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Triple-Combination Pharmacotherapy for Medically Ill Smokers

A Randomized Trial

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Background: Smokers with medical illnesses are at particular risk for complications caused by tobacco. Clinical trial data on the effectiveness of triple-combination pharmacotherapy for tobacco dependence treatment in these high-risk smokers are not available.

Objective: To evaluate extended duration of a triple-medication combination versus standard-duration therapy with the nicotine patch alone and 6-month abstinence rates in smokers with medical illnesses.

Design: Randomized clinical trial from 2005 to 2007.

Setting: Single primary care setting.

Patients: 127 smokers 18 years or older with predefined medical illnesses were recruited from the local community.

Intervention: Participants were allocated by blocked randomization to receive either the nicotine patch alone for a standard 10-week, tapering course ($n = 64$) or the combination of nicotine patch, nicotine oral inhaler, and bupropion ad libitum ($n = 63$). Nonstudy staff, who used computer-generated tables, assigned participants by telephone. No study staff had access to the randomization tables before randomization, thus maintaining concealment. Participants and study personnel were not blinded to treatment assignment.

Measurements: The primary outcome was 7-day, exhaled carbon monoxide–confirmed point abstinence at 26 weeks after target quit date. Secondary outcomes were the time to first relapse, duration of medication use, and adverse effects of medications. Analyses were conducted on an intention-to-treat basis with participants who were lost to follow-up (patch alone [$n = 13$] and combination therapy [$n = 18$]) classified as still smoking.

Results: Both treatment groups had similar baseline characteristics. Abstinence rates at 26 weeks were 35% (22 of 63 patients) for the combination group versus 19% (12 of 64 patients) for the patch–alone group (relapse benefit, 16% [95% CI, 1% to 31%]; $P = 0.040$). The adjusted odds ratio for abstinence in the combination group was 2.57 (CI, 1.05 to 6.32; $P = 0.041$). The median time to relapse was significantly longer in the combination group than in the patch-alone group (65 days vs. 23 days; $P = 0.005$). Some side effects occurred more frequently in the combination group (for example, insomnia [25% vs. 9%] and anxiety [22% vs. 3%]), but the proportion of participants who discontinued study medications because of adverse events was similar in both groups (6%).

Limitations: Approximately 25% of participants were lost to follow-up (proportions were similar between treatment groups). Treatment personnel and participants were unblinded.

Conclusion: Flexibly dosed triple-combination pharmacotherapy for up to 6 months was more effective than standard-duration nicotine patch therapy for outpatient smokers with medical illnesses.

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Despite a steady decline in tobacco use among adults over the past several decades, smokers with medical illnesses make up a disproportionately high proportion of current smokers (1). In a recent review, up to 58% of smokers continued to use tobacco after a new cancer diagnosis (2) and 50% of smokers started to smoke again within 6 months of myocardial infarction (3). Evidence has shown that smokers with substantial nicotine dependence may benefit from higher-intensity treatment, including combined regimens (4–8) and extended durations of medications beyond the typical 8- to 12-week course (9). Considerable barriers to effective tobacco dependence treatments continue to exist for smokers (10, 11), especially those with medical illnesses, because of a fear of adverse effects of cessation medications on their medical conditions despite contrary evidence (12). Clinical trials of cessation medications often exclude smokers with medical illnesses, so efficacy and safety data on these smokers are limited. In addition, product labeling negatively affects use of cessation medications by advising against combinations and setting strict 8- to 12-week durations of therapy (13, 14), despite contradictory clinical practice guidelines (8).

Observational data from our tobacco treatment clinic indicate the benefit of a triple-medication combination for dependent smokers (15) and the benefit of extended-duration pharmacotherapy (16). To date, only 1 randomized trial has examined a triple-medication combination; this trial was conducted in a selected group of schizophrenic smokers, with treatment duration limited to 12 weeks (17). We sought to evaluate 6-month tobacco abstinence rates for outpatient smokers with medical illnesses who received a combination regimen of nicotine patch, nicotine inhaler,

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Context

Few studies have examined interventions for smokers with medical illnesses.

Contribution

In this trial, 127 smokers with medical illness (for example, cardiovascular or chronic obstructive pulmonary disease) were randomly assigned to a nicotine patch for 10 weeks or a combination of a nicotine patch, a nicotine oral inhaler, and bupropion for an ad libitum duration. Abstinence rates at 26 weeks for the groups were 19% and 35%, respectively. Fewer patients who received the nicotine patch versus combination therapy had insomnia (9% vs. 25%) and anxiety (3% vs. 22%).

Caution

About 25% of participants did not complete follow-up.

Implication

Combination therapy may improve abstinence rates but causes more insomnia and anxiety than the nicotine patch in smokers with medical illnesses.

—The Editors

and bupropion or standard-duration nicotine patch therapy alone.

METHODS

Design Overview

We conducted our randomized clinical trial from 2005 to 2007 in a primary care medical setting. We compared a flexible-duration, triple-combination treatment regimen with a standard-duration nicotine patch therapy. We recruited participants with predefined medical illnesses from the local community, randomly allocated them to 1 of the treatment groups, and followed them for 6 months after setting a target quit date. We started recruiting smokers on 27 September 2005 and completed follow-up on 18 November 2007. The institutional review board at the University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey, approved the study protocol.

Setting and Participants

Participants included smokers who reported smoking an average of at least 10 cigarettes per day (confirmed by high [>10 parts per million] exhaled carbon monoxide level), were 18 years or older, were interested in quitting within the next 30 days, smoked during at least 20 of the past 30 days, and had 1 or more predefined medical illnesses (including cardiovascular disease, other vascular disease, chronic pulmonary disease, cancer, hypertension, diabetes, hyperlipidemia, and recurrent pulmonary infections) but no contraindications to pharmacotherapy (including unstable angina, myocardial infarction within 2 months, severe arrhythmia, seizure disorder, and serious mental illness requiring antipsychotic medications). We excluded participants if they currently used other tobacco products (smokeless tobacco, cigars, or pipes) or bupropion, clonidine, nortriptyline, or nicotine replacement medications or if they were pregnant, planning on becoming pregnant within the next 6 months, or actively abusing other substances.

We recruited participants from the local community through flyers and referrals from staff at local clinics and hospitals. We assessed and followed participants in a single outpatient medical office shared by the general internal medicine faculty practice. We described the purpose and methods of the study to potential participants and obtained informed consent from those interested and eligible to participate.

Randomization and Interventions

During the initial study session, we collected baseline data, including the Fagerström test score for nicotine dependence, number of cigarettes smoked per day, time to first cigarette after waking, exhaled carbon monoxide levels, motivation to quit and confidence in ability to quit (Likert scale of 1 to 10), number of years smoked, number of previous quit attempts and duration of previous abstinence, past use of cessation medications, psychiatric comorbid conditions, demographic characteristics (age, sex, race, education), perception of smoking's influence on health, general medical history, and smoking behaviors (triggers, barriers, and motivators). We measured exhaled carbon monoxide levels in all participants by having participants hold their breath for 15 seconds, then exhale into a hand-held carbon monoxide monitor (Smokerlyzer Micro III, Bedfont Scientific, Rochester, United Kingdom). A cut-off value of carbon monoxide (8 parts per million) discriminates smokers from nonsmokers with 90% sensitivity and 89% specificity (18).

We randomly assigned participants to either a control group given the nicotine patch alone or a group given the nicotine patch, nicotine inhaler, and sustained-release bupropion (combination group). We created computer-generated randomization tables by using block sizes of 4 by the 4 combinations of cigarette consumption (<20 cigarettes/d or ≥20 cigarettes/d) and severity of medical illness (moderate [cardiovascular risk factors or tobacco caused symptoms] or severe [cardiovascular disease, cancer, or chronic pulmonary disease]).

The research nurse called a staff member (unaffiliated with the study) to record the participant on the randomization table, and he or she relayed back the treatment assignment. The assignment was not revealed to the nurse until after the participant was randomly assigned.

Participants in both treatment groups received an American Heart Association smoking cessation pamphlet as standard care behavioral intervention. A goal of the study design was to simulate a real-world, primary care experience of tobacco dependence treatment. Therefore, the behavioral intervention component was limited. Partic-

ipants chose a target quit date that was within 2 weeks from the initial contact. One study physician met with all participants to deliver a strong quit message, do a brief physical examination, and answer questions about use of the medications.

We provided nicotine patches to smokers assigned to the patch alone (Nicoderm, GlaxoSmithKline, Research Triangle Park, North Carolina) for a standard 10-week tapering protocol, as described in the package labeling (21 mg/d for 6 weeks, followed by 14 mg/d for 2 weeks and then 7 mg/d for 2 weeks). This treatment was chosen because it represents the most commonly used pharmacologic aid worldwide. Participants in the combination medication group were given a nicotine patch starting at 21 mg/d; a nicotine oral inhaler (to be used as needed); and sustained-release bupropion, 150 mg/d. The duration of treatment in this group was symptom-triggered. We instructed participants to continue their initial medication doses until they had gone 14 consecutive days without noteworthy withdrawal symptoms or cravings for tobacco. At that point, they were instructed to reduce the nicotine patch dosage to 14 mg/d for 2 weeks. If participants continued to feel comfortable, they would further reduce to 7 mg/d for 2 weeks. After this period, if participants remained symptom-free, they would entirely discontinue the patch. During the next 2 weeks, if participants were comfortable, they would then discontinue the bupropion treatment. We used this sequence to maximize the duration that participants used medications with differing mechanisms of action. After this, participants would continue to use a nicotine inhaler as long as they felt it was needed. If the participant had worsening withdrawal symptoms after reducing a level of medication, the medication level would be increased to the previous level until participants were comfortable.

Outcomes and Follow-up

A single study nurse assessed all participants and conducted all follow-up procedures by using a standard protocol. We scheduled participants for follow-up at weeks 2, 4, 8, 12, 16, 20, 24, and 26 after their target quit date. If they did not attend these appointments, we made up to 5 attempts to contact them by telephone to reschedule before they were considered lost to follow-up. During the initial study session, we provided participants with a 2-week supply of medications until their next appointment, when they were provided with the next 2-week supply. At the 4-week follow-up visit and at subsequent 4-week intervals, we provided participants with a new 4-week supply of medications. At these appointments, we asked participants about tobacco use since their quit date, nicotine withdrawal symptoms, medication use, adverse medication effects, and any medical complications that had occurred. We obtained adverse medication effects by the study nurse through open-ended questions. Each specific symptom or event was documented, along with possible cause, duration, severity, and treatment. The study physician was contacted if necessary to assess the participant. We had no data safety monitoring board, and we did no interim analyses.

A final face-to-face contact was made at week 26. At this contact, we gave participants who still used medications a weaning plan for the medications and invited them to continue follow-up at the local tobacco dependence clinic for continued treatment after completion of the study. We classified participants lost to follow-up as smoking from the last point of contact.

The primary outcome of this study was 7-day, exhaled carbon monoxide–confirmed point abstinence (no smoking for the past 7 days) at 26 weeks from the target quit date; 26 weeks is a standard follow-up period reported in the literature as a reasonable clinical outcome. Secondary end points were 7-day point abstinence rates at 4 weeks, time to first relapse (smoking for 2 or more consecutive days), duration of medication use, and adverse effects of medications. We used data about perceived health, number of years smoked, previous quit attempts, and past use of cessation medications in data analyses but do not report them here.

Figure 1. **Study flow diagram.**

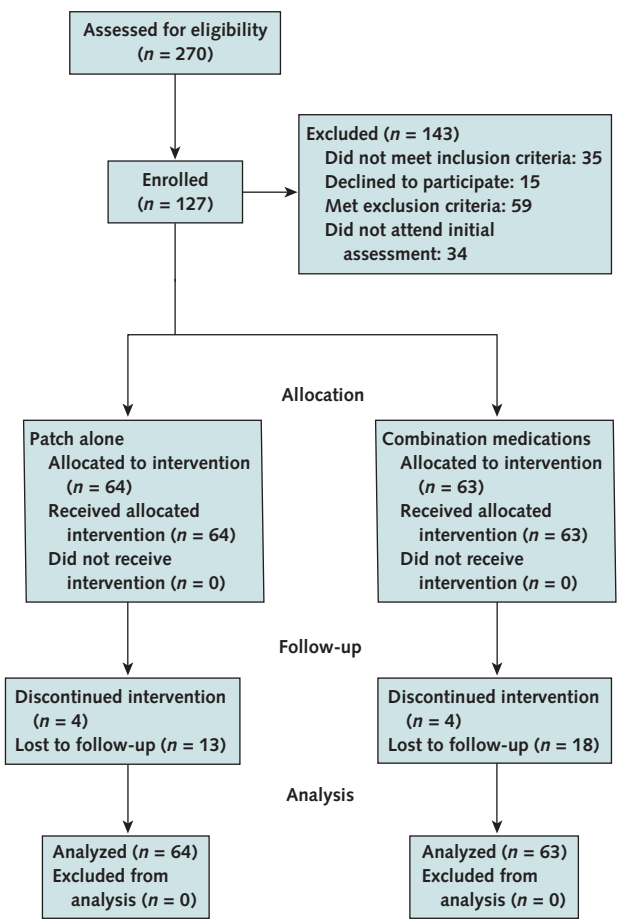


Table 1. **Baseline Demographic, Medical, and Tobacco Use Characteristics, by Treatment Group**

Characteristic	Total (*n* = 127)	Combination Group (*n* = 63)	Patch-Alone Group (*n* = 64)
Age, *n* (%)			
<35 y	16 (12.6)	7 (11.1)	9 (14.1)
35–49 y	52 (40.9)	26 (41.3)	26 (40.6)
50–64 y	48 (37.8)	24 (38.1)	24 (37.5)
≥65 y	11 (8.7)	6 (9.5)	5 (7.8)
Sex, *n* (%)			
Male	45 (35.4)	23 (36.5)	22 (34.4)
Female	82 (64.6)	40 (63.5)	42 (65.6)
Race, *n* (%)			
Black or non-Hispanic	40 (31.5)	17 (27.0)	23 (35.9)
Hispanic	8 (6.3)	4 (6.3)	4 (6.3)
White or non-Hispanic	77 (60.6)	41 (65.1)	36 (56.3)
Other	2 (1.6)	1 (1.6)	1 (1.6)
Education, *n* (%)			
High school graduate or less	51 (40.2)	27 (42.9)	24 (37.5)
Some college	52 (40.9)	25 (39.7)	27 (42.2)
College graduate or more	24 (18.9)	11 (17.5)	13 (20.3)
Employment, *n* (%)			
Full-time	74 (58.3)	36 (57.1)	38 (59.4)
Part-time	14 (11.0)	7 (11.1)	7 (10.9)
Other	38 (29.9)	20 (31.7)	18 (28.1)
Medical history, *n* (%)			
Any cancer	17 (13.4)	8 (12.7)	9 (14.1)
Abnormal Papanicolaou smear*	20 (24.4)	10 (23.8)	10 (25.0)
Cardiovascular disease			
Heart disease	18 (14.2)	7 (11.1)	11 (17.2)
Stroke	7 (5.5)	3 (4.8)	4 (6.3)
Vascular disease	9 (7.1)	4 (6.3)	5 (7.8)
Chronic obstructive pulmonary disease	31 (24.4)	17 (27.0)	14 (21.9)
Cardiovascular disease risk factors			
Diabetes	20 (15.7)	9 (14.3)	11 (17.2)
Hyperlipidemia	55 (43.3)	24 (38.1)	31 (48.4)
Hypertension	52 (40.9)	28 (44.4)	24 (37.5)
Psychological or psychiatric condition			
Depression	46 (36.2)	23 (36.5)	23 (35.9)
Anxiety	33 (26.0)	14 (22.2)	19 (29.7)
Alcohol abuse	27 (21.3)	13 (20.6)	14 (21.9)
Substance abuse	14 (11.0)	9 (14.3)	5 (7.8)
Tobacco use, *n* (%)			
<20 cigarettes/d	44 (34.6)	21 (33.3)	23 (35.9)
≥20 cigarettes/d	83 (65.4)	42 (66.7)	41 (64.1)
Mean Fagerström test score for nicotine dependence (SD)†	5.20 (2.08)	5.16 (1.91)	5.23 (2.25)
Mean scores on tobacco belief scales (SD)‡			
Smoking negatively affects health	7.8 (2.4)	7.7 (2.5)	7.9 (2.3)
Quitting will improve health	9.3 (1.6)	9.4 (1.5)	9.3 (1.6)
Importance of quitting	9.4 (1.2)	9.3 (1.3)	9.4 (1.1)
Confidence in quitting	6.9 (2.3)	6.9 (2.5)	6.9 (2.2)
Readiness to quit	8.4 (1.9)	8.1 (2.0)	8.7 (1.7)

* Percentage relative to total female patients.
† The Fagerström test for nicotine dependence is a validated 6-item instrument to measure the level of dependence to nicotine. The total score range is 0 to 10, with ≥6 indicating high dependence.
‡ Belief scales were Likert scales (0 = no effect; 10 = extreme effect).

Statistical Analysis

On the basis of previous work with combination therapy, we did sample size calculations based on expected abstinence rates of 18% for patch alone and 35% for combination therapy. We needed approximately 127 participants to detect this effect with 80% power ($P < 0.05$).

We calculated frequencies of participant demographic characteristics. We used exact tests to measure differences between groups among categorical variables, and *t* tests for continuous variables. Kaplan–Meier and proportional hazards survival analyses measured time to relapse among groups. Logistic regression measured odds ratios for abstinence by a fixed period (with previous withdrawal patients considered to still be smoking, as described earlier). We preplanned these analyses, and multivariate models included all demographic variables and factors that have been shown in previous studies to influence abstinence (dependence and consumption). We defined significance as a 2-sided *P* value less than 0.05. We conducted statistical analyses with SAS software, version 9.1 (SAS Institute, Cary, North Carolina).

Role of Funding Source

The Cancer Institute of New Jersey and Robert Wood Johnson Foundation funded this study. The funding sources had no role in the design, implementation, or results of the study or the preparation of or decision to submit the manuscript for publication.

RESULTS

Figure 1 shows the participant flow through the study. We screened 270 persons for eligibility and excluded 143 (53%). Overall, 24% (31 of 127) of participants were lost to follow-up by 26 weeks (20% [13 of 64] in the patch-alone group and 28% [18 of 63] in the combination group; $P = 0.28$). No treatment crossovers between groups occurred. **Table 1** reports demographic characteristics of participants in each treatment group.

All participants reported that the most common motivational factors for quitting were health (100%), dislike of being addicted (87%), family concerns (85%), and money (69%). The most common withdrawal symptoms reported from previous quit attempts among all participants were cravings for cigarettes (83%), irritability (69%), restlessness (67%), and anxiety (57%). The most commonly reported triggers to smoking included stress (95%), having had a meal (95%), feeling anxious (89%), seeing other smokers (86%), boredom (84%), coffee (78%), and driving (76%).

Participants in the combination group used medications for a mean duration of 89 days, whereas those in the patch-alone group used medications for a mean of 35 days. Despite this, only 3% (2 of 63) in the combination group still used all medications at 26 weeks; 3% (2 of 63) still used 2 medications (bupropion and in-

haler), and 17% (11 of 63) still used at least 1 of the 3 medications. Those continuing use of a single medication all used the inhaler. Although use varied, most participants who used bupropion during the study continued to use it for 2 to 3 months.

The primary outcomes of the study were tobacco abstinence rates. Four weeks after the target quit date, the abstinence rate was nonsignificantly higher in the combination group (41 of 63 [65%]) than in the patch-alone group (31 of 64 [48%]) (relapse benefit, 17% [95% CI, −2% to 32%]; $P = 0.059$). At this point, participants in both groups were still receiving the 21-mg dose of the nicotine patch. By the 26-week follow-up, the abstinence rate was significantly higher in the combination group (22 of 63 [35%] vs. 12 of 64 [19%]; relapse benefit, 16% [CI, 1% to 31%]; $P = 0.040$).

Figure 2 compares time to relapse between the treatment groups. Participants in the combination group had a significantly longer Kaplan–Meier time to relapse than those in the patch-alone group (median, 65 days vs. 23 days). The hazard ratio for time to relapse was 0.55 (CI, 0.36 to 0.85) for the combination group ($P = 0.005$).

Table 2 shows univariate and adjusted analyses of abstinence rates at 26 weeks, by subgroup characteristics. Participants with a history of medical conditions had 26-week abstinence rates of 18% (any cancer), 33% (cardiovascular disease), 25% (pulmonary disease), 26% (depression), 30% (anxiety), 26% (alcohol abuse), and 14% (substance abuse). However, the differences in abstinence rates between participants with or without these conditions or among participants with different conditions were not statistically significant. A full multivariate logistic regression model for abstinence at 26 weeks was used, including age, sex, race, education, Fagerström test score for nicotine dependence, cigarettes smoked per day, and treatment group. After controlling for all factors, we found that some college education (adjusted odds ratio, 2.97 [CI, 1.06 to 8.30]) and use of combination medications (adjusted odds ratio, 2.57 [CI, 1.05 to 6.32]) were associated with higher abstinence at 26 weeks. The regression was rerun in a stepwise fashion, producing the same results.

Table 3 describes the frequency of adverse events reported by participants in the trial. Although most participants in both groups reported some type of adverse event, few (5% in each group) reported serious adverse events. No difference in the rates of treatment discontinuation due to adverse events between the 2 groups (6% in each) occurred. No discontinuation adverse event was directly related to a participant's underlying medical illness. The most common adverse events reported in both groups were dream disturbance and rash at the patch site. Insomnia, anxiety, fatigue, and diarrhea occurred at higher rates in the combination group than in the patch-alone group.

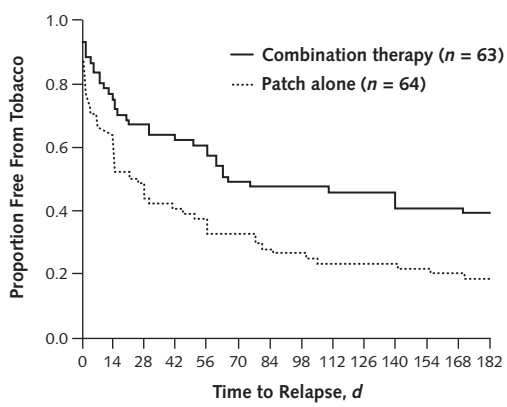
DISCUSSION

Our randomized trial demonstrates that smokers with medical illnesses who used the extended-duration combination of nicotine patch, nicotine inhaler, and bupropion had a 16% higher abstinence rate at 6 months than did smokers who used standard-duration patch therapy alone (35% vs. 19% [CI, 1% to 31%]). To our knowledge, this is the first randomized trial to demonstrate the benefit of a triple-medication combination for an extended duration in medically ill smokers.

To place our findings in context, we did a MEDLINE search of articles published in English up to November 2008. Previous studies suggest the benefit of combining nicotine medications with bupropion (7, 8, 15, 17, 19) and the benefit of combining different forms of nicotine medications (5, 6, 20–24). The flexibility to use medications for an extended period may also help prevent relapse (13, 15). Our findings are consistent with the current clinical practice guidelines' meta-analysis of dual nicotine-medication combination therapy compared with the patch alone (8). However, the studies reviewed did not focus on smokers with medical illnesses.

Use of this flexible, combined regimen may have several advantages. First, the simultaneous use of nicotine medications with bupropion addresses tobacco withdrawal through different mechanisms of action. Second, the combination of a passive, continuous form of nicotine medication (patch) with an active, shorter-acting form (inhaler) to be used in response to cravings allows more individualized delivery of medication as needed by patients, giving them more control over their dosing. Third, the ability of participants in the combination group to use the medications

Figure 2. **Time to relapse, by treatment group.**



	Day				
	0	28	42	70	180
Persons at Risk, *n*					
Patch	64	31	26	21	12
Combination	63	41	39	30	24

Table 2. **Abstinence Rates and Unadjusted and Adjusted Odds Ratios 26 Weeks After Target Quit Date, by Subgroup***

Characteristic	26-Week Abstinence, *n/n (%)*	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)	*P* Value
Age				
<35 y	2/16 (12.5)	0.38 (0.05–2.78)	0.43 (0.05–3.62)	0.44
35–49 y	9/52 (17.3)	0.56 (0.12–2.52)	0.67 (0.13–3.55)	0.63
50–64 y	20/48 (41.7)	1.91 (0.45–8.09)	2.30 (0.47–11.31)	0.31
≥65 y	3/11 (27.3)	Referent	Referent	–
Sex				
Women	19/82 (23.2)	Referent	Referent	–
Men	15/45 (33.3)	1.66 (0.74–3.71)	2.20 (0.85–5.70)	0.11
Race or ethnicity				
White	22/77 (28.6)	Referent	Referent	–
Black	8/40 (20.0)	0.63 (0.25–1.57)	0.62 (0.21–1.84)	0.39
Hispanic	3/8 (37.5)	1.50 (0.33–6.82)	2.32 (0.41–13.12)	0.34
Other	1/2 (50.0)	2.50 (0.15–41.76)	4.97 (0.06–403.71)	0.47
Education				
High school graduate or less	11/51 (21.6)	Referent	Referent	–
Some college	18/52 (34.6)	1.93 (0.80–4.63)	2.97 (1.06–8.30)	0.04
College graduate or more	5/24 (20.8)	0.96 (0.29–3.15)	1.11 (0.28–4.43)	0.88
Fagerström test score for nicotine dependence				
Low–medium (≤5)	18/73 (24.7)	Referent	Referent	–
High–very high (≥6)	16/54 (29.6)	1.29 (0.58–2.84)	1.41 (0.55–3.63)	0.47
Cigarettes per day				
<20	12/44 (27.3)	Referent	Referent	–
≥20	22/83 (26.5)	0.96 (0.42–2.19)	0.46 (0.15–1.39)	0.17
Treatment group				
Patch alone	12/64 (18.8)	Referent	Referent	–
Combination	22/63 (34.9)	2.33 (1.03–5.25)	2.57 (1.05–6.32)	0.04

* Full multivariate logistic regression model included all above variables. A stepwise procedure was also done, with similar findings.

Table 3. **Adverse Events, by Treatment Group**

Variable, *n (%)*	Patch-Alone Group (*n* = 64)	Combination Group (*n* = 63)
Death	0 (0)	0 (0)
Discontinued treatment because of adverse events	4 (6)	4 (6)
Reported any adverse event	41 (64)	48 (76)
Reported a serious adverse event	3 (5)	3 (5)
Most common adverse events		
Dream disturbance	14 (22)	22 (35)
Rash	15 (23)	19 (30)
Insomnia*	6 (9)	16 (25)
Anxiety*	2 (3)	14 (22)
Fatigue*	2 (3)	14 (22)
Diarrhea*	1 (2)	8 (13)
Upper respiratory tract infection	7 (11)	10 (16)
Nausea	5 (8)	10 (16)
Muscle pain	8 (12.5)	5 (8)
Headache	6 (9)	6 (9.5)
Dizziness	6 (9)	3 (5)
Other gastrointestinal symptoms	2 (3)	4 (6)
Palpitation	1 (2)	4 (6)
Cough	0 (0)	4 (6)

* $P < 0.05$ for difference between treatment groups.

for as long as they felt necessary allowed them to tailor their medication treatment duration. This flexibility to use medications for an extended period may have contributed to the longer time to relapse seen in the combination group (**Figure 2**). Ultimately, the treatment goal is to be tobacco-free, regardless of continued medication use. These findings support ad libitum duration as an advantage of a treatment regimen.

Even though persons with medical illnesses smoke at high rates, they are often not prescribed intensive smoking cessation pharmacotherapy because of concern about adverse events, such as cardiac events with nicotine replacement. Although our study was not powered as a safety study, we did not find evidence that combinations of tobacco dependence medications resulted in higher rates of adverse effects requiring discontinuation compared with the patch alone. The current product labeling of over-the-counter nicotine replacement discourages combining the patch with other forms of nicotine replacement and strictly limits the duration of treatment. Experts have suggested revision to the current labeling that would allow more liberal and individualized use of these products (13, 25). In addition, extended duration of treatment is impeded by

inadequate funding coverage for tobacco treatment medications. This coverage is typically not provided for smoking cessation (26) as it is for other chronic conditions.

Our study has specific strengths. Many previous trials excluded smokers with medical illnesses, making the results more difficult to generalize to smokers with concurrent illnesses. The smokers in our trial have similar characteristics to those typically treated in an outpatient medical office. Although the total number of contacts was higher than normal for a medical practice, the treatment protocol included feasible behavioral treatment (including a commonly used pamphlet) and medications that can be routinely used. Therefore, our protocol's major strength is its generalizability for adoption. Second, our study adds randomized trial data on combination and extended-duration treatments to our existing observational data from our specialty tobacco clinic (15). Finally, the primary outcome included measurements of abstinence that were biochemically verified by exhaled carbon monoxide measurement.

Our study also has some limitations. First, we did not blind treatment assignment. However, we used objective criteria for abstinence (carbon monoxide measures) to reduce bias in outcomes. Second, we could not measure which components of the combination group contributed to the increased abstinence rates (combination of medications or longer duration). We designed the study to compare the overall effectiveness of this flexibly dosed treatment plan as a whole and not to distinguish among these components. However, the findings do suggest that each of these components (combination and duration) contributed to the overall advantage. At the 10-week point, although both treatment groups were receiving study medications, abstinence rates were higher in the combination group. This indicates a treatment advantage for the combination group before duration of treatment becomes an issue. In addition, longer duration of medication use in the flexibly dosed combination group was related to higher abstinence rates. Further studies could investigate the relative benefit of each component of this treatment regimen. Third, about one quarter of participants were lost to follow-up during the trial, with a similar number lost in each treatment group. Most, if not all, of these participants probably had smoking relapse and thus did not wish to continue participation. In order to take a conservative approach, we considered all smokers lost to follow-up as still smoking after their last date seen in the study. Finally, participants did not include smokers with all medical illnesses, such as those with unstable cardiac disease, seizures, or psychotic conditions, and most participants were women.

Medically ill smokers are often highly addicted and at great risk for complications from continued smoking. These patients need intensive treatment to be successful in quitting. Our findings suggest that a flexible-duration, triple-medication combination therapy nearly doubles the abstinence rate for smokers with medical illnesses compared with standard-duration therapy with the nicotine patch alone. This intervention design is feasible in a general medical practice and is consistent with the latest guidelines, which suggests combination pharmacotherapy as a first-line treatment of tobacco dependence (8).

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