OTC rates were significantly higher than the Rx rates. To control for the differences among the non-randomized study populations, we analyzed abstinence rates while adjusting for individual differences among study participants in age, sex, education, income, race, cigarettes per day, years smoking, previous quit attempt (yes/no), number of previous quit attempts and reasons for quitting. With these adjustments, the ORs favoring OTC increased, and OTC success rates were significantly higher than Rx rates at both 6 weeks and 6 months.

Nicotine gum

Under simulated OTC conditions, smokers using nicotine gum achieved abstinence rates of 16.1% at 6 weeks and 8.4% at 6 months (Table 4). Real-world Rx users achieved abstinence rates of 7.7% at 6 weeks and 7.7% at 6 months. The OTC abstinence rates were significantly higher at 6 weeks and trended higher at 6 months. To control for the differences among the non-randomized

study populations, we analyzed abstinence outcomes while adjusting for individual differences among study participants in age, sex, education, income, race, cigarettes per day, years smoking, previous quit attempt (yes/no), number of previous quit attempts and reasons for quitting. With these adjustments, the effect in favor of OTC increased; OTC success rates were significantly higher than Rx rates at 6 weeks and higher, but not statistically so, at 6 months.

Compliance and patterns of use

Nicotine patch

In the OTC study, 92.9% of participants reported using patches during weeks 1 and 2. They reported using patches on 10.9 (SD = 3.7) of the initial 14 days (i.e. 77.9% of days). As might be expected in a relapsing population, patch use declined subsequently (76.6% for weeks 3–4 and 63.2% for weeks 5–6). At 6 weeks, 45.6% of users reported electing to use the patch for 24 hours, and 40.1% reported 16-hour use; the groups did not differ in outcome ($\chi^2(1) = 1.01$; $p = 0.315$).

In the real-world Rx sample, 65.9% of participants reported using the prescribed patch. Those who did were more likely to be abstinent (6-week sample: 19.0% versus 9.1%; $\chi^2(1) = 6.16$; $p = 0.013$ and 6-month sample: 4.3% versus 0.9%; $\chi^2(1) = 2.56$; $p = 0.109$). Most participants said they wore the patch for 24 hours (72.0%); 19.5% reportedly wore it for 16 hours, and the rest indicated mixed usage. This had no effect on abstinence ($\chi^2(1) = 0.028$; $p = 0.866$).

As there were differences in use of the patch between the Rx and OTC studies, we compared outcomes among those who reported having actually used the patch. The results of this analysis mirror those seen in the intent-to-treat (ITT) sample, with the OTC sample providing consistently higher abstinence rates (22.8% versus 19.0%, OR = 1.26, 95% CI = 0.92–1.73, $\chi^2(1) = 2.01$; $p = 0.156$ at 6 weeks and 10.9% versus 4.3%, OR = 2.72, 95% CI = 1.26–5.87, $\chi^2(1) = 7.00$; $p = 0.008$ at 6 months). As in the ITT sample, the differences were maintained when we adjusted the comparison for participants' characteristics.

Nicotine gum

At the 6-week visit, 98.3% of participants in the OTC study reported using nicotine gum during the study. Some (19.2%) reported using the directed nine or more pieces per day, and this subset had significantly greater abstinence rates at 6 weeks (29.0% versus 18.4%; $\chi^2(1) = 25.58$; $p < 0.001$) than those using fewer gums per day. Both abstinence rates are elevated because this

Table 1 Comparison of baseline characteristics and smoking history between the OTC and Rx study participants for the nicotine patch and nicotine gum.

Item	Nicotine patch			Nicotine gum			OTC versus Rx comparison
	OTC (n = 2367)	Rx 6 weeks (n = 400)	Rx 6 months (n = 269)	OTC (n = 2981)	Rx 6 weeks (n = 169)	Rx 6 months (n = 155)	
Demographic characteristics							
Age (years)	43.2 ± 11.7	48.0 ± 13.3	48.0 ± 12.9	44.0 ± 11.9	49.3 ± 13.6	48.0 ± 12.2	F = 43.54; p < 0.001
Female (%)	56.4	62.5	62.5	56.7	72.2	72.9	$\chi^2 = 30.00$; p < 0.001
Caucasian (%)	89.6	94.2	97.0	89.7	95.3	92.9	$\chi^2 = 6.53$; p = 0.011
Any college education (%)	69.2	51.0	50.2	70.3	61.0	55.5	$\chi^2 = 19.74$; p < 0.001
Income > \$25 000 (%)	74.6	72.8	62.3	73.0	58.7	70.7	$\chi^2 = 10.04$; p = 0.001
Reasons for quitting							
Health (%)	96.2	93.2	94.0	89.6	95.9	93.5	$\chi^2 = 8.71$; p = 0.003
Family (%)	56.4	81.5	72.5	44.9	82.7	78.7	$\chi^2 = 150.7$; p < 0.001
Job (%)	20.4	23.2	24.2	18.4	24.3	23.2	$\chi^2 = 5.58$; p = 0.018
Cost (%)	53.3	61.2	62.1	42.1	68.6	67.1	$\chi^2 = 78.42$; p < 0.001
Laws (%)	20.5	30.0	31.3	14.1	26.0	26.4	$\chi^2 = 33.03$; p < 0.001
Smoking history							
Cigarettes per day	27.1 ± 12.3	25.4 ± 13.8	25.9 ± 13.4	26.5 ± 11.4	21.8 ± 13.5	22.1 ± 11.7	F = 45.77; p < 0.001
Years of smoking	23.8 ± 11.5	26.8 ± 12.7	26.1 ± 13.0	23.4 ± 11.8	27.6 ± 13.8	25.6 ± 11.7	F = 21.93; p < 0.001
Previous cessation experience							
Previous quit attempt (yes/no) (%)	92.1	84.5	83.3	89.2	91.1	87.1	$\chi^2 < 0.01$; p = 0.984
Number of life-time quit attempts	4.9 ± 9.5	4.5 ± 8.9	5.5 ± 11.2	5.6 ± 13.4	5.4 ± 7.9	4.1 ± 5.1	F = 1.08; p = 0.299

Entries are percentages or means with associated standard deviations. Comparisons of OTC study versus aggregated Rx studies are χ^2 tests for dichotomous variables and F-tests for continuous variables (with associated p-value).

Table 2 Participant disposition for the simulated OTC nicotine patch and gum studies.

Disposition	Nicotine patch (n = 2367)	Nicotine gum (n = 2981)
Initially screened	2875	3631
Not enrolled	508 (17.7%)	650 (17.9%)
Declined use of NRT	229 (45.1%)	299 (46.0%)
Declined enrollment	111 (21.8%)	260 (40.0%)
Did not meet inclusion criteria ¹	168 (33.1%)	91 (14.0%)
Enrolled	2367 (82.3%)	2981 (82.1%)
Attended the 6-week visit	1801 (76.1%)	2421 (81.2%)
Eligible for the 6-month visit ²	571	1005
Attended the 6-month visit	402 (70.4%)	759 (75.5%) ³

Entries are numbers or percentage of larger denominator. ¹Includes those who met at least one exclusionary criterion or were not enrolled because of a listed high-risk medical condition. ²Those who were not smoking at the end of treatment were followed at the 6-month visit. ³Excludes those who refused to re-enroll (n = 226), and therefore were never asked to return for 6-month follow-up. These participants were treated as failures at 6 months.

Table 3 Participant disposition for the real-world Rx nicotine patch and nicotine gum studies.

Disposition	Nicotine patch		Nicotine gum	
	6 weeks (n = 400)	6 months (n = 269)	6 weeks (n = 169)	6 months (n = 155)
Filled prescription for NRT/sent letter	1822	1309	812	844
Responded to letter	678 (37.2%)	428 (32.7%)	293 (36.1%)	269 (31.9%)
Not screened—called after sample size met	178	91	37	6
Screened for enrollment	500	337	256	263
Not enrolled	100 (20.0%)	68 (20.2%)	87 (34.0%)	108 (41.1%)
Used NRT within previous 6 months	57 (57.0%)	44 (64.7%)	58 (66.7%)	76 (70.4%)
Not primarily a cigarette smoker	15 (15.0%)	4 (5.9%)	11 (12.6%)	5 (4.6%)
Used other cessation product	16 (16.0%)	12 (17.6%)	12 (13.8%)	22 (20.4%)
Claimed no NRT prescription use	9 (9.0%)	7 (10.3%)	5 (5.7%)	3 (2.8%)
Refused consent	3 (3.0%)	1 (1.5%)	1 (1.1%)	2 (1.8%)
Enrolled	400 (80.0%)	269 (78.8%)	169 (66.0%)	155 (58.9%)

Entries are numbers or percentage of larger denominator.

question was only asked of those who appeared for the 6-week visit; thus, many smokers otherwise deemed treatment failures are excluded.

In the Rx study, 65.4% reported having used the gum. Abstinence rates trended higher for those who used gum, but not significantly so (6-week sample: 8.5% versus 5.8%; $\chi^2(1) = 0.39$; $p = 0.532$ and 6-month sample: 9.5% versus 5.0%; $\chi^2(1) = 1.03$; $p = 0.310$). No data were available on amount of use.

When we compared OTC and Rx outcomes among those in both groups who reported using the gum, the results mirrored those of the ITT analysis (20.2% versus 8.5%; OR = 2.70; 95% CI = 1.40–5.20; $\chi^2(1) = 9.54$; $p = 0.002$ at 6 weeks and 10.6% versus 9.5%; OR = 1.13; 95% CI = 0.56–2.27; $\chi^2(1) = 0.12$; $p = 0.730$ at 6 months). As in the ITT sample, the differences were

maintained when we adjusted the comparison for participants' characteristics.

Dose selection

Nicotine patch

Both the Rx and OTC indications instructed users to start on the 21 mg dose, stepping down later to the 14 mg and 7 mg dose patches. In the Rx samples (combining the 6-week and 6-month cohort), 23.7% of those who used patches started on one of the lower doses (20.4% on 14 mg, 3.3% on 7 mg). In the OTC sample, 11.0% of those who used patches started on one of the lower doses (9.6% on 14 mg, 1.4% on 7 mg). To control for patch dose, we compared OTC and Rx quit rates among smokers

Table 4 Comparison of abstinence rates between the OTC and Rx studies for the nicotine patch and nicotine gum.

CO-verified abstinence rates	Nicotine patch				Nicotine gum			
	OTC	Rx 6 weeks	Rx 6 months	Adjusted OR ¹ (95% CI)	OTC	Rx 6 weeks	Rx 6 months	Adjusted OR ¹ (95% CI)
All participants (intent-to-treat)	(n = 2367)	(n = 400)	(n = 269)		(n = 2981)	(n = 169)	(n = 155)	
6 weeks	19.01%	16.00%	—	1.23 (0.92–1.64)	16.14%	7.69%	—	2.31 (1.30–4.10)*
6 months	9.17%	—	2.97%	3.29 (1.61–6.75)	8.45% ²	—	7.74%	1.10 (0.60–2.01)
Used appropriate starting dose	Smoked ≥ 10 cigarettes/day started on 21 mg patch				Smoked ≤ 24 cigarettes/day, started on 2 mg gum			
6 weeks	(n = 1725)	(n = 187)	(n = 98)	1.44 (0.95–2.19)	(n = 812)	(n = 63)	(n = 62)	3.48 (1.38–8.79)*
6 months	22.09%	18.72%	5.10%	2.19 (0.86–5.54)	21.92%	7.46%	—	1.69 (0.66–4.32)
	10.43%	—	—		12.93% ²	—	8.06%	2.47 (0.91–6.71)

OR = odds ratio; 95% CI = 95% confidence interval of odds ratio. ¹ORs adjusted for baseline demographic characteristics (i.e. age, sex, education, income, and race) and smoking history of participants (i.e., cigarettes per day, years of smoking, previous quit attempt (yes/no), number of previous quit attempts, and reasons for quitting). ²This was computed counting as failures 226 abstinent participants who at 12 weeks were abstinent and eligible for 6-month follow-up but declined to enroll in the follow-up study. The success rates would be higher if these were excluded from the denominator (effectively assuming that their outcomes were similar to those who did enroll).

*Significant at $p < 0.05$.

who smoked at least 10 cigarettes per day and who used the 21 mg dose. The relationship of dose to outcome was not analyzed, as the dose seems to have been selected systematically to match the smoker's needs. The results were consistent with those reported for the whole sample (Table 4)—OTC users demonstrated higher 6-week and 6-month abstinence rates consistently, trending towards significance.

Nicotine gum

Both the 2 mg and 4 mg doses were available in the Rx and OTC contexts. In actual Rx practice, 4 mg gum was rarely used; only 5.5% of respondents reported using the 4 mg dose. By the smoking rate criterion alone, at least 32.5% were indicated for the 4 mg dose. In the OTC sample, the majority (60.2%) selected the 4 mg dose. In the OTC trial, 84.3% of smokers selected a dose as dictated by the label. Thus, significantly more OTC subjects used the 4 mg gum ($\chi^2(1) = 223.60$; $p < 0.001$).

To analyze outcomes controlling for gum dose, we compared Rx and OTC outcomes among those who smoked less than 25 cigarettes per day and who started on the 2 mg gum (i.e. those who qualified for the 2 mg dose under both Rx and OTC labeling). Within this group, outcomes paralleled those seen in the full sample. OTC abstinence rates were consistently higher than Rx rates, and were significantly higher at 6 weeks (see Table 4). The number of Rx participants ($n = 5$) who were properly assigned to the 4 mg dose was too low to allow for reliable estimation or comparison of quit rates.

Safety

Nicotine patch

Among OTC participants who used nicotine patch, 22.8% reported at least one AE possibly related to nicotine patch usage. The most common ($\geq 2\%$ prevalence) AEs associated with nicotine patch use were application site reactions (3.6%), abnormal dreams (3.3%), headaches (3.2%), rash (3.2%), insomnia (2.5%), itchiness (2.4%) and nausea (2.0%). Based on the medical investigators' judgement, 96.6% (95% CI = 95.6–97.6%) of AEs were handled appropriately by smokers.

Nicotine gum

Among OTC nicotine gum users, 50.2% reported at least one AE possibly related to nicotine gum. The most common AEs ($\geq 2\%$ prevalence) were headache (13.3%), nausea (10.7%), heartburn (9.3%), hiccups (8.7%), throat irritation (5.6%), dizziness (5.0%), canker

sores (3.8%), taste perversion (3.2%), tooth disorders (2.7%), pain (2.7%), nervousness (2.6%) and insomnia (2.4%).

DISCUSSION

This study evaluated outcomes achieved with nicotine patch and gum in two contexts: in a real-world prescription context and a simulated OTC context. The results of separate studies on nicotine patch and gum were highly consistent: OTC use yielded success rates at least as good as those achieved in real-world prescribing practice.

The comparatively favorable outcomes of OTC usage were seen both at 6 weeks, while smokers could still use NRT, and at a 6-month follow-up, long after end of treatment. The pattern also held for both nicotine gum, which demands substantial effort and compliance from smokers and for nicotine patch, which does not. Similar results were seen for the entire treatment sample and among smokers who used comparable, correct doses of patch and gum. Controlling for differences in the OTC and Rx study samples generally widened the gap in favor of OTC usage. The results at least support comparability of Rx and OTC outcomes.

The observed abstinence rates and the Rx-to-OTC comparisons are consistent with reports from other OTC trials. Indeed, the efficacy rates reported for different nicotine patches across four substantially different OTC simulation studies are remarkably similar (Davidson *et al.* 1998; Hays *et al.* 1999; Jolicoeur *et al.* 2000; Shiffman *et al.* 2002). The present study is unique in that we estimated Rx outcomes achieved by real-world providers treating smokers in the course of their everyday clinical practice, whereas the other studies recruited smokers to participate in a smoking cessation trial. The consistency of outcomes lends credibility to the conclusion that OTC treatment with NRT is as effective as treatment in real-world prescription contexts.

The comparability of OTC and Rx outcomes seems surprising, as physician intervention might be expected to boost efficacy through counseling and enhanced compliance (Kottke *et al.* 1988; Fiore *et al.* 2000; Lancaster *et al.* 2000; Silagy *et al.* 2000). However, reports from participants in the Rx samples (the data are too complex to be included here, but are the subject of a separate publication) suggested that physicians often failed to provide the essential elements of counseling and instruction in smoking cessation: prescriptions were sometimes issued without seeing the patient, advice on quitting was rarely given, and less than a quarter of patients had any follow-up conversations with the physician. Conversely, the user's guide and audiotape packaged with OTC NRT

provide explicit instructions for product use and smoking cessation. Thus, behavioral instruction may actually be stronger in OTC situations. All OTC NRT products also offer additional optional written cessation materials, and two programs have been shown to improve cessation rates (Shiffman *et al.* 2000, 2001).

The patterns of NRT use seen in the Rx studies also suggest room for improvement in prescribing practices. Smokers prescribed gum or patch were under-dosed, which can undermine cessation (Transdermal Nicotine Study Group 1991; Herrera *et al.* 1995). However, dosing differences did not account for the difference between OTC and Rx: analysis of similarly dosed smokers still yielded OTC success rates comparable to or better than Rx. Training physicians and pharmacists on proper prescribing and counseling may promote cessation and proper use of effective treatments (Smith, McGhan & Lauger 1995; Wilson & Tweed 1984). However, given increasing pressures on physicians' time, and the barriers that deter physicians from undertaking this effort, achieving widespread smoking cessation through this channel seems unlikely. In any case, requiring a prescription to access smoking cessation treatment presents significant barriers for patients (Gallup Organization 1993). Far larger numbers of smokers use NRT when it is made freely accessible through OTC availability (Shiffman *et al.* 1997; Burton *et al.* 2000).

The study also demonstrated that nicotine patch and gum could be used safely without physician intervention. The AEs observed under OTC conditions were comparable in character and severity to those in clinical trial and prescription settings (Tonnesen *et al.* 1988; Abelin *et al.* 1989; Transdermal Nicotine Study Group 1991; Herrera *et al.* 1995). Further, smokers almost always self-managed AEs appropriately. This was true even though, unlike most clinical trials, the OTC trials permitted patients to enroll even if they had medical conditions thought to increase the risks of NRT (i.e. those listed on the OTC label). In another study of OTC nicotine patch (Shiffman *et al.* 2002), smokers who used NRT despite label warnings experienced no more AEs than patients without such medical conditions. NRT has been shown to carry little risk, even in patients with cardiovascular disease (Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. 1994; Mahmarian *et al.* 1997). While smokers appear to be able to safely self-treat with NRT for smoking cessation, some have been concerned that, absent the controls of prescription status, smokers might use OTC NRT for purposes other than quitting or might persist in using NRT beyond the indicated treatment period (Hughes 1998). There are no published data supporting or contradicting these concerns; the issues need to be evaluated.

Limitations

The analyses reported here are methodologically complex, and subject to several limitations. The Rx studies attempted to recruit samples of smokers to represent real-world prescribing practices, and sampled from prescriptions that had actually been filled. This may represent a bias favorable to Rx outcomes, as approximately 50% of NRT prescriptions are never filled (IMS America Ltd 2000). The sample was ascertained from pharmacies from a single national chain of stores in the United States and may not be representative of all Rx patients, even through the chain is one of the largest national mass merchandising chains in the United States. Only about one-third of those eligible responded to a letter soliciting their participation in a study, so respondents may not be representative. The solicitation letter never mentioned smoking, NRT or smoking cessation, so smokers' decision to respond could not have been based on factors relating to smoking, such as embarrassment about their smoking status. However, there is unknown potential for bias due to non-response. The real-world Rx study could underestimate quit rates because many respondents, having little allegiance to the study, failed to appear for CO validation; some may have, in fact, been abstinent.

The OTC simulation studies also presented methodological challenges. Since NRT was not actually sold OTC at the time of the study, participants had to be actively recruited, rather than buying NRT during the course of a store visit. This resulted in a sample of heavy smokers typical of treatment studies (Hughes *et al.* 1997). These treatment-seekers could find it harder to quit or, on the other hand, may be more motivated to achieve success. In any case, other aspects of the OTC environment—notably the lack of behavioral intervention—were well simulated in the study.

Smoking cessation rates were calculated very conservatively, requiring biochemical verification of abstinence and counting all participants lost to follow-up as treatment failures. These are deeply ingrained standards in analysis of smoking cessation trials (e.g. Silagy *et al.* 2000) and allow for comparability across studies. However, it is possible that they may introduce bias into the comparisons, even when the comparison groups are treated similarly. The treatment of participants lost to follow-up in smoking trials warrants more attention.

The biggest methodological limitation attended the comparison between Rx and OTC outcomes. Smokers were not randomized to Rx or OTC usage; the Rx and OTC studies were based on different samples recruited by different methods. Thus, comparisons across the two modalities could be confounded by differences in samples. We corrected statistically for known differences between the samples (which actually widened the gap in abstinence

rates), but this does not rule out the influence of other unmeasured factors. Also, there were differences in how the studies were conducted and how data were collected. For example, unlike smokers in the Rx samples, smokers in the OTC trials had initially enrolled in a study and expected the follow-up visits. Also, while OTC and Rx participants had one visit prior to the 6-week assessment, those in the OTC trial had three visits prior to the 6-month follow-up, versus just one in the Rx trial. The lack of randomization and identical procedures precludes the strong causal inference that would normally come from a randomized experimental design. Nonetheless, the OTC outcomes observed here conform closely with those in a randomized placebo-controlled OTC trial of the same patch, which showed active patch to be better than placebo (Shiffman *et al.* 2002) in the absence of extraneous study contacts and any intervention. Thus, together the OTC literature presents strong evidence that Rx and OTC usage of NRT result in similar outcomes.

The fact that OTC use of NRT yields abstinence rates comparable to Rx rates is significant to public health because OTC access to NRT results in very large increases in the utilization of NRT (Shiffman *et al.* 1997; Burton *et al.* 2000). With efficacy held constant, increasing the utilization, or 'reach', of the treatment results in dramatically increased numbers of abstaining smokers, which should have substantial public health impact. Indeed, it is estimated that the introduction of OTC NRT may have increased total quitting in the United States by 20% (Shiffman *et al.* 1997), and may have resulted in fewer smoking-attributable deaths and increased life expectancy (Oster *et al.* 1996; Lawrence *et al.* 1998). NRT is being made more accessible to smokers by removing regulatory barriers to access world-wide (e.g. France, Australia, Brazil), with early results suggesting favorable public health impact (Shiffman & Gitchell 2000). Removing regulatory barriers to treatment is particularly compelling against the backdrop of nearly unregulated sales and promotion of tobacco, which is known to cause addiction, disease and death (Food and Drug Law Institute 1998).

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Dr Shiffman and Mr Di Marino serve as consultants to GlaxoSmithKline Consumer Healthcare (GSKCH) on an exclusive basis regarding matters relating to smoking cessation. Dr Shiffman has a financial interest (acquired after the study and analyses were completed) in a venture to develop a new nicotine gum. Dr Rolf was an employee of Marion Merrell Dow Pharmaceuticals when these studies were completed. He is currently retired and does consulting work. Dr Hellebusch was the principal investigator for the four real-world studies. His firm, Q2 Marketing Research, was compensated by GSKCH for conducting these studies. He currently serves as a consultant to GSKCH on a variety of marketing and sales issues. Dr Gorsline was an employee of ALZA Corporation when these studies were completed. She is currently an independent consultant for pharmaceutical and biotechnology companies. Dr Gorodetzky was an employee of Marion Merrell Dow (MMD) and its immediate successor, Hoechst Marion Roussel (HMR), at the time of completion of these studies. He is currently a full-time employee of Quintiles, Inc., a later successor to the Kansas City facilities of MMD and HMR. Dr Chiang was an employee of ALZA Corporation at the time of completion of these studies. He is currently employed by Essence Sciences, Inc. Ms Schleusener is currently employed by Aventis Pharmaceuticals.

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