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Comparative effectiveness of intervention components for producing long-term abstinence from smoking: a factorial screening experiment

Tanya R. Schlam[1,2], Michael C. Fiore[1,2], Stevens S. Smith[1,2], David Fraser[1], Daniel M. Bolt[3], Linda M. Collins[4], Robin Mermelstein[5], Megan E. Piper[1,2], Jessica W. Cook[1,2,6], Douglas E. Jorenby[1,2], Wei-Yin Loh[7] & Timothy B. Baker[1,2]

University of Wisconsin School of Medicine and Public Health Center for Tobacco Research and Intervention Madison, WI, USA,[1] University of Wisconsin School of Medicine and Public Health Department of Medicine Madison, WI, USA,[2] University of Wisconsin Department of Educational Psychology Madison, WI, USA,[3] The Pennsylvania State University The Methodology Center and Department of Human Development and Family Studies State College, PA, USA,[4] University of Illinois at Chicago, Institute for Health Research and Policy, Chicago, IL, USA,[5] William S. Middleton Memorial Veterans Hospital, Madison, WI, USA[6] and University of Wisconsin, Department of Statistics, Madison, WI, USA[7]

ABSTRACT

Aims To identify promising intervention components that help smokers attain and maintain abstinence during a quit attempt. **Design** A 2 × 2 × 2 × 2 × 2 randomized factorial experiment. **Setting** Eleven primary care clinics in Wisconsin, USA. **Participants** A total of 544 smokers (59% women, 86% white) recruited during primary care visits and motivated to quit. **Interventions** Five intervention components designed to help smokers attain and maintain abstinence: (1) extended medication (26 versus 8 weeks of nicotine patch + nicotine gum); (2) maintenance (phone) counseling versus none; (3) medication adherence counseling versus none; (4) automated (medication) adherence calls versus none; and (5) electronic medication monitoring with feedback and counseling versus electronic medication monitoring alone. **Measurements** The primary outcome was 7-day self-reported point-prevalence abstinence 1 year after the target quit day. **Findings** Only extended medication produced a main effect. Twenty-six versus 8 weeks of medication improved point-prevalence abstinence rates (43 versus 34% at 6 months; 34 versus 27% at 1 year; $P = 0.01$ for both). There were four interaction effects at 1 year, showing that an intervention component's effectiveness depended upon the components with which it was combined. **Conclusions** Twenty-six weeks of nicotine patch + nicotine gum (versus 8 weeks) and maintenance counseling provided by phone are promising intervention components for the cessation and maintenance phases of smoking treatment.

Keywords Chronic care smoking treatment, comparative effectiveness, electronic medication monitoring, factorial experiment, medication adherence, Multiphase Optimization Strategy (MOST), nicotine replacement therapy, Phase-Based Model of smoking treatment, primary care, relapse prevention, smoking cessation, tobacco dependence.

Correspondence to: Tanya R. Schlam, University of Wisconsin School of Medicine and Public Health, Center for Tobacco Research and Intervention, 1930 Monroe Street, Suite 200, Madison, WI, 53711, USA. E-mail: trschlam@ctri.wisc.edu
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INTRODUCTION

Most smokers would like to quit [1]. Of those who try to quit without evidence-based treatment, however, only approximately 5% succeed in maintaining long-term abstinence [2]. Even with evidence-based treatment, only approximately 15–35% succeed long-term [3]. The majority of smokers relapse early in their quit attempts [4], but even those who achieve abstinence face a meaningful risk of relapse for many months (e.g. [5]). While current cessation treatments increase initial abstinence quite effectively, there is a need for treatments that maintain it more effectively [6–8]. As per the Phase-Based Model of smoking treatment [8,9], the identification of intervention components that maintain abstinence is critical to treat smokers effectively in the maintenance phase: the phase of smoking treatment that follows establishment of initial abstinence in the cessation phase and extends from approximately 2 to 4 weeks post-quit and onward as needed, and

whose goal is maintaining abstinence [9,10]. Typical challenges to this goal include medication discontinuation or non-adherence, and failure to use coping skills and support.

This research evaluated three promising approaches to increasing long-term abstinence: extended medication, interventions to increase medication adherence and extended counseling involving coping skills training. This is one of four linked papers. One [10] reviews the theory and methods behind this research; the others report factorial experiments of intervention components for the motivation [11] and preparation/cessation [12] phases of smoking treatment. This experiment evaluated components for the cessation and maintenance phases.

Clinical trials comparing extended versus briefer medication have produced mixed results [13–17]. However, research suggests that providing extended versus briefer medication helps smokers regain abstinence if they lapse [15,18–20]. Research on cessation medication [3] may not reflect its full potential benefit, because only approximately half or fewer smokers adhere to their prescribed dose and duration of medication [21–24]. Increasing adherence could potentially boost long-term abstinence because medication adherence typically decreases markedly over time (e.g. [25,26]). However, while medication adherence is correlated positively with abstinence [24,27–31], the directionality of the causal relation is unclear ([21,23,27,29], although see [32]). Potential adherence approaches include addressing negative beliefs about medications (e.g. [33], although see [34]) and monitoring, prompting and providing feedback regarding medication use [23,34].

Counseling involving coping skills training and support [35,36] is the most studied approach to increasing long-term abstinence. Such counseling boosts initial cessation, but it is less clear that it increases long-term abstinence reliably (cf. [3,6,13,37–39]). Findings are also mixed concerning the benefit of extending such counseling [14,40–42], illustrating a need for further research.

This experiment evaluated five promising intervention components designed to increase long-term abstinence by addressing challenges patients face during the cessation and maintenance phases of smoking treatment. The five components were: extended medication, maintenance counseling and three components designed to increase medication adherence (medication adherence counseling, automated adherence calls and electronic medication monitoring with feedback and counseling). Consistent with pragmatic research principles [43], all components and delivery systems were designed for application in real-world health-care settings. Additionally, this research was guided by the Multiphase Optimization Strategy (MOST: [44–46]), which advocates the use of efficient factorial screening experiments to evaluate multiple intervention components simultaneously. Promising components identified in screening experiments can then be combined into a treatment package to be evaluated subsequently in a randomized controlled trial (RCT [10]).

METHODS

Procedure

This experiment was conducted from June 2010 to November 2013. Participants were recruited from 11 primary care clinics in two health-care systems in southern Wisconsin. Existing clinical care staff (i.e. medical assistants)—prompted by electronic health record technology—invited identified smokers during clinic visits to participate in a research program to help them quit smoking [47,48]. Patients interested in quitting were assigned randomly to either this experiment or the other cessation experiment described in this issue [12]. It should be noted that although there were three related experiments (this experiment and [11,12]), each used an independent, non-overlapping sample.

Interested patients were referred electronically to research staff, who then called patients to assess their eligibility. Inclusion criteria were: age ≥ 18 years; smoking $\geq$ five cigarettes/day for the previous 6 months; being motivated to quit; able to read, write and speak English; agreeing to complete assessments; planning to remain in the area for ≥ 12 months; not currently taking bupropion or varenicline; agreeing to use only study cessation medication during treatment (e.g. discontinuing ongoing nicotine replacement therapy [NRT] use); no medical contraindications to NRT; and, for women of childbearing potential, agreeing to use an approved birth control method during treatment.

Eligible patients were invited to return to their primary care clinic to learn about the study and provide informed consent. A research database created intervention and assessment schedules based on participants' randomly assigned treatment conditions. Clinic-based case managers (bachelor's-level research staff supervised by licensed clinical psychologists) provided study treatment.

Experimental design

This $2 \times 2 \times 2 \times 2 \times 2$ factorial experiment evaluated the effects of five experimental, two-level factors. Participants were randomized to one of 32 unique experimental conditions (see Supporting information, Table S1) via a database that used stratified, computer-generated, permuted block randomization, with stratification by gender and clinic, and with a fixed block size of 32 (conditions were randomized within each block). Thus, all 32 conditions were available in each clinic. Staff could not view the allocation sequence. The database did not reveal participants'

treatment condition to staff until participants' eligibility was confirmed; participants were blinded to treatment condition until they provided consent.

The five experimental factors

All participants received a standard cessation intervention: 8 weeks of nicotine patch + nicotine gum and 50 minutes of counseling delivered over four sessions [in visits 1 week before and 1 week after the target quit day (TQD), and in calls on the TQD and at week 2]. In addition, they were randomized to receive one of two levels of each factor: either an 'On' (or more intense) level or an 'Off' (or less intense) level. (See Supporting information for outlines of counseling protocols and how counseling fidelity was monitored.) The five factors were as follows.

Extended medication

All participants were asked to use nicotine patch + nicotine gum starting on their TQD. Half were assigned to 8 weeks of patches (> nine cigarettes/day = 4 weeks of 21-mg, 2 weeks of 14-mg and 2 weeks of 7-mg patches; five to nine cigarettes/day = 4 weeks of 14-mg and 4 weeks of 7-mg patches) and gum (smoke within 30 minutes of waking = 4 mg; smoke >30 minutes after waking = 2 mg), and half were assigned to 26 weeks of patches (> nine cigarettes/day = 22 weeks of 21-mg, 2 weeks of 14-mg and 2 weeks of 7-mg; five to nine cigarettes/day = 22 weeks of 14-mg and 4 weeks of 7-mg) and gum (dosed as above). Participants were advised to use the gum every 1–2 hours and at least five pieces/day barring adverse effects.

Maintenance counseling

Half the participants were assigned to receive maintenance counseling consisting of eight 15-minute phone sessions at weeks 3, 4, 6, 8, 10, 14, 18 and 22 after the TQD. The counseling was designed to provide support and encourage continued use of coping skills. Participants who relapsed received counseling aimed at motivating and planning a renewed quit attempt, which has been shown to be effective when delivered via phone [49,50]. The remaining participants received no maintenance counseling.

Medication adherence counseling (MAC)

Half the participants received two 10-minute MAC sessions (at visits 1 week pre-TQD and 1 week post-TQD), tailored to correct misconceptions about NRT that might interfere with adherent use [51]. The remaining participants received no MAC.

Automated adherence calls

Half the participants received automated medication reminder calls (8 weeks medication group = seven calls on days 1, 3, 10, 17, 24, 31 and 45; 26 weeks medication group = 11 calls with the additional calls on days 73, 101, 129 and 157). The calls included strategies for remembering to use the medication, and brief motivational, supportive and educational messages to encourage medication compliance [52,53]. The remaining participants received no adherence calls.

Helping hand (HH) with feedback and counseling

All participants carried an HH [54]—a medication dispenser that electronically recorded when the nicotine gum placard was removed from the container. Half the participants received a printout showing how much gum they used daily (as recorded by the HH) plus 10-minute adherence counseling sessions based on the printout (8 week medication group = three in-person and two phone sessions; 26 week medication group = five in-person and four phone sessions). The remaining participants received no HH feedback or related counseling.

Assessments

Participants completed baseline assessments at 1 week pre-TQD, including: exhaled carbon monoxide using the Bedfont Smokerlyzer (Bedfont Scientific, Rochester, UK), demographics, smoking history and tobacco dependence (Fagerström Test of Nicotine Dependence; FTND [55]). Participants completed assessments during visits at weeks 1, 4 and 8 (plus week 16 if receiving extended medication) with case managers, and during follow-up calls at weeks 16, 26, 39 and 52 with assessors. Medication adverse events were assessed where relevant. Automated calls assessed medication use and occurred periodically from 9 days pre-TQD to 6 months post-TQD.

Outcome measures

The primary outcome was self-reported 7-day point-prevalence abstinence at 52 weeks, with a secondary outcome at 26 weeks.[1] During all post-TQD visits with case managers and during follow-up calls (including those at 26 and 52 weeks) with assessors not involved in treatment (but not blind to treatment assignment), participants reported cigarettes per day on each of the last 7 days and whether they smoked on each day since last contact in a time-line follow-back interview [56]. Week 52 was primary, because this experiment's chief goal was to increase long-term abstinence. Week 26 was selected because its proximity to treatment delivery might enhance its sensitivity to treatment effects [9] and because it permits comparison with other treatment research.

[1]Based upon reviewer recommendations, the designation of primary and secondary outcomes was altered from what was listed in trial registration materials.

Analytical plan

Logistic regression (computed with SPSS [57]) was used to examine point-prevalence abstinence at 26 and 52 weeks. Initial models included all five main effects and all interactions. The logistic regression used effect coding [10] where the 'Off' level of a factor was coded as −1 and the 'On' level was coded as +1. At week 52, the full logistic regression model could not be fitted (due to a null value cell), so the five-way interaction was omitted from that model. Analyses were conducted with and without adjustment for a predetermined set of demographic and tobacco dependence covariates: gender, race (white versus non-white), age, education (up to high school diploma/General Educational Development [GED] versus at least some college), the Heaviness of Smoking Index [58], baseline exhaled carbon monoxide and health-care system (A versus B).

All models were intent-to-treat analyses assuming missing = smoking. Primary outcome analyses were supplemented with sensitivity analyses using multiple imputation for missing data [59], which assumed that only 80% of dropouts returned to smoking, and that the likelihood of a smoking outcome was related to baseline smoker covariates. Results of the missing = smoking and sensitivity/multiple imputation analyses were highly similar, so we present the missing = smoking results only (see Supporting information for sensitivity analyses).

RESULTS

Participants

Of smokers recruited during a clinic visit and interested in quitting, 1116 were referred to this experiment, and 544 consented (Fig. 1; see Supporting information for sample size justification). See Table 1 for the sample's demographic and tobacco dependence characteristics. Each of the 11 clinics recruited between 28 and 87 participants.

Treatment engagement

Participants completed a mean of 3.55 [standard deviation (SD) = 2.83] of eight maintenance counseling sessions and a mean of 1.76 (SD = 0.43) of two MAC sessions. Participants in the 8-week medication condition completed a mean of 3.67 (SD = 1.53) of five HH sessions and answered a mean of 3.59 (SD = 2.56) of seven adherence calls. Those in the 26-week medication condition completed a mean of 5.65 (SD = 2.74) of nine HH sessions and answered a mean of 4.85 (SD = 3.95) of 11 adherence calls.

Patch and gum use were calculated based on the first 6 or 16 weeks of medication use for the 8- and 26-week medication conditions, respectively. Those assigned 8 versus 26 weeks of medication used the patch a mean of 86.7 and 83.8% of days, respectively (assessed via answered automated calls), and used a mean of 2.67 (SD = 2.08) and 2.37 (SD = 1.97) pieces of gum/day, respectively (assessed via the HH). More extensive medication adherence analyses will be reported in a subsequent paper.

Safety

There were no serious adverse events related to study participation. The most common adverse events for 8 versus 26 weeks of nicotine patch + nicotine gum were, respectively: vivid dreams (19 versus 16%), skin rash (19 versus 23%), nausea (14 versus 15%) and insomnia (12 versus 11%).

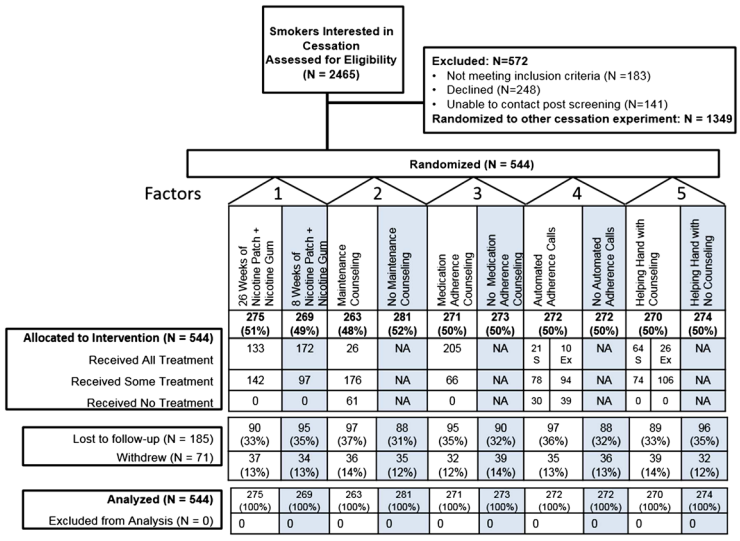

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. S = randomized to standard 8 weeks of nicotine patch + nicotine gum; Ex = randomized to extended 26 weeks of nicotine patch + nicotine gum. See Supporting information for reasons participants withdrew from the study

Table 1 Demographic and smoking history characteristics.

	Total sample	*Extended medication (nicotine patch + nicotine gum)*		*Maintenance (phone) counseling*		*Medication adherence counseling (MAC)*		*Automated (medication) adherence calls*		*Helping hand (HH) with counseling*	
		26 weeks	*8 weeks*	*Maintenance Counseling*	*No Maintenance Counseling*	*MAC*	*No MAC*	*Calls*	*No Calls*	*HH Counseling*	*No HH Counseling*
Women (%)	59.0%	58.9	59.1	60.1	58.0	57.2	60.8	59.6	58.5	58.5	59.5
Age (mean, SD)	46.2 (12.8)	46.9 (12.2)	45.4 (13.3)	46.4 (12.6)	46.0 (12.9)	45.7 (12.5)	46.7 (13.0)	46.6 (12.6)	45.8 (13.0)	46.1 (13.4)	46.2 (12.1)
High school diploma or General Educational Development (GED) only (%)	33.6	31.0	36.3	38.7	28.9	33.1	34.2	34.8	32.5	31.6	35.7
At least some college (%)	56.9	58.4	55.4	54.4	59.2	57.2	56.6	55.2	58.6	57.7	56.3
White (%)	87.4	84.7	86.2	85.2	85.8	86.0	85.0	87.5	83.5	87.4	83.6
African American (%)	9.6	10.5	7.8	9.9	8.5	7.7	10.6	8.5	9.9	8.9	9.5
Hispanic (%)	4.2	3.3	5.0	2.8	5.4	4.9	3.4	4.2	4.2	3.1	5.2
Health-care System A[a] (%)	59.0	64.7	53.2	58.2	59.8	58.7	59.3	57.4	60.7	58.5	59.5
Cigarettes/day (mean, SD)	18.6 (8.8)	19.0 (9.0)	18.2 (8.5)	18.5 (9.2)	18.8 (8.4)	18.6 (8.8)	18.6 (8.7)	18.4 (8.4)	18.9 (9.1)	18.2 (8.4)	19.1 (9.1)
Baseline carbon monoxide (mean, SD)	18.5 (9.9)	19.1 (10.0)	18.0 (9.7)	18.8 (9.7)	18.3 (10.0)	18.6 (9.6)	18.5 (10.1)	18.2 (9.4)	18.9 (10.3)	18.3 (9.6)	18.8 (10.1)
FTND (mean, SD)	4.9 (2.3)	4.9 (2.3)	4.8 (2.2)	4.8 (2.3)	4.9 (2.2)	4.9 (2.3)	4.9 (2.2)	4.9 (2.3)	4.9 (2.2)	4.8 (2.3)	4.9 (2.2)
Heaviness of Smoking Index (mean, SD)	3.2 (1.5)	3.3 (1.5)	3.2 (1.5)	3.2 (1.5)	3.3 (1.4)	3.2 (1.5)	3.2 (1.4)	3.3 (1.4)	3.2 (1.5)	3.2 (1.5)	3.2 (1.4)

[a]The study was conducted in two health-care systems (A and B). FTND = Fagerstrom Test of Nicotine Dependence; SD = standard deviation.

Missing data

The percentage of participants missing abstinence outcome data was 20.4% at week 26 and 30.0% at week 52, with no differences observed in missingness across the two levels (On versus Off) of any of the factors.

Smoking status outcomes

Table 2 shows the self-reported 7-day point-prevalence abstinence rates for each main effect at weeks 26 and 52. Table 3 presents the logistic regression results for the unadjusted (primary) and covariate adjusted week 26 and 52 outcomes. We discuss data from the unadjusted models except where noted; patterns of statistical significance were generally consistent with the adjusted models.

Only one factor produced a significant main effect: 26 versus 8 weeks of medication increased abstinence rates (43 versus 34% at week 26; 34 versus 27% at week 52). At week 52, there was an extended medication × MAC interaction, showing that among participants who received 26 weeks of medication, those who received no MAC had a higher mean abstinence rate at week 52 than those who received MAC (39 versus 29%; Supporting information, Fig. S1). There were two two-way antagonistic interactions (i.e. the effects of two or more components when combined were less than would be expected based on their summed main effects). In the MAC × adherence calls interaction (Fig. 2), those receiving no MAC and no adherence calls had disproportionately higher abstinence rates than those receiving one or both of these adherence interventions. In the adherence calls × HH counseling interaction (Fig. 3), HH counseling without adherence calls (week 52) and adherence calls without HH counseling (week 26 unadjusted model $P = 0.07$; adjusted model $P = 0.047$) resulted in the highest abstinence rates, but the combination did not improve abstinence further.

There were two three-way interactions at week 52. The extended medication × MAC × adherence calls interaction (Fig. 4) revealed that extended medication produced superior results with no adherence calls and no MAC (week 52) or with adherence calls but no MAC (week 26 unadjusted model $P = 0.050$; adjusted model $P = 0.03$). The maintenance counseling × MAC × HH counseling interaction at weeks 26 and 52 (Fig. 5) revealed that among participants receiving neither MAC nor HH counseling, those receiving maintenance counseling showed substantially higher abstinence rates than those not receiving maintenance counseling (38 versus 24% at week 52). Also, HH counseling (with no MAC) appeared to interact antagonistically with maintenance counseling at weeks 26 and 52, yielding higher abstinence rates without maintenance counseling than with it.

Finally, there was a four-way interaction at week 52 at $P = 0.053$ involving extended medication × maintenance Counseling × MAC × HH counseling (Fig. 6). Unpackaging this non-significant interaction further informs hypotheses concerning the component interrelations. Among those receiving no MAC and no HH counseling, 8 weeks of medication with no maintenance counseling resulted in the lowest abstinence rates (15%); 8 weeks of medication with maintenance counseling or 26 weeks of medication with no maintenance counseling resulted in intermediate quit rates (31 and 32%, respectively), and 26 weeks of medication with maintenance counseling resulted in the highest quit rates (44% at week 52). Among those receiving no MAC, HH counseling appeared to compensate for an absence of maintenance counseling, bringing abstinence rates to approximately the same level as those who received maintenance counseling and no HH counseling. Receiving HH counseling in addition to maintenance counseling did not, however, appear to improve abstinence rates.

Early abstainer outcomes

We conducted exploratory analyses to examine results in just those who established early abstinence because such analyses should reflect effects on maintenance of abstinence *per se*. All full-sample analyses were repeated using the 266 participants (49% of the full sample) who established initial abstinence (being smoke-free for at least 5 of the first 7 days of the quit attempt and smoke-free on the 7th day; this subsample was selected because early

Table 2 Main effects for self-reported point-prevalence abstinence rates at 26 and 52 weeks after the target quit day ($N = 544$).

	% Abstinent at 26 weeks		*% Abstinent at 52 weeks*	
Factor	*On*	*Off*	*On*	*Off*
Extended medication (nicotine patch + nicotine gum)	42.9	33.5	34.2	26.8
Maintenance (phone) counseling	39.2	37.4	33.1	28.1
Medication adherence counseling	37.3	39.2	28.4	32.6
Automated (medication) adherence calls	39.7	36.8	29.4	31.6
Helping hand with counseling	37.8	38.7	33.3	27.7

On = factor was present or at the longest duration (e.g. 26 weeks of medication). Off = factor was not present or was at the shortest duration (e.g. 8 weeks of medication).

Table 3 Logistic regression models for 26 and 52 week point-prevalence abstinence.

	26 Weeks post-target quit day				*52 Weeks post-target quit day*			
	Unadjusted		*Adjusted*[a]		*Unadjusted*		*Adjusted*[a]	
Variable	*b*	*P-value*	*b*	*P-value*	*b*	*P-value*	*b*	*P-value*
Intercept	**–0.55**	**< 0.001**	–0.19	0.72	**−1.01**	**< 0.001**	**−1.30**	**0.02**
Extended medication	**0.25**	**0.01**	**0.28**	**0.01**	**0.34**	**0.01**	**0.35**	**0.01**
Maintenance counseling	–0.01	0.96	0.01	0.92	0.01	0.96	–0.01	0.94
Medication adherence counseling (MAC)	–0.04	0.70	–0.05	0.60	0.02	0.89	0.04	0.78
Automated adherence calls	0.06	0.58	0.06	0.57	–0.16	0.21	–0.18	0.18
Helping hand (HH) counseling	–0.01	0.94	–0.05	0.61	0.09	0.51	0.07	0.62
Extended medication × maintenance counseling	0.07	0.46	0.04	0.70	0.06	0.68	0.06	0.68
Extended medication × MAC	–0.13	0.20	–0.10	0.35	**–0.25**	**0.046**	–0.24	0.06
Extended medication × adherence calls	0.02	0.82	–0.03	0.80	0.18	0.15	0.16	0.21
Extended medication × HH counseling	0.04	0.73	0.03	0.76	0.03	0.82	0.03	0.84
Maintenance counseling × MAC	–0.02	0.87	–0.05	0.67	0.12	0.36	0.11	0.42
Maintenance counseling × adherence calls	0.02	0.85	–0.01	0.93	0.15	0.26	0.11	0.40
Maintenance counseling × HH counseling	–0.01	0.93	–0.04	0.71	–0.18	0.15	–0.21	0.10
MAC × adherence calls	**0.23**	**0.02**	**0.21**	**0.047**	**0.44**	**0.001**	0.43	**< 0.01**
MAC × HH counseling	0.09	0.38	0.07	0.50	0.17	0.21	0.18	0.20
Adherence calls × HH counseling	–0.18	0.07	**–0.21**	**0.047**	**–0.31**	**0.03**	**–0.33**	**0.02**
Extended medication × maintenance counseling × MAC	–0.13	0.20	–0.13	0.23	–0.20	0.12	–0.20	0.14
Extended medication × maintenance counseling × adherence calls	0.00	0.97	–0.02	0.87	0.08	0.56	0.09	0.50
Extended medication × maintenance counseling × HH counseling	–0.08	0.41	–0.19	0.07	0.16	0.20	0.12	0.34
Extended medication × MAC × adherence calls	–0.19	0.050	**–0.23**	**0.03**	**–0.35**	**< 0.01**	**–0.38**	**< 0.01**
Extended medication × MAC × HH counseling	–0.01	0.96	0.01	0.92	–0.13	0.34	–0.14	0.35
Extended medication × adherence calls × HH counseling	0.15	0.12	0.13	0.22	0.26	0.06	0.24	0.10
Maintenance counseling × MAC × adherence calls	0.16	0.11	0.17	0.11	0.17	0.23	0.18	0.22
Maintenance counseling × MAC × HH counseling	**0.32**	**0.001**	**0.36**	**0.001**	**0.35**	**< 0.01**	**0.37**	**< 0.01**
Maintenance counseling × adherence calls × HH counseling	–0.14	0.17	–0.15	0.16	–0.24	0.08	–0.24	0.08
MAC × adherence calls × HH counseling	**–0.22**	**0.03**	**–0.25**	**0.02**	0.02	0.87	0.00	0.97
Extended medication × maintenance counseling × MAC × adherence calls	–0.17	0.08	–0.15	0.15	–0.13	0.37	–0.10	0.51
Extended medication × maintenance counseling × MAC × HH counseling	–0.18	0.07	–0.20	0.06	–0.26	0.053	–0.27	0.053
Extended medication × maintenance counseling × adherence calls × HH counseling	0.12	0.23	0.12	0.26	0.18	0.18	0.19	0.18
extended medication × MAC × adherence calls × HH counseling	–0.13	0.19	–0.13	0.23	–0.20	0.14	–0.20	0.14
Maintenance counseling × MAC × adherence calls × HH counseling	0.06	0.54	0.06	0.54	0.13	0.29	0.12	0.33
Extended medication × maintenance counseling × MAC × adherence calls × HH counseling[a]	0.12	0.22	0.13	0.21	–	–	–	–

Bold type indicates $P < 0.05$. [a]Adjusted model controlled for gender, race (white versus non-white), age, education (up to high school diploma versus at least some college), the Heaviness of Smoking Index, baseline exhaled carbon monoxide and health-care system (A versus B) ($n = 539$ due to missing covariates). [b]At week 52, the full logistic regression model could not be fitted (due to a null value cell) so the five-way interaction was omitted from that model.

abstinence is predictive of long-term outcome [4,60]). Long-term abstinence rates in this abstainer sample were ~15–20 percentage points higher than in the full sample, but the pattern of abstinence levels was quite similar (albeit *P*-values were higher due to the smaller sample size; see Supporting information, Tables S3–S4).

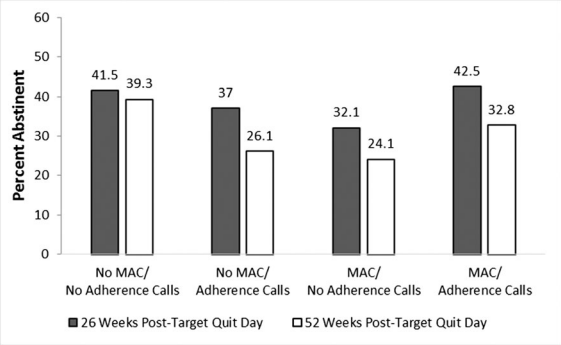

Figure 2 A significant interaction from the 7-day point-prevalence abstinence outcome models: medication adherence counseling (MAC) × automated adherence calls interaction (significant at week 26 and 52)

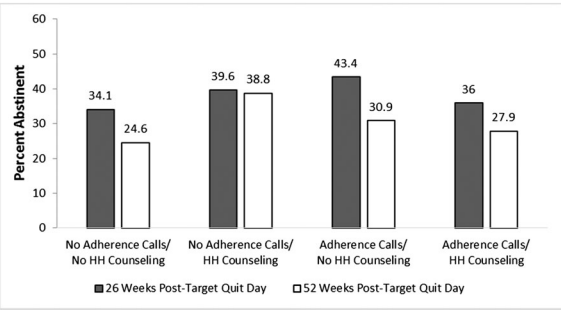

Figure 3 An interaction from the 7-day point-prevalence abstinence outcome models: automated adherence calls × helping hand (HH) counseling (week 26 unadjusted model $P = 0.07$ and adjusted model $P = 0.047$; significant at week 52 in both the unadjusted and adjusted models)

DISCUSSION

This factorial screening experiment demonstrated that execution of a five-factor factorial design was feasible, and revealed a single main effect (extended medication) and multiple interaction effects. This experiment identified intervention components that exerted especially promising effects on long-term abstinence (extended medication and maintenance counseling). Extended medication increased abstinence rates significantly at both 26 and 52 weeks post-TQD. Interaction effects suggested that maintenance counseling also meaningfully increased abstinence rates depending on the components with which it was combined; i.e. maintenance counseling (when not combined with MAC or HH counseling) generally produced relatively high abstinence rates that were not incremented significantly by other components (Figs 5 and 6). Among the medication adherence factors, adherence calls and HH counseling showed modest and mixed evidence of effectiveness, while MAC produced little or no benefit.

The interpretation of the interactions obtained is challenging, due to their complexity. To simplify interpretation, we focus on what we see as the strongest signals among the interacting components. There was evidence that either adherence calls or HH counseling by themselves were beneficial, relative to receiving neither of those components (Fig. 3). The combination of these two components did not boost abstinence rates further, however. HH counseling showed some promise when offered with no MAC and no maintenance counseling (Fig. 5). However, HH counseling and maintenance counseling appeared to play similar roles (both offered regular contact and social support), and offering them together did not appear more effective than offering maintenance counseling without HH counseling (Figs 5 and 6). Moreover, maintenance counseling and extended medication appeared to be the strongest combination, all things considered (Fig. 6).

None of the three adherence factors (MAC, adherence calls, HH counseling) produced meaningful long-term benefit beyond that produced by extended medication and maintenance counseling. In addition, matching previous findings with MAC [51], none of the adherence factors produced a significant main effect (if anything, MAC lowered abstinence somewhat). These findings suggest that reminding people to take their medication, and tracking and providing feedback on medication use, produced only modest and inconsistent increases in abstinence, and attempting to assess and then correct beliefs about cessation medication may have actually been counterproductive. Further research on cessation medication adherence is clearly needed [32].

Interaction effects among components were common, and many were antagonistic [10]. For example, maintenance counseling generally produced better results when used with neither HH counseling nor MAC (Figs 5 and 6). Thus, combining components into treatments without a comprehensive analysis of interactions could result in treatment packages comprising inert or suboptimal components. Antagonistic interactions may be caused by several factors. In some cases an added component might increase distraction or burden, interfering with the effectiveness of the component with which it is paired (see [14,40,61,62] for other cases where adding intervention components appears to reduce benefit). In addition, components may activate mechanisms that are antagonistic to one another. For instance, the provision of a very directive behavioral intervention that stresses avoidance of smoking cues and urges might produce attentional effects that interfere with the effects of acceptance and commitment therapy, which emphasizes non-suppressive processing and acceptance of such stimuli (e.g. [63]). Finally, it is important to note that in some cases intervention components may produce an antagonistic interaction, but the effect of the component combination is still greater than is the effect of each component by itself (the joint effects are only partially additive). Such combinations might,

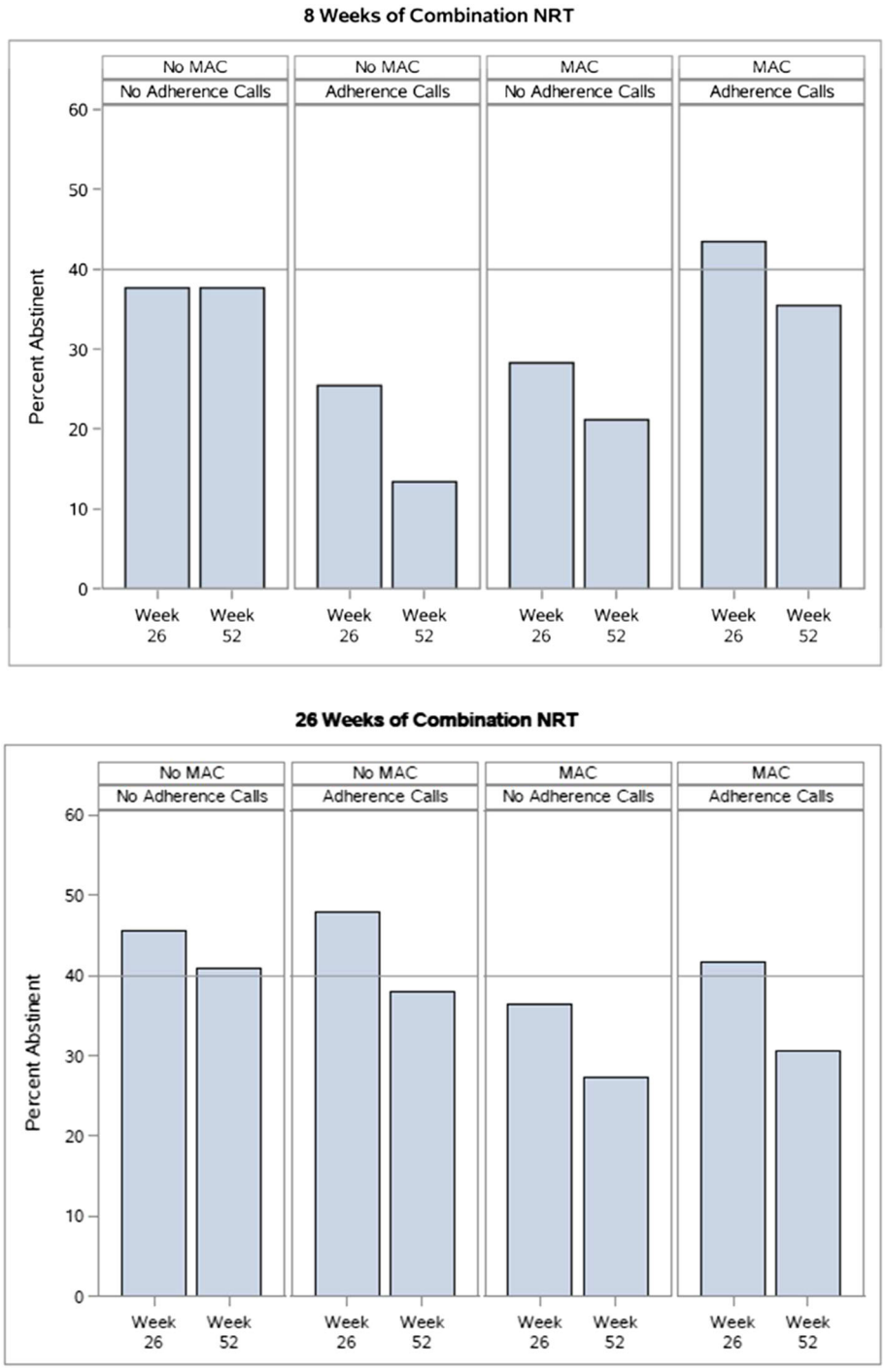

Figure 4 An interaction from the 7-day point-prevalence abstinence outcome models: extended medication (26 versus 8 weeks of combination NRT (nicotine replacement therapy) × medication adherence counseling (MAC) × adherence calls interaction (week 26 unadjusted model $P = 0.050$ and adjusted model $P = 0.03$; significant at week 52 in both the unadjusted and adjusted models]

therefore, be considered for possible inclusion in a treatment package.

This research highlights the value of the MOST approach [44]. In particular, the factorial design allowed for the screening of five unique intervention components in a single experiment. However, one limitation of this research is that it only suggests which components might work well together; a definitive test requires an RCT. Also, consistent with this screening experiment's goal of hypothesis generation, this experiment was not powered for simple effects (i.e. conditional main effects) tests; therefore, interactions were interpreted via an appraisal of consistent patterns of effects (see [10]) and require replication to support strong inference. Further, the effects obtained in this experiment

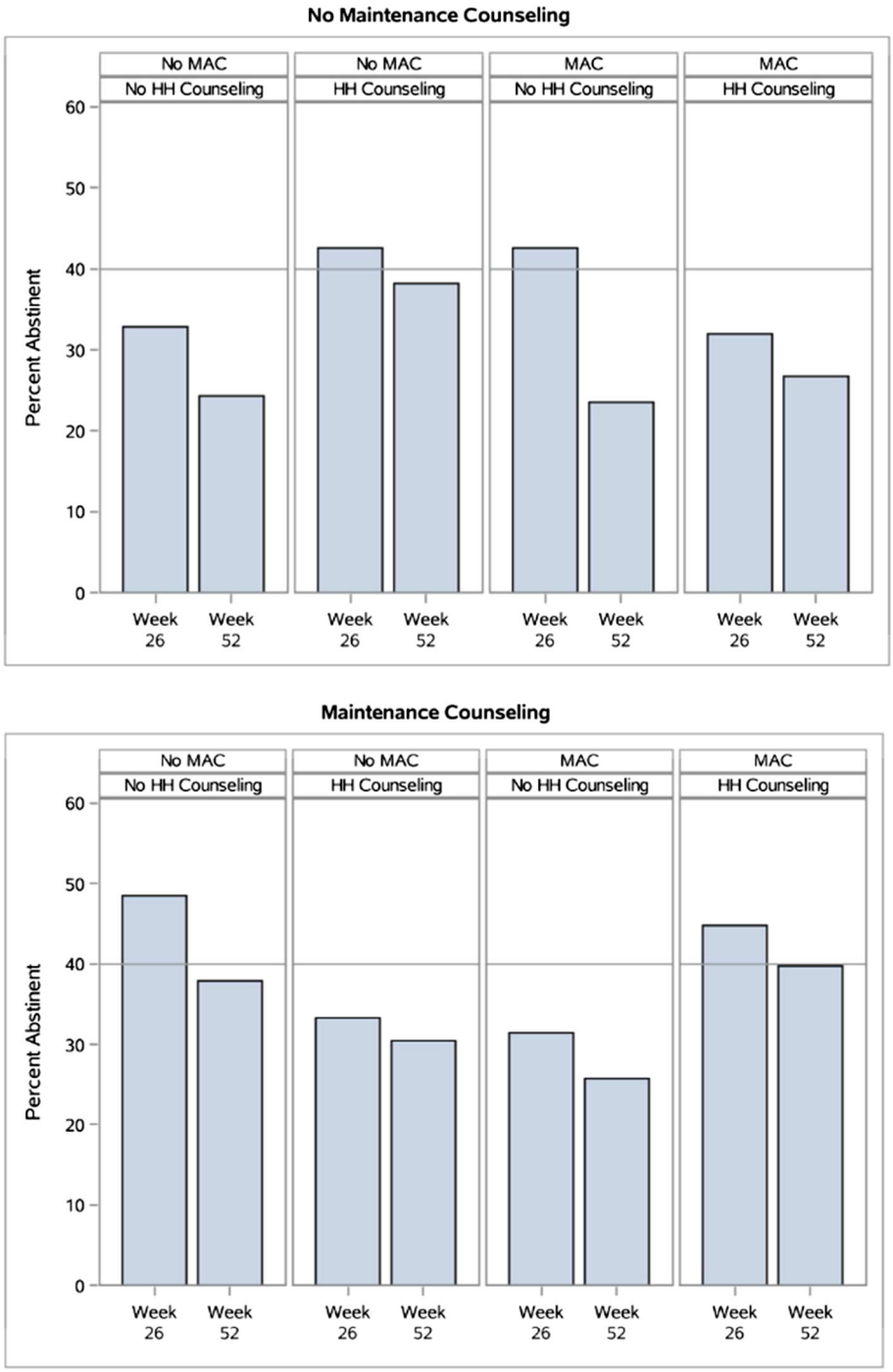

Figure 5 A significant interaction from the 7-day point-prevalence abstinence outcome models: maintenance counseling × medication adherence counseling (MAC) × helping hand (HH) counseling (significant at weeks 26 and 52)

reflect effects on both initial abstinence attainment and maintenance (relapse prevention, late re-quitting). When we examined treatment effects in only those who had attained initial abstinence (to test maintenance effects *per se*), we obtained a similar pattern of findings as in the full sample but few findings were significant, reflecting, in part, a lack of power due to the reduced sample. Compliance with the intervention components was adequate considering the pragmatic nature of the research; future analyses will address the effects of the medication adherence components on compliance. Clearly, future research is needed to replicate these findings, evaluate a broader range and intensity of components and provide additional insight into the complex interactions.

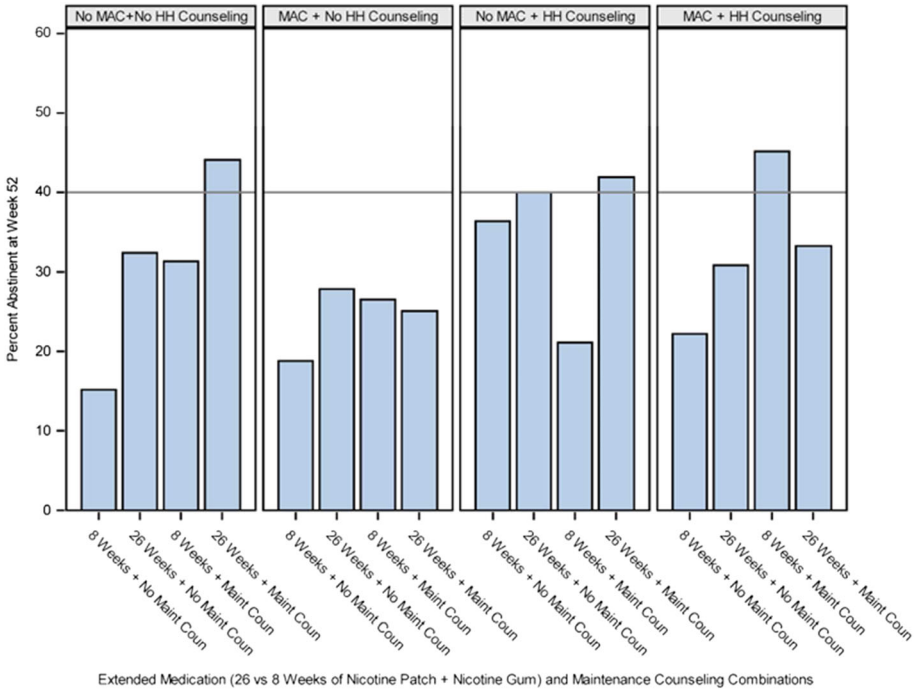

Figure 6 A non-significant interaction from the 7-day point-prevalence abstinence outcome model at week 52: extended medication × maintenance counseling × medication adherence counseling (MAC) × helping hand (HH) counseling ($P = 0.053$)

CONCLUSION

The goal of this research was to use the MOST approach to identify cessation- and maintenance-phase intervention components that increase long-term abstinence among smokers. This research demonstrated the feasibility of executing factorial designs that test multiple intervention components, and it identified components that enhanced long-term abstinence from smoking. In particular, extended medication (26 weeks of combination NRT) and maintenance counseling yielded promising effects and appeared to work well together. While these components are good candidates for possible inclusion in a comprehensive, chronic care treatment for smoking, additional research is needed in the form of an RCT to determine how well they work as an integrated treatment package [44]. Finally, this research showed that components often interacted with one another, and such interactions sometimes reflected a component's diminished effect when paired with other components. These findings raise questions about the relation between treatment intensity and benefit and underscore the importance of evaluating both intervention component main and interaction effects, as this research did, prior to combining promising components into a smoking treatment package.

Clinical trial registration

ClinicalTrials.gov NCT01120704.

Declaration of interests

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Figure S1 A Significant Interaction from the 7-Day Point-Prevalence Abstinence Outcome Models: Extended Medication x Medication Adherence Counseling (MAC) (Significant at Week 52)
Table S1 Experimental Conditions
Table S2a 52-Week Point-Prevalence Abstinence Model (adjusted) with Two Different Missing Data Assumptions
Table S2b 52-Week Point-Prevalence Abstinence Model (Adjusted) with Two Different Missing Data Assumptions

