Original Investigation

Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks
A Randomized Clinical Trial

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IMPORTANCE Smoking cessation medications are routinely used in health care; it is vital to identify medications that most effectively treat this leading cause of preventable mortality.

OBJECTIVE To compare the efficacies of varenicline, combination nicotine replacement therapy (C-NRT), and the nicotine patch for 26-week quit rates.

DESIGN, SETTING, AND PARTICIPANTS Three-group randomized intention-to-treat clinical trial occurring from May 2012 to November 2015 among smokers recruited in the Madison, Wisconsin, and Milwaukee, Wisconsin, communities; 65.5% of smokers offered the study (2687/4102) refused participation prior to randomization.

INTERVENTIONS Participants were randomized to one of three 12-week open-label smoking cessation pharmacotherapy groups: (1) nicotine patch only (n = 241); (2) varenicline only (including 1 prequit week; n = 424); and (3) C-NRT (nicotine patch + nicotine lozenge; n = 421). Six counseling sessions were offered.

MAIN OUTCOMES AND MEASURES The primary outcome was carbon monoxide–confirmed self-reported 7-day point-prevalence abstinence at 26 weeks. Secondary outcomes were carbon monoxide–confirmed self-reported initial abstinence, prolonged abstinence at 26 weeks, and point-prevalence abstinence at weeks 4, 12, and 52.

RESULTS Among 1086 smokers randomized (52% women; 67% white; mean age, 48 years; mean of 17 cigarettes smoked per day), 917 (84%) provided 12-month follow-up data. Treatments did not differ on any abstinence outcome measure at 26 or 52 weeks, including point-prevalence abstinence at 26 weeks (nicotine patch, 22.8% [55/241]; varenicline, 23.6% [100/424]; and C-NRT, 26.8% [113/421]) or at 52 weeks (nicotine patch, 20.8% [50/241]; varenicline, 19.1% [81/424]; and C-NRT, 20.2% [85/421]). At 26 weeks, the risk differences for abstinence were, for patch vs varenicline, −0.76% (95% CI, −7.4% to 5.9%); for patch vs C-NRT, −4.0% (95% CI, −10.8% to 2.8%); and for varenicline vs C-NRT, −3.3% (95% CI, −9.1% to 2.6%). All medications were well tolerated, but varenicline produced more frequent adverse events than did the nicotine patch for vivid dreams, insomnia, nausea, constipation, sleepiness, and indigestion.

CONCLUSIONS AND RELEVANCE Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or C-NRT produced no significant differences in biochemically confirmed rates of smoking abstinence at 26 weeks. The results raise questions about the relative effectiveness of intense smoking pharmacotherapies.

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Due to the profound health effects of tobacco smoking,[1] it is important to identify treatments that increase rates of long-term smoking abstinence. Research on pharmacotherapies for cessation is especially important because pharmacotherapies can be disseminated broadly via health care systems.

Two pharmacotherapies for smoking seem particularly effective: combination nicotine replacement therapy (C-NRT) and varenicline. A Cochrane meta-analysis[2] showed that both varenicline and C-NRT were superior to NRT monotherapy in increasing the odds of quitting but did not differ from one another. Other meta-analyses[3,4] and large individual clinical trials[5-9] also support the superiority of varenicline and C-NRT relative to monotherapies. Although these 2 pharmacotherapies are frequently used in the clinical treatment of smokers,[10] to our knowledge, they have never been directly contrasted in a randomized clinical trial.

C-NRT *combination nicotine replacement therapy*

FTND *Fagerstrom Test of Nicotine Dependence*

TQD *target quit day*

The US Food and Drug Administration (FDA) has issued warnings on varenicline, noting that it may increase the risk of serious neuropsychiatric or cardiovascular events; in October 2014, the FDA retained its black box neuropsychiatric warning. Although most recent evidence suggests that varenicline can be used safely[11] (but see Ahmed et al[12]), care still must be taken in patient screening and monitoring. Conversely, C-NRT, now approved by the FDA, appears to pose no meaningfully greater risk than does NRT monotherapy,[8] which is very safe and well tolerated.[13] Because varenicline and C-NRT differ in cost, the need for a prescription, and the intensity of screening and ongoing monitoring, a comparison in a head-to-head randomized clinical trial seemed warranted. It also seemed warranted to test their effectiveness relative to nicotine patch monotherapy, which might be considered a usual-care smoking cessation medication.[3] The aim of this study was to evaluate the comparative efficacies of the nicotine patch, varenicline, and combination NRT.

Methods

Participants

The trial protocol is available in Supplement 1. Participants were recruited via 2 sources: (1) by contacting participants in an ongoing longitudinal study of smokers, the Wisconsin Smokers Health Study[8,14,15] and (2) via media and community outreach. The **Figure** shows the study flow for both cohorts. Contacted individuals were screened and potentially eligible smokers were scheduled for an orientation visit.

Inclusion criteria were smoking (≥5 cigarettes per day), age older than 17 years, ability to read and write English, desire to quit smoking but not engaged in smoking treatment, willingness to use the tested cessation treatments and not use e-cigarettes, telephone access, and use of suitable birth control. Specific exclusion criteria were exhaled carbon monoxide (measured via Bedfont Smokerlyzer, Bedfont Scientific) value of less than 4 ppm; end-stage renal disease with hemodialysis; prior suicide attempts within the last 5 years or current suicidal ideation; diagnosis of or treatment for psychoses within the last 10 years; moderately severe depression via the Patient Health Questionnaire[18]; untreated hypertension of greater than 200/100 mm Hg; current use of bupropion; hospitalization for stroke, myocardial infarction, congestive heart failure, or diabetes within the last year; exclusionary incidental findings from study health assessments or interview (eg, appearance of >60% carotid stenosis, third-degree heart block, stress-induced ischemia); or use of other forms of tobacco more than twice in the past week.

Randomization

Participants passing initial telephone screening were required to (1) undergo additional in-person screening, assessments, and written informed consent procedures at baseline visit 1; (2) attend baseline visit 2 to complete baseline physiological assessments (eg, carotid ultrasonography and pulmonary function tests); and (3) attend a treatment initiation visit that included computer-based randomization to treatment. Treatment assignment was unblinded. Computer-based randomization was stratified by site (Madison or Milwaukee) and by sex and race (nonwhite or white) within each site. By design, the varenicline, C-NRT, and nicotine patch conditions comprised approximately 38.5%, 38.5%, and 23% of the total sample. This sample size strategy enhanced power for the varenicline vs C-NRT comparison, which we believed would yield a smaller effect size, and yielded good power for all targeted comparisons. This research was approved by the University of Wisconsin Health Sciences Institutional Review Board.

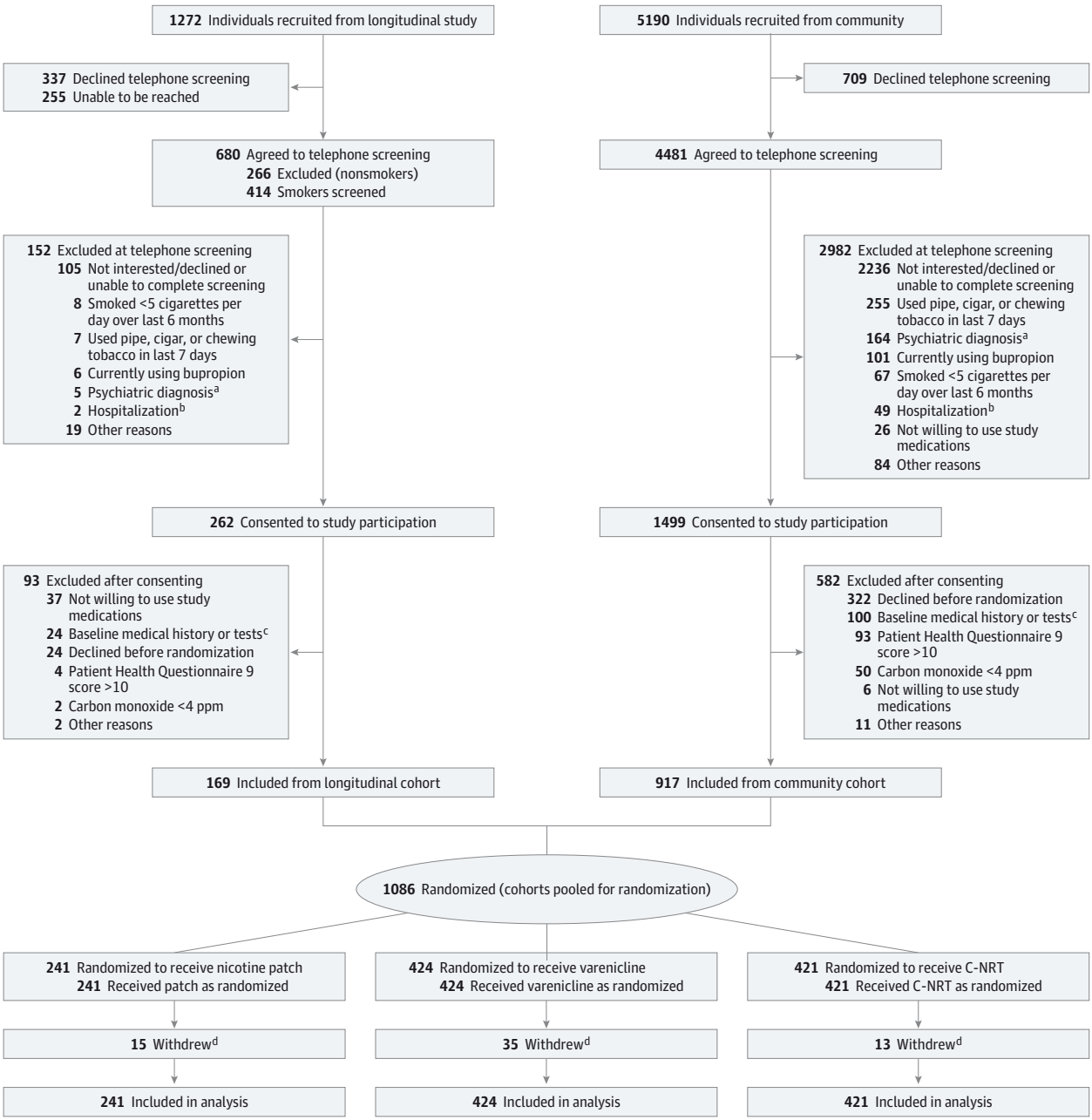
Treatment and Assessment Contacts

Questionnaire assessments occurred at orientation and baseline visit 1 and targeted smoking history, dependence, and affective and psychiatric symptom domains. These included a smoking history questionnaire and measures of tobacco dependence including the Fagerstrom Test of Nicotine Dependence (FTND).[19]

Treatment began 1 week after baseline visit 2 and involved counseling in 5 treatment visits and 1 telephone call. Treatment visits 1 through 5 occurred 1 week prior to the target quit day (TQD), on the TQD, and at weeks 1, 4, and 12 post-TQD, respectively. The treatment telephone call occurred at week 8 post-TQD. Counseling time was 20 minutes per contact in visits 1 through 3 and 10 minutes per contact for the telephone call and visits 4 and 5. Study medication was dispensed at treatment visits 1 through 4. Treatment contacts included assessment of nicotine withdrawal, carbon monoxide, adverse events/safety, and medication adherence.

Participants were contacted at weeks 26 and 52 post-TQD for telephone follow-up assessments of smoking status and use of other nicotine products and cessation aids. The follow-up telephone assessments were intended to be blinded, but a

Figure. Flow of Participants From a Longitudinal Cohort and a Community-Based Cohort in a Trial of Nicotine Patch vs Varenicline vs C-NRT for Smoking Cessation



C-NRT indicates combination nicotine replacement therapy. Cohort 1 comprises participants recruited from an ongoing longitudinal study of smokers, the Wisconsin Smokers Health Study,[14,16,17] while cohort 2 participants were recruited for this study from the community via media and community outreach.

[a] Exclusion due to diagnosis of or treatment for schizophrenia, a psychotic disorder, or bipolar disorder in the last 10 years.

[b] Exclusion due to hospitalization for stroke, myocardial infarction, congestive heart failure, or diabetes in the last year.

[c] Exclusion reasons: carotid stenosis (60% visual or peak systolic velocity 130 cm/s), n = 50; cardiac ischemia, n = 16; cardiac arrhythmia, n = 15; long QT interval, n = 12; other, n = 31.

[d] Data on withdrawals were collected through 52 weeks.

database search by interviewers could have revealed treatment assignment. Participants claiming abstinence were asked to attend a visit for carbon monoxide testing.

Participants provided ecological momentary assessment data for 1 week prior to quitting through week 4 post-TQD. Participants responded to a morning, afternoon, and evening prompt every day for the first 3 weeks, then every other day for the next 2 weeks. These assessments targeted smoking, medication use, tobacco withdrawal, and other smoking-relevant variables.

Treatment

Pharmacotherapy

Participants were randomized to receive open-label varenicline, C-NRT (nicotine patch + nicotine lozenges), or nicotine patch. Pharmacotherapy duration was 12 weeks. The pre-quit varenicline regimen was a 0.5-mg pill once daily for 3 days; a 0.5-mg pill twice daily for 4 days; and a 1-mg pill twice daily for 3 days; starting on the TQD, participants took a 1-mg pill twice daily for 11 weeks. Dosage reduction was counseled in response to adverse events such as nausea. The NRT patch regimens (patch only and C-NRT), beginning on the morning of the quit day were 8 weeks of 21-mg patches, then 2 weeks of 14-mg patches, then 2 weeks of 7-mg patches (those smoking 5-10 cigarettes per day before quitting received 10 weeks of 14-mg patches, then 2 weeks of 7-mg patches). Participants in the C-NRT condition were also given either 2-mg or 4-mg nicotine lozenges based on morning smoking latency and were asked to use at least 5 lozenges per day for the full 12 weeks unless this amount produced adverse effects. All participants were instructed about possible adverse effects and to contact the research staff in case of significant problems.

Counseling

Counseling was based on 2008 Public Health Service Clinical Practice Guideline recommendations for an intensive counseling intervention (comprising motivational, supportive, and skill-training elements).[3] Counselors were bachelor-level health educators supervised by licensed psychologists.

Outcome Measures

The primary outcome was self-reported 7-day point-prevalence abstinence at 26 weeks post-TQD with biochemical confirmation via exhaled carbon monoxide. Biochemical confirmation of abstinence required a carbon monoxide level of 9 ppm or lower in the original study registration, but because of subsequent research that indicated that a lower carbon monoxide criterion (ie, ≤5 ppm) optimally distinguishes smokers from nonsmokers,[20] we conducted analyses using carbon monoxide cutoffs of both 9 ppm or lower and 5 ppm or lower (the latter was deemed the primary analysis). Secondary abstinence outcomes included carbon monoxide-confirmed 7-day point-prevalence abstinence at post-TQD weeks 4 and 12 (end of treatment) and at 52 weeks, as well as initial and prolonged abstinence. Initial abstinence was defined as 24 hours or longer of abstinence in the first week of treatment. Prolonged abstinence was defined as no smoking from day 7 to day 181 post-TQD (TQD = day 0).

The evening ecological momentary assessment report yielded 2 prespecified withdrawal measures: (1) the mean of 4 withdrawal items (negative mood, unable to concentrate or think clearly, thinking about food or hungry, and wanting to smoke) and (2) a single craving item (scale, 1 = not at all; 7 = extremely for all items). These were computed as means within 2 periods, the 7 days prior to quitting and the first 7 days post-TQD.

Medication adherence was measured using visit-based reports of medication use for 7 days prior to study visits at weeks 1, 4, and 8. Past-week adherence (0 = nonadherent and 1 = adherent) was defined respectively as 1 patch per day for 6 or 7 days, 1 or 2 pills per day for 6 or 7 days, and at least 2 lozenges per day for 6 or 7 days. Adherence at week 12 was not evaluated because that visit often occurred after the assigned medication use period had elapsed.

Statistical Analysis

The dichotomous primary outcome was analyzed via logistic regression, with model effects comparing the varenicline and C-NRT conditions each with the nicotine patch (reference) condition using reference cell (dummy) coding[21,22] and by comparing varenicline vs C-NRT. Similar logistic regression models were used to analyze secondary abstinence outcomes. Risk differences were calculated using Proc Freq (SAS Institute Inc) via the RISKDIFF option and are reported for abstinence end points. Also, a Cox regression survival analysis was run (via SAS Proc Phreg) to analyze time to relapse up to 6 months post-TQD. Abstinence outcome models included the full intention-to-treat sample (N = 1086). Similar results were obtained with both carbon monoxide cutoffs (≤5 ppm and ≤9 ppm).

A priori covariates for the adjusted models were cohort, site, sex, race, income, FTND total score, FTND item 1 score (with binary scoring), self-reported likelihood of quitting, age, baseline carbon monoxide level, home smoking, prior cessation medication use, and menthol cigarette use. Each a priori covariate was tested in separate logistic regression models that included treatment coding (dummy-coded variables; eg, patch vs varenicline), the covariate, and the interaction of the covariate with treatment (for moderation analysis). A χ^2 analysis was used to test the association between nicotine dependence (FTND item 1 score) and treatment (C-NRT vs patch) with abstinence at 26 weeks.

The 2 withdrawal outcomes were analyzed via linear regression models both with and without a corresponding baseline withdrawal covariate (mean score 1 week pre-TQD).

For abstinence outcomes, our analyses were run assuming that missing observations reflected smoking. Sensitivity analyses were applied to test this assumption via multiple imputation per Hedeker et al,[23] combined with an assumption that missingness was related to smoking at odds ratios of 2 or 5. These analyses were conducted with the primary outcome (carbon monoxide cutoff ≤5 ppm). Results were essentially the same as those in which missing was treated as smoking; only the latter are reported.

A priori power analyses (via SAS Proc Power) focused on the primary outcome and comparisons of either varenicline or C-NRT with the patch condition and assumed a 10-percentage-point difference based on treatment differences observed in meta-analyses and estimates of clinical significance.[3] We hypothesized a 26-week abstinence rate of 24% for the nicotine patch control condition (approximate n = 227) and greater than 34%, for the varenicline and C-NRT conditions (approximate n = 387 for both groups),[3,6,8] yielding a power of greater than 80% (2-tailed test; $\alpha = .05$). Additionally, there was 80% power to show greater than a 9-percentage-point difference between the varenicline and C-NRT treatments (eg, 34% vs 44%) (no directional hypotheses were formulated).

Table 1. Demographic Characteristics and Baseline Smoking-Related Variables

Characteristics	Overall (n = 1086)	Nicotine Patch Only (n = 241)	Varenicline (n = 424)	Nicotine Patch + Nicotine Lozenge (n = 421)
Female, No. (%)	566 (52.1)	125 (51.9)	222 (52.4)	219 (52.0)
Race, No. (%)[a]				
White	728 (67.0)	158 (65.6)	283 (66.8)	287 (68.2)
Native American/Alaska Native	6 (0.6)	2 (0.8)	1 (0.2)	3 (0.7)
Black/African American	309 (28.4)	72 (29.9)	120 (28.3)	117 (27.8)
Asian	3 (0.3)	1 (0.4)	0 (0.0)	2 (0.5)
>1 Race	22 (2.0)	6 (2.5)	11 (2.6)	5 (1.2)
Other	18 (1.7)	2 (0.8)	9 (2.1)	7 (1.7)
Hispanic ethnicity, No. (%)	28 (2.6)	8 (3.3)	11 (2.6)	9 (2.1)
Age, mean (SD), y	48.1 (11.6)	49.4 (10.9)	48.5 (11.8)	47.1 (11.7)
Income ≥$35 000/y, No. (%)	476 (46.1)	103 (45.2)	192 (47.3)	181 (45.4)
Cigarettes/d, mean (SD)	17.0 (8.3)	16.4 (7.8)	17.1 (7.7)	17.3 (9.2)
Years of smoking, mean (SD)	28.6 (12.0)	29.4 (11.3)	27.7 (11.9)	29.1 (12.5)
FTND score, mean (SD)[b]	4.8 (2.1)	4.9 (2.2)	4.8 (2.1)	4.8 (2.0)
FTND item 1 (smoking within 30 min of waking), No. (%)[b]	836 (77.3)	188 (78.0)	324 (76.6)	324 (77.5)
HSI, mean (SD)[c]	3.0 (1.3)	3.0 (1.4)	3.1 (1.3)	3.0 (1.3)
Exhaled carbon monoxide, mean (SD), ppm	15.1 (8.4)	15.0 (8.6)	15.2 (8.3)	15.0 (8.4)
Smokes menthol cigarettes, No. (%)	547 (50.6)	115 (47.9)	224 (53.2)	208 (49.5)
Prior cessation medication use, No. (%)[d]	767 (70.6)	163 (67.6)	305 (71.9)	299 (71.0)
Other smokers in the home, No. (%)	439 (40.6)	98 (40.7)	165 (39.2)	176 (42.1)
Likelihood of quitting success, mean (SD)[e]	5.5 (1.7)	5.6 (1.7)	5.5 (1.6)	5.5 (1.7)

[a] Participants were asked to endorse 1 or more race categories with the question "What race do you identify with most?"; participants who endorsed more than 1 race were designated as such.

[b] The Fagerstrom Test of Nicotine Dependence (FTND) is a 6-item score containing 4 items with binary responses (0 or 1) and 2 items with multiple-choice response options (0-3); higher scores indicate greater smoking dependence.[19]

[c] The Heaviness of Smoking Index (HSI), a 2-item score derived from the FTND with 2 items with multiple-choice response options (0-3) assessing cigarettes smoked per day and latency to smoke after waking; higher scores indicate greater smoking dependence.[24]

[d] Prior use of varenicline or nicotine patch, gum, or lozenge.

[e] Rated on a scale of 1 to 7 (1 = not at all; 7 = extremely).

Results

Participant Characteristics

Participant demographics and smoking-related variables are listed in **Table 1**. The longitudinal study-recruited cohort (n = 169) and the community-recruited cohort (n = 917) differed significantly on multiple dimensions, including race, age, income, years of smoking, and prior use of cessation medication ($P<.01$ for all) (eTable 1 in Supplement 2).

Smoking Outcomes

Table 2 shows 7-day biochemically confirmed point-prevalence abstinence rates (carbon monoxide cutoff ≤5 ppm) for the 3 treatment conditions. A logistic regression analysis (unadjusted) contrasted the patch-only condition with the varenicline or the C-NRT condition on the primary outcome (7-day point-prevalence abstinence at 26 weeks post-TQD); neither the patch vs varenicline (22.8% vs 23.6%, respectively; risk difference, −0.76%; 95% CI, −7.4% to 5.9%) nor the patch vs C-NRT (22.8% vs 26.8%, respectively; risk difference, −4.0%; 95% CI, −10.8% to 2.8%) contrast was significant (model fit likelihood ratio, 1.77_2; $P = .49$). Neither contrast was significant in covariate-adjusted models (eTable 2 in Supplement 2). A similar pattern of results was obtained using a carbon monoxide cutoff of 9 ppm or lower (eTable 3 in Supplement 2). We also computed unadjusted and covariate-adjusted models contrasting the varenicline and C-NRT groups on the primary outcome; neither model type yielded a significant group effect. Outcome analyses revealed that treatment effects were not significantly moderated by cohort.

Additional secondary abstinence outcomes were analyzed using both unadjusted and adjusted logistic regression models (Table 2). No significant treatment condition effects were found for biochemically confirmed point-prevalence abstinence at weeks 4 or 52 or for 26-week prolonged abstinence or survival analysis (26-week relapse interval) (eTable 4 in Supplement 2). Of 1086 participants, 917 (84%) provided 12-month follow-up data. For initial abstinence, the patch-only group differed from the C-NRT group (73.0% vs 80.5%, respectively; risk difference, −7.5%; 95% CI, −14.3% to −0.7%) in the unadjusted model but not the covariate-adjusted model (eTable 4 in Supplement 2). Also, the varenicline group differed from the C-NRT group in initial abstinence in the unadjusted model (68.2% vs 80.5%, respectively; risk difference, −12.4; 95% CI, −18.2 to −6.5) and in the adjusted model. Last, the patch-only group did not differ from the varenicline group in the week 12 point-prevalence abstinence outcome in the unadjusted model (25.7% vs 31.8%, respectively; risk difference, −6.1%; 95% CI, −13.2 to 0.97) but did differ in the adjusted model (eTable 2 in Supplement 2).

Covariate Effects on Week 26 Abstinence

Covariate effects were tested in bivariable and multivariable logistic regression analyses with the primary outcome (7-day point-prevalence abstinence at 26 weeks post-TQD; carbon monoxide ≤5 ppm) as the dependent variable, with no treatment coding (**Table 3**). Although many of the covariates pre-

Table 2. Initial Abstinence, Biochemically Confirmed 7-Day Point-Prevalence Abstinence Rates (Carbon Monoxide Cutoff ≤5 ppm), and Prolonged Abstinence by Treatment Condition

Post-TQD Abstinence Measure	Abstinence Rates, No. (%)			Abstinence Risk Difference, % (95% CI)[a]					Unadjusted Odds Ratio (95% CI)[b]		
	Nicotine Patch (n = 241)	Varenicline (n = 424)	C-NRT (n = 421)[c]	Patch vs Varenicline	*P* Value	Patch vs C-NRT[c]	*P* Value	Varenicline vs C-NRT[c]	Patch vs Varenicline	Patch vs C-NRT[c]	Varenicline vs C-NRT[c]
Primary outcome											
7-Day point-prevalence abstinence (26 wk)[d]	55 (22.8)	100 (23.6)	113 (26.8)	−0.76 (−7.43 to 5.9)	.82	−4.0 (−10.8 to 2.8)	.25	−3.3 (−9.1 to 2.6)	.28	1.0 (0.7-1.5)	1.2 (0.9-1.8)	0.8 (0.6-1.1)
Initial abstinence[e]	176 (73.0)	289 (68.2)	339 (80.5)	5.9 (−2.3 to 1.2)	.19	−7.5 (−14.3 to −0.73)	.03	−12.4 (−18.2 to −6.5)	<.001	0.8 (0.6-1.1)	1.5 (1.1-2.2)	0.5 (0.4-0.7)
7-Day point prevalence abstinence[d]												
At 4 wk	79 (32.8)	152 (35.9)	150 (35.6)	−3.1 (−10.6 to 4.4)	.42	−2.9 (−10.3 to 4.6)	.46	0.2 (−6.2 to 6.7)	.95	1.1 (0.8-1.6)	1.1 (0.8-1.6)	1.0 (0.8-1.3)
At 12 wk	62 (25.7)	135 (31.8)	124 (29.5)	−6.1 (−13.2 to 0.97)	.10	−3.7 (−10.8 to 3.3)	.30	2.4 (−3.8 to 8.6)	.45	1.3 (0.9-1.9)	1.2 (0.8-1.7)	1.1 (0.8-1.5)
At 52 wk	50 (20.8)	81 (19.1)	85 (20.2)	1.6 (−4.7 to 8.0)	.61	0.56 (−5.8 to 7.0)	.86	−1.1 (−6.4 to 4.3)	.69	0.9 (0.6-1.3)	1.0 (0.7-1.4)	0.9 (0.7-1.3)
Prolonged abstinence (26 wk)[f]	36 (14.9)	70 (16.5)	65 (15.4)	−1.6 (−7.3 to 4.2)	.59	−0.50 (−6.2 to 5.2)	.86	1.1 (−3.9 to 6.0)	.67	1.1 (0.7-1.7)	1.0 (0.7-1.6)	1.1 (0.7-1.6)

Abbreviations: C-NRT, combination nicotine replacement therapy; TQD, target quit day.

[a] Pairwise comparisons of abstinence risk differences were tested via SAS Proc Freq by specifying the RISKDIFF option, which provides standard Wald asymptotic confidence limits for the risks.

[b] Based on logistic regression analysis.

[c] Therapy included nicotine patch and nicotine lozenge.

[d] Abstinence self-report was biochemically confirmed via exhaled carbon monoxide testing, with abstinence confirmed with a carbon monoxide value of ≤5 ppm.

[e] Initial abstinence was defined as achieving at least 24 hours of abstinence in the first week of treatment.

[f] Prolonged abstinence was defined as no smoking from day 7 to day 181 after the TQD.

dicted the primary outcome, none of the covariates differed significantly across treatment conditions.

Treatment Moderation

Prior data suggested that C-NRT is especially effective relative to the nicotine patch among those who are highly dependent on tobacco.[9] Therefore, we examined C-NRT and patch effects in individuals with high vs low dependence in exploratory analyses. Among those who smoked more than 30 minutes after waking (ie, who were less dependent via the FTND item 1[25]) the 26-week abstinence rates for the patch-only and C-NRT conditions were 36% and 31%, respectively; among those smoking within 30 minutes of waking (ie, more dependent), abstinence rates were 19.1% and 25.3%, respectively (risk difference, −6.2; 95% CI, −13.2 to 1.2). These differences were not significant, nor was there a significant interaction effect between dependence and pharmacotherapy. No covariate × treatment interaction effects were statistically significant in predicting the primary outcome in any of the models (this applies to all covariates listed in Table 3; covariate values as a function of treatment group are reported in eTable 5 in Supplement 2).

Withdrawal Suppression

The dependent variables were mean total withdrawal and mean craving, examined in separate analyses over the first week post-TQD and tested with and without mean pre-quit week score as a covariate. For the total score, participants using C-NRT had significantly lower total withdrawal ratings compared with participants using patch monotherapy (mean difference, 0.28; 95% CI, 0.11-0.46) in both the unadjusted and covariate-adjusted models (*P*<.05 for both). Participants using varenicline had significantly lower total withdrawal score ratings compared with participants using patch monotherapy (mean difference, 0.22; 95% CI, 0.05-0.40) only in the unadjusted model (*P* = .01). The C-NRT group did not differ from the varenicline group on the total withdrawal score (mean difference, 0.06; 95% CI, −0.08 to 0.20). Corresponding analyses showed that the C-NRT group reported significantly lower craving than the patch-only group (mean difference, 0.55; 95% CI, 0.25-0.84), as did the varenicline group vs the patch-only group (mean difference, 0.58; 95% CI, 0.29-0.87), in both the adjusted and unadjusted models (*P*<.05 for both); the C-NRT group did not differ from the varenicline group (mean difference, −0.04; 95% CI, −0.28 to 0.21).

Medication Adherence, Visit Attendance, and Adverse Events

At week 8, medication adherence rates were 45.2% for the patch-only condition, 49.3% for the varenicline condition, and 49.6% (patch) and 43.0% (lozenge) for the C-NRT condition. eTable 6 in Supplement 2 shows rates of medication adherence (past 7 days) by treatment group at weeks 1, 4, and 8. Mean visit attendance (ranging from 1-6 contacts) was 4.91, 4.86, and 5.19 contacts for the patch, varenicline, and C-NRT groups, respectively. The treatment conditions differed in reports of some adverse events (**Table 4**).

Table 3. A Priori Covariates and Week 26 Biochemically Confirmed Point-Prevalence Abstinence (Carbon Monoxide Cutoff ≤5 ppm)[a]

Variable	Week 26 Carbon Monoxide–Confirmed Point-Prevalence Abstinence			
			P Value for Covariate Effect From Logistic Regression	
	Abstinence, No. (%)	Risk Difference (95% CI)	Bivariable Model	Multivariable Model
Cohort (n = 1086)				
Longitudinal (n = 169)	49 (29.0)	5.1 (−2.3 to 12.5)	.79	.69
Community (n = 917)	219 (23.9)			
Site (n = 1086)				
Madison (n = 368)	100 (27.2)	3.8 (−1.7 to 9.3)	.17	.66
Milwaukee (n = 718)	168 (23.4)			
Sex (n = 1086)				
Female (n = 566)	138 (24.4)	−0.6 (−5.8 to 4.5)	.81	.81
Male (n = 520)	130 (25.0)			
Race (n = 1086)				
Nonwhite (n = 358)	60 (16.8)	−11.8 (−16.9 to −6.7)	<.001	.06
White (n = 728)	208 (28.6)			
Income per y, $ (n = 1033)				
<20 000 (n = 345)	66 (19.1)	−8.6 (−14.0 to −3.3)	.003	.38
≥20 000 (n = 688)	191 (27.8)			
FTND total score (n = 1081)				
0-4 (n = 463)	130 (28.1)	6.2 (1.0 to 11.5)	.02	.41
5-10 (n = 618)	135 (21.8)			
Likelihood of quitting (n = 1070)[b]				
1-5 (n = 425)	84 (19.8)	−8.0 (−13.1 to −2.9)	.003	.02
6-7 (n = 645)	179 (27.8)			
Age, y (n = 1086)				
18-49 (n = 521)	117 (22.5)	−4.3 (−9.4 to 0.9)	.10	.047
≥50 (n = 565)	151 (26.7)			
Carbon monoxide, ppm (n = 1086)				
5-14 (n = 616)	164 (26.6)	4.5 (−0.6 to 9.6)	.09	.03
≥15 (n = 470)	104 (22.1)			
Smoking in the home (n = 1080)[c]				
No (n = 641)	173 (27.0)	5.8 (0.6 to 10.9)	.03	.17
Yes (n = 439)	93 (22.1)			
Prior use of cessation of medications (n = 1086)[d]				
No (n = 319)	69 (21.6)	−4.3 (−9.8 to 1.2)	.13	.57
Yes (n = 767)	199 (26.0)			
Menthol smoking (n = 1081)				
No (n = 534)	161 (30.2)	11.0 (5.9 to 16.1)	<.001	.07
Yes (n = 547)	105 (19.2)			
FTND item 1 score (n = 1082)				
Smoking >30 min after waking (n = 246)	79 (32.1)	9.8 (3.3 to 16.2)	.002	.09
Smoking ≤30 min after waking (n = 836)	187 (22.4)			

Abbreviation: FTND, Fagerstrom Test of Nicotine Dependence.[19]

[a] Covariate effects were tested in a series of bivariable and multivariable logistic regression analyses with the primary outcome (7-day point-prevalence abstinence at 26 weeks post–target quit day [carbon monoxide ≤5 ppm]) as the dependent variable, with no treatment coding. The multivariate model included all the covariates in the table.

[b] Likelihood of quitting success was rated on at 1- to 7-point scale (1 = not at all; 7 = extremely).

[c] Defined as presence of any smokers living in the home of the participant.

[d] Prior use of varenicline or nicotine patch, gum, or lozenge.

Discussion

To our knowledge, this open-label study is the first to directly contrast varenicline and C-NRT pharmacotherapies, both with one another and with the nicotine patch. Results showed no significant differences among these 3 pharmacotherapies in any of the 26- or 52-week abstinence measures.

Compared with the nicotine patch, both varenicline and C-NRT significantly reduced withdrawal and craving symp-

Table 4. Adverse Events Among Patients Treated With Nicotine Patch, Varenicline, or C-NRT[a]

Adverse Events[b]	No. (%) With Event			Risk Difference, % (95% CI)	
	Nicotine Patch (n = 241)	Varenicline (n = 424)	C-NRT (n = 421)	Patch vs Varenicline	Patch vs C-NRT
Itching/hives	53 (22.0)	7 (1.7)	74 (17.6)	20.3 (15.0 to 25.7)	4.4 (−2.0 to 10.8)
Vivid dreams	40 (16.6)	98 (23.1)	55 (13.1)	−6.5 (−12.7 to −0.3)	3.5 (−2.2 to 9.2)
Insomnia	35 (14.5)	94 (22.2)	45 (10.7)	−7.7 (−13.6 to −1.7)	3.8 (−1.5 to 9.2)
Rash	27 (11.2)	9 (2.1)	48 (11.4)	9.1 (4.9 to 13.3)	−0.2 (−5.2 to 4.8)
Nausea	20 (8.3)	121 (28.5)	62 (14.7)	−20.2 (−25.8 to −14.7)	−6.4 (−11.3 to −1.6)
Vomiting	6 (2.5)	22 (5.2)	13 (3.1)	−2.7 (−5.6 to 0.1)	−0.6 (−3.2 to 2.0)
Constipation	5 (2.1)	29 (6.8)	13 (3.1)	−4.8 (−7.8 to −1.8)	−1.0 (−3.5 to 1.4)
Dizziness	18 (7.5)	27 (6.4)	20 (4.8)	1.1 (−3.0 to 5.2)	2.7 (−1.2 to 6.6)
Headache	15 (6.2)	29 (6.8)	28 (6.7)	−0.6 (−4.5 to 3.3)	−0.4 (−4.3 to 3.4)
Sleepiness	10 (4.2)	68 (16.0)	26 (6.2)	−11.9 (−16.2 to −7.6)	−2.0 (−5.4 to 1.4)
Indigestion	4 (1.7)	22 (5.2)	42 (10.0)	−3.5 (−6.2 to −0.9)	−8.3 (−11.6 to −5.0)
Mouth problems	3 (1.2)	7 (1.7)	33 (7.8)	−0.4 (−2.3 to 1.5)	−6.6 (−9.5 to −3.7)
Hiccups	0	1 (0.2)	26 (6.2)	−0.2 (−0.7 to 2.3)	−6.2 (−8.5 to −3.9)

[a] Combination nicotine replacement therapy (C-NRT) included nicotine patch and nicotine lozenge.

[b] Only symptom reports that exceeded 5% of any treatment group are listed. One patient had a serious adverse event that was definitely related to medication; this patient was hospitalized for an allergic reaction to varenicline.

toms during the early post-TQD period. In addition, C-NRT produced higher initial abstinence rates than did the other 2 pharmacotherapies. However, neither of these early post-TQD effects translated into superior 26- or 52-week abstinence.

The lack of long-term pharmacotherapy effects in this research does not appear to be due to low power but, rather, to small effect sizes. In the 2008 Public Health Service Clinical Practice Guideline meta-analysis,[3] varenicline, C-NRT, and the nicotine patch yielded model-estimated abstinence rates of 33%, 37%, and 23% at 5 months or longer post-TQD, respectively (guideline table 6.26). The differences in the nicotine patch vs varenicline and C-NRT were of smaller magnitude in this study than the differences suggested by prior meta-analyses (and by individual studies[8,9,26,27]). At 26 and 52 weeks, the 3 pharmacotherapy conditions were essentially equivalent in their point-prevalence and prolonged abstinence rates (Table 2).

It is unclear why the treatment effect sizes were relatively small in this study. As in some other studies, adherence to the medication was somewhat low in this study, which could have affected results.[16,17,26] One possible explanation is that secular changes affected the level of tobacco dependence of the sample and this, in turn, altered the relative benefits of the pharmacotherapies. In general, smokers are smoking fewer cigarettes per day now than they did in the past.[28] Thus, relative to participants in other varenicline and C-NRT studies (from 2004-2009), the current sample not only reported smoking fewer cigarettes per day (by about 5-6 per day on average) but also scored lower on some dependence indexes (eg, on the FTND by about 0.5 point on a 0- to 10-point scale on average[8,9,29,30]) (Table 1). It is possible that stronger treatment effects might have been found had the sample comprised a greater proportion of heavier or more highly dependent smokers; eg, research suggests that C-NRT is especially beneficial to more highly dependent smokers.[9] However, while exploratory analyses suggested modestly greater benefit of C-NRT vs the nicotine patch in more dependent smokers (25.3% vs 19.1% abstinence at 6 months, respectively), the interaction effect between dependence and C-NRT status was not significant. Moreover, it is important to note that participants in our sample smoked somewhat more cigarettes per day than the 2013 national average of daily smokers in the United States (ie, about 17 cigarettes per day in our sample vs 14 cigarettes per day for daily smokers in general).[31]

The limitations of this study must be acknowledged. First, this was efficacy research, so the results may overestimate the effects of the tested medications as they would occur in clinical practice (eg, because of recruitment of more highly motivated study participants). However, the levels of abstinence outcomes do not seem high relative to other relevant studies.[3] Also, the availability of 6 counseling sessions and the fairly good attendance at such sessions may have diluted the effects of the pharmacotherapies (although some of the earlier studies showing the superiority of varenicline and C-NRT over monotherapies offered similarly intense counseling[6,8]). Because this was an open-label study, the outcome measures may have been influenced by expectations or biases of the participants or staff.

Earlier research suggested the superior effectiveness of varenicline and C-NRT compared with the nicotine patch; this was not evident in the current findings. Furthermore, varenicline and C-NRT did not differ from one another in their effects on 26- or 52-week abstinence. Although the causes of such null effects are unknown, some evidence points to the relatively low level of dependence of the participating smokers. However, this attribution is clearly post hoc and speculative.

Conclusions

Among adults motivated to quit smoking, 12 weeks of open-label treatment with nicotine patch, varenicline, or C-NRT produced no significant differences in biochemically confirmed rates of smoking abstinence at 26 or 52 weeks. The results raise questions about the current relative effectiveness of intense smoking cessation pharmacotherapies.

ARTICLE INFORMATION

Author Contributions: Dr Smith had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Baker, Piper, Stein, Fraser, Fiore.
Acquisition, analysis, or interpretation of data: Baker, Piper, Smith, Bolt, Fiore.
Drafting of the manuscript: Baker, Smith, Fiore.
Critical revision of the manuscript for important intellectual content: Baker, Piper, Stein, Bolt, Fraser, Fiore.
Statistical analysis: Baker, Smith, Bolt.
Obtained funding: Baker, Piper, Stein, Fraser, Fiore.
Administrative, technical, or material support: Baker, Fraser, Fiore.
Study supervision: Baker, Piper, Fraser, Fiore.

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