

Identifying effective intervention components for smoking cessation: a factorial screening experiment

Megan E. Piper^{1,2}, Michael C. Fiore^{1,2}, Stevens S. Smith^{1,2}, David Fraser¹, Daniel M. Bolt³, Linda M. Collins⁴, Robin Mermelstein⁵, Tanya R. Schlam^{1,2}, Jessica W. Cook^{1,2,6}, Douglas E. Jorenby^{1,2}, Wei-Yin Loh⁷ & Timothy B. Baker^{1,2}

Center for Tobacco Research and Intervention, University of Wisconsin School of Medicine and Public Health, 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 Methodology Center, The Pennsylvania State University, University Park, 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, USA⁶ and University of Wisconsin, Department of Statistics, Madison, WI, USA⁷

ABSTRACT

Aims To identify promising intervention components intended to help smokers to attain and maintain abstinence in their quit smoking attempts. **Design** A fully crossed, six-factor randomized fractional factorial experiment. **Setting** Eleven primary care clinics in southern Wisconsin, USA. **Participants** A total of 637 adult smokers (55% women, 88% white) motivated to quit smoking who visited primary care clinics. **Interventions** Six intervention components designed to prepare smokers to quit, and achieve and maintain abstinence (i.e. for the preparation, cessation and maintenance phases of smoking treatment): (1) preparation nicotine patch versus none; (2) preparation nicotine gum versus none; (3) preparation counseling versus none; (4) intensive cessation in-person counseling versus minimal; (5) intensive cessation telephone counseling versus minimal; and (6) 16 versus 8 weeks of combination nicotine replacement therapy (nicotine patch + nicotine gum). **Measurements** Seven-day self-reported point-prevalence abstinence at 16 weeks. **Findings** Preparation counseling significantly improved week 16 abstinence rates ($P = .04$), while both forms of preparation nicotine replacement therapy interacted synergistically with intensive cessation in-person counseling ($P < 0.05$). Conversely, intensive cessation phone counseling and intensive cessation in-person counseling interacted antagonistically ($P < 0.05$)—these components produced higher abstinence rates by themselves than in combination. **Conclusions** Preparation counseling and the combination of intensive cessation in-person counseling with preparation nicotine gum or patch are promising intervention components for smoking and should be evaluated as an integrated treatment package.

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

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

Submitted 4 February 2015; initial review completed 21 April 2015; final version accepted 8 September 2015

INTRODUCTION

The health, economic, and human costs of tobacco use are profound [1], and while there are effective smoking treatments, long-term abstinence rates have increased only modestly during the past two decades [2–6] and remain disappointing (15–35% [2]). This slow progress may be due, in part, to reliance upon randomized controlled trials (RCTs), to the exclusion of other experimental designs. RCTs often compare two multi-component treatments with

one another (skill training, support, relapse prevention counseling + active medication versus the same counseling interventions + placebo medication), and therefore do not reveal the effects of individual intervention components or their interactions with one another. Such information would permit treatment development on a methodologically principled basis [7,8].

The present research, which is based on the Multiphase Optimization Strategy (MOST) [7–10], uses factorial designs to screen multiple intervention components

simultaneously and identify the most promising ones based on main effects and interactions. This is one of four linked papers. One reviews the theory and methods behind this research [11]; the others report factorial experiments of intervention components for the motivation [12] and maintenance [13] phases of smoking treatment.

This research experimentally evaluated intervention components designed for three phases of the cessation process: preparation, cessation, and maintenance [14,15]. These phases, as described in the Phase-Based Model of smoking treatment [11,14,15], present distinct challenges and opportunities that can be addressed with different types of intervention components delivered at different times in the cessation process. The preparation phase prepares smokers for a quit attempt and comprises the ~3 weeks prior to the quit day. The goal of the cessation phase is to establish abstinence and comprises the first ~2–4 weeks post-quit, when withdrawal symptoms tend to peak and most lapses occur [16–19]. The goal of the subsequent maintenance phase, lasting ~1–12 months, is to support abstinence and prevent relapse during a time when withdrawal typically diminishes but other risks are present—treatment non-adherence [20,21], decreased self-efficacy (especially after lapses [22,23]) and exacerbations of craving [24].

The intervention components tested in the current experiment were selected to address phase-specific challenges, designed for translation into real-world health-care settings (with low staff and patient burden and cost [25–27]) and implemented and tested in primary care clinics. For the preparation phase, we tested preparation nicotine patch, preparation nicotine gum and preparation counseling. Preparation nicotine replacement therapy (NRT) may prepare smokers for cessation by blunting the pharmacological effects of smoking, allowing practice of NRT self-administration, reducing smoking and degrading the smoking-reward contingency [28–30]. Preparation counseling, which included practice quit attempts, may inculcate relevant skills (coping, medication use [2,31,32]), increase self-efficacy [33,34], provide intra-treatment social support [2,31], reduce cue-smoking contingencies [35–37] and reduce smoking contexts and smoking rate [35,36,38–42].

Challenges in the cessation phase include withdrawal [43,44], exposure to smoking cues [45–47] and lapse occurrences [16]. In-person counseling and phone counseling were designed to: (1) promote avoidance of smoking triggers, (2) train coping responses to address withdrawal and lapsing and (3) provide intra-treatment social support to buffer withdrawal distress.

Finally, we tested 16 versus 8 weeks of post-quit combination NRT to address maintenance-phase threats such as withdrawal exacerbation [17,24] and late lapses [5,22,23,48–50]. Longer-term medication may reduce

both lapse–relapse progression [51,52] and the likelihood or severity of prolonged or recurrent withdrawal (e.g. anhedonia, craving [53]). We used combination NRT as the post-target quit date (TQD) medication for all participants based on its efficacy [2,54], ability to suppress withdrawal [55–57], cost and translatability into real-world health-care settings [2].

In sum, using state-of-the-art theory and methods, this research used a factorial experiment to screen multiple intervention components that were selected to be effective for the preparation, cessation and maintenance phases of smoking treatment and that had high translation potential. We examined their main and interactive effects to identify effects on initial (2-week), end-of-treatment (16-week) and long-term (6-month) abstinence. The 16-week time-point was the primary outcome because of its hypothesized sensitivity, occurring shortly after the delivery of all treatment but before encounters with relapse precipitants unrelated to treatment that could introduce error [14]. Thus, this research yields valuable comparative effectiveness data on multiple intervention components, which should help to guide future treatment development (e.g. additional factorial experiments, an RCT that evaluates a multi-component treatment).

METHODS

Procedure

This experiment was conducted from June 2010 to October 2013. Participants were recruited from 11 primary care clinics in two health systems in southern Wisconsin. During clinic visits, clinical care staff (i.e. medical assistants) were prompted by electronic health record technology to invite identified smokers to participate in a research program to help them to quit smoking [58,59]. Interested patients were referred electronically by clinic staff and then contacted by research staff to assess their eligibility. The inclusion criteria were: aged ≥ 18 years; ≥ 5 cigarettes/day for the previous 6 months; motivation to quit; ability to read, write and speak English; no plan to move from the area for at least 12 months; not currently taking bupropion or varenicline; agreement to use only study medication for the duration of the study (e.g. discontinuing ongoing NRT use); no medical contraindications to NRT use; and, for women of childbearing potential, agreement to use an approved method of birth control during treatment. Participants interested in quitting were assigned randomly to either this experiment or the cessation experiment described in [13] in this issue. It should be noted that although there were three related experiments (this experiment, [12] and [13]), each used an independent sample.

Eligible patients were invited to return to their primary care clinic to hear more about the study, provide written informed consent and complete initial assessments. A

research database then created intervention and assessment schedules, based on randomly assigned treatment conditions, which guided delivery of interventions by bachelor's-level case managers supervised by licensed clinical psychologists.

Experimental design

This experiment used a balanced fractional factorial design with six factors: (1) preparation nicotine patch versus none; (2) preparation nicotine gum versus none; (3) preparation counseling versus none; (4) intensive cessation in-person counseling versus minimal; (5) intensive cessation phone counseling versus minimal; and (6) 16 versus 8 weeks of combination NRT. The fractional nature of the design calls for delivery of half of the experimental component combinations that would have been delivered in a full factorial design (32 versus 64), making the research more logistically manageable. However, this design allows for the estimation of only main effects and two-way interactions (see Supporting Information for additional detail [60]).

Participants were randomized to treatment conditions via a database that used stratified permuted block randomization; we stratified by gender and clinic with a fixed block size of 32 based on the 32 unique treatment conditions (in random order within each block). Staff were blinded to randomization until eligibility was confirmed; participants were blinded until consent was provided.

Experimental factors

The intervention components were designed to be consistent with the 2008 US Public Health Service Clinical Practice Guideline recommendations [2], address phase-specific cessation challenges and opportunities and be feasible for real-world health-care. See Supporting information for counseling protocol summaries and fidelity assessments.

Preparation-phase intervention components

Preparation nicotine patch. Participants assigned to the active level (i.e. the active condition) received 14-mg patches for the 3 weeks prior to the TQD, while the other half did not receive pre-quit patches.

Preparation nicotine gum. Participants in the active condition received 2-mg nicotine gum for the 3 weeks prior to the TQD ($\geq$ nine/day, one piece/1–2 hours); the other half did not receive gum. Participants who received both preparation patch and gum were told to use at least five pieces/day of gum, unless such use produced adverse effects.

Preparation counseling. Participants in the active condition received 20-minute counseling sessions 1 (in-person), 2 (phone) and 3 (in-person) weeks prior to the TQD. The counseling focused on smoking reduction, withdrawal

coping, environmental restrictions on smoking, intra-treatment social support and autonomous motivation. Participants were also asked to engage in two 8-hour practice quit attempts. The other half of participants did not receive this counseling.

Cessation-phase intervention components

Cessation in-person counseling. Participants in the intensive condition received three 20-minute face-to-face counseling sessions: 1 week pre-TQD (week –1), TQD and week 1. The counseling emphasized intra-treatment social support and skill-building [2]. Participants assigned to the minimal level received one 3-minute in-person session at week –1 [2].

Cessation phone counseling. Participants in the intensive condition received three 15-minute phone sessions (TQD, days 2 and 10). These calls emphasized intra-treatment social support, skill execution and avoidance of danger situations [61–64]. Participants assigned to the minimal condition received one 10-minute session on the TQD that provided support and addressed motivation to quit, strategies for coping with craving and medication use. Thus, all participants received some TQD phone counseling.

Cessation and maintenance-phase intervention component

Extended medication. All participants received cessation- and maintenance-phase combination NRT (nicotine patch + nicotine gum), starting on their TQD. Half were assigned to receive 8 weeks of patches ($>$ nine cigarettes/day = 4 weeks of 21-mg, 2 weeks of 14-mg and 2 weeks of 7-mg nicotine patches; five to nine cigarettes/day = 4 weeks of 14-mg and 4 weeks of 7-mg nicotine patches) and 8 weeks of nicotine gum (smoke within 30 minutes of waking = 4-mg; smoke more than 30 minutes after waking = 2-mg). The other half received 16 weeks of patches ($>$ nine cigarettes/day = 21-mg for 12 weeks, 14-mg for 2 weeks and 7-mg for 2 weeks; five to nine cigarettes/day = 14-mg for 12 weeks and 7-mg for 4 weeks) and 16 weeks of gum. Participants were advised to use one piece of gum every 1–2 hours until 2 weeks before treatment termination [2], and at least five pieces/day unless such use produced adverse effects. Participants were instructed to decrease gum use over the final 2 weeks of medication treatment.

Combinations of intervention components. The intervention components were designed to be distinct but also complementary (e.g. when a participant received phone and in-person counseling, the case manager would integrate information across the two types of contacts). Even the timing was complementary; i.e. contacts were shifted slightly to prevent conflicts. Thus, intervention components were independent, but integrated when offered together, as would occur in real-world use.

Assessments

All participants had three study visits (weeks -3, -1 and 4); those assigned to intensive in-person cessation counseling also had two counseling-only visits (TQD and week 1). Participants completed baseline assessments of vital signs, exhaled carbon monoxide using the Bedfont Smokerlyzer (Bedfont Scientific, Rochester, UK), demographics, smoking history and tobacco dependence (Fagerström Test of Nicotine Dependence; FTND [65]). At subsequent study contacts (visits at weeks -1 and 4 and calls at weeks 8, 16 and 26) participants were asked about medication adverse events and about their smoking since last contact and in the last 7 days, using the validated time-line follow-back method [66]. These data were used to establish self-reported 7-day point-prevalence abstinence at 2, 16 and 26 weeks post-TQD. Medication adherence was assessed during automated calls that occurred every other evening from week -3 to week 2.

Outcome measures

The primary outcome was self-reported 7-day point-prevalence abstinence (PPA) at 16 weeks, with secondary outcomes at 2 and 26 weeks, assessed by staff who were not involved in treatment, but were not blind to treatment assignment.¹ These time-points were selected to index sensitively the effects of intervention components that were delivered at different treatment phases [14]. The 16-week outcome was deemed to be an early, sensitive index of treatment effects, occurring shortly after treatment completion. The 2-week outcome reflects the effects of the preparation and cessation-phase components on early cessation, and week 26 reflects maintenance-phase effects, permitting comparison with other treatment research.

Analytical plan

Initial analyses characterized the study population and examined treatment engagement and safety. We examined the likelihood of participant dropout in relation to treatment components to inform missingness analyses. Logistic regression (SPSS [67]) modeled the six main effects and 15 two-way interactions using effect coding (levels are coded -1 and +1 [11]), to analyze self-reported PPA at each time-point. Analyses were conducted with and without adjusting for a predetermined set of demographic and tobacco dependence covariates: gender, race (white versus non-white), age, education [up to high school/general educational development (GED) versus at least some college], the Heaviness of Smoking Index [68], baseline exhaled carbon monoxide and health-care system (A versus B). Reported results reflect

intent-to-treat analyses assuming that missing = smoking. These analyses were supplemented with multiple imputation (MI)/sensitivity analyses (see Supporting Information [69]). The results of the missing = smoking and MI/sensitivity analyses were similar; therefore, we present only the results of the former.

RESULTS

Participants

Of the smokers who were interested in quitting, 1349 were referred to this experiment, and 637 consented (see Fig. 1 for the CONSORT diagram and Supporting information for sample size justification). Table 1 describes the demographic and tobacco dependence characteristics of the sample. The 11 clinics recruited 23–89 participants each.

Treatment engagement

On average, participants in the preparation counseling condition attended 2.50 [standard deviation (SD) = 0.74] of three counseling sessions and 69% reported making a practice quit attempt. Participants in the intensive cessation in-person counseling condition completed 2.13 (SD = 1.13) of three sessions, significantly more than those in the intensive cessation phone counseling condition (mean = 1.74 of three sessions, SD = 1.19, $P < 0.01$). Participants in the preparation patch condition used an average of 6.24 patches/week (SD = 3.97) and those in the preparation gum condition used an average of 3.19 pieces of gum/day (SD = 2.37). Participants in the 16 versus 8 weeks medication duration conditions did not differ in post-quit patches used/week (mean = 4.59, SD = 2.87 versus mean = 4.98, SD = 2.77) or post-quit pieces of gum/day (mean = 4.02, SD = 3.31 versus mean = 3.81, SD = 3.34).

Safety

Reports of adverse events were low (e.g. 10% of those who received preparation patch or gum reported vivid dreams, skin rash occurred in 8% of participants while on combination NRT post-quit) and there were no serious adverse events related to study participation or study medications.

Missing data

Rates of missing PPA data went from 15.1% at week 2 to 23.7% at week 16 to 30.0% at week 26. Missingness was significantly more likely among participants receiving no preparation patch versus those receiving preparation patch (28.6 versus 19.1%; week 16) and those receiving 16 weeks of combination NRT versus 8 weeks (33.9 versus 26.4%; week 26).

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

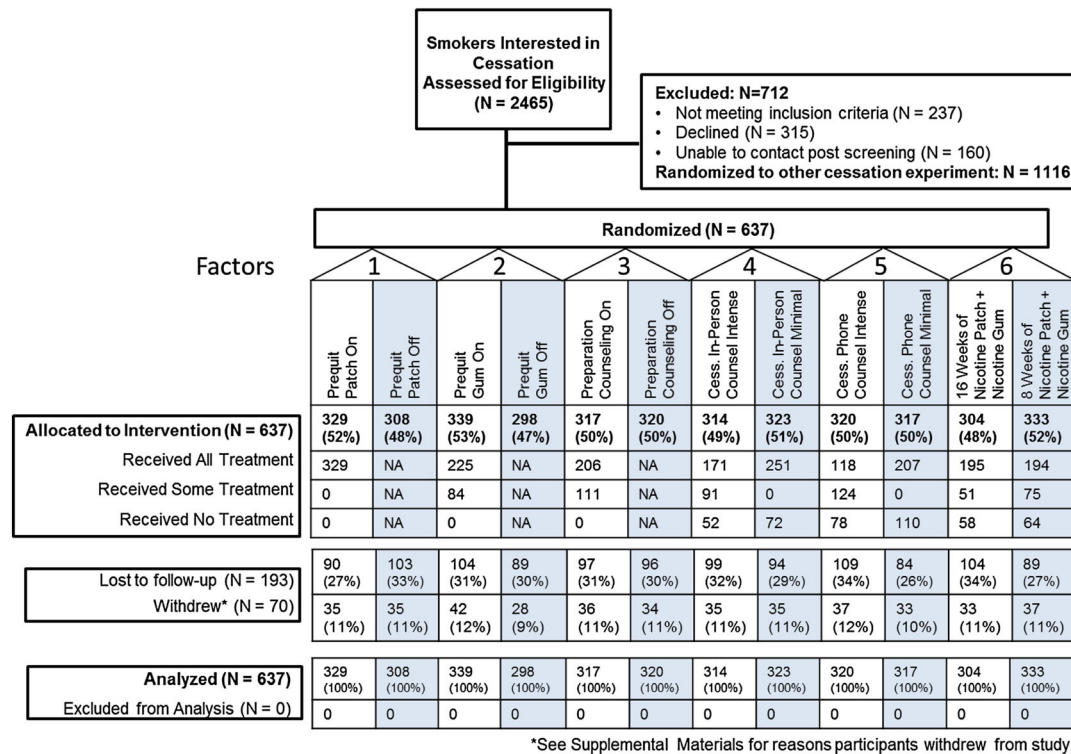


Figure 1 Consolidated Standards of Reporting Trials (CONSORT) diagram. NA = not applicable.

Cessation outcome

Table 2 presents the self-reported 7-day PPA rates for each main effect at 2, 16 and 26 weeks post-quit. Table 3 presents the logistic regression results for the 2-, 16- and 26-week outcomes. The patterns of statistical significance were consistent between the adjusted and unadjusted models. The only significant main effect on the week 16 primary outcome was that participants who received preparation counseling had higher abstinence rates.

There were five significant two-way interactions at week 16: preparation patch $\times$ cessation phone counseling, preparation patch $\times$ cessation in-person counseling, preparation gum $\times$ cessation in-person counseling, cessation in-person counseling $\times$ cessation phone counseling and preparation counseling $\times$ cessation phone counseling. The three interactions involving preparation NRT and cessation-phase counseling interventions were synergistic; i.e. the combination of preparation NRT and cessation counseling yielded better 16-week abstinence rates than would be expected based upon summing the main effects (Figs 2a–c). As Fig. 2c shows, participants who received preparation gum and intensive cessation in-person counseling had a higher 16-week PPA rate (42.8%), than did participants who received only one of these components (31.1 or 29.1%) or neither (36%). Similar patterns were found at week 26; differences tended to be less pronounced at week 2 (Fig. 2c).

The cessation in-person counseling $\times$ cessation phone counseling interaction was antagonistic—participants receiving either of those interventions without the other had higher abstinence rates at weeks 16 and 26 than did participants receiving both (Fig. 2d). The week 16 preparation counseling $\times$ phone counseling interaction was also antagonistic (Fig. 2e). The preparation patch $\times$ preparation counseling interaction was significant only at week 2. Participants receiving either of those components, without the other, actually had lower abstinence rates than those receiving both components or neither (Fig. 2f).

DISCUSSION

The goal of this screening experiment was to identify preparation, cessation and maintenance-phase intervention components that yield patterns of promising effects on smoking abstinence when used in a primary care setting. In keeping with MOST, after these components are identified, they would then undergo further research evaluation such as an RCT that would determine their effects when they are used together as an integrated treatment (see [11] for more detail about subsequent experiments). This research also provides important comparative effectiveness data that suggest that preparation-phase treatment can indeed enhance abstinence rates (cf. [30]) and that

Table 1 Demographic and smoking history characteristics.

	Total sample	Preparation gum		Preparation patch		Preparation counseling		In-person counseling		Phone counseling		Medication duration	
		On	Off	On	Off	On	Off	On	Off	On	Off	On	Off
Women (%)	54.6	54.3	55.0	55.3	53.9	54.6	54.7	55.4	53.9	53.8	55.5	56.3	53.2
Age (mean, SD)	45.8 (12.0)	45.3 (11.9)	46.2 (12.2)	45.2 (11.8)	46.3 (12.3)	46.2 (12.2)	45.3 (11.9)	45.8 (12.2)	45.7 (11.9)	45.1 (12.0)	46.4 (12.0)	45.1 (12.2)	46.4 (11.6)
High School diploma or GED only (%)	31.4	32.0	30.7	31.4	31.5	34.5	28.4	30.1	32.7	32.5	30.4	30.6	32.2
At least some college (%)	58.7	57.2	60.2	57.6	59.7	55.7	61.5	58.7	58.2	58.1	59.1	60.1	57.3
White (%)	87.8	87.8	87.8	87.8	87.7	88.5	87.0	87.8	87.7	89.5	86.0	87.0	88.4
African American (%)	7.8	9.0	6.5	8.6	7.0	6.7	8.9	8.4	7.2	7.0	8.6	9.3	6.4
Hispanic (%)	3.9	4.5	3.1	3.1	4.7	4.2	3.5	4.2	3.5	4.5	3.2	5.1	2.8
Health system A (%)	57.3	55.5	59.4	59.9	54.5	56.8	57.8	61.1	53.6	59.1	55.5	60.9	54.1
Cigs/day (mean, SD)	17.7 (8.2)	17.5 (8.4)	17.9 (7.9)	18.1 (8.0)	17.2 (8.4)	17.8 (8.4)	17.5 (8.1)	17.9 (8.2)	17.4 (8.2)	18.1 (8.4)	17.3 (7.9)	17.8 (7.8)	17.6 (8.5)
Baseline carbon monoxide (mean, SD)	20.3 (11.4)	20.3 (11.7)	20.4 (11.0)	20.6 (10.7)	20.0 (12.1)	20.6 (11.3)	20.0 (11.4)	20.3 (11.6)	20.4 (11.1)	20.2 (11.4)	20.4 (11.3)	19.6 (10.8)	21.0 (11.9)
FTND (mean, SD)	4.8 (2.2)	4.8 (2.1)	4.8 (2.3)	4.9 (2.2)	4.7 (2.1)	4.9 (2.2)	4.7 (2.1)	4.9 (2.1)	4.7 (2.1)	4.9 (2.2)	4.8 (2.1)	4.8 (2.2)	4.8 (2.1)
Heaviness of Smoking Index (mean, SD)	3.1 (1.4)	3.1 (1.4)	3.1 (1.4)	3.2 (1.4)	3.0 (1.4)	3.1 (1.5)	3.0 (1.4)	3.2 (1.4)	3.0 (1.5)	3.2 (1.4)	3.0 (1.4)	3.1 (1.4)	3.1 (1.4)

On = factor was present or at the intensive level or longest duration (e.g. intensive counseling, 16 weeks of medication). Off = factor was not present or was at the minimal level or shortest duration (e.g. minimal counseling, 8 weeks of medication). The study was conducted in two healthcare systems (A and B). FTND = Fagerström Test of Nicotine Dependence; SD = standard deviation; GED = general educational development.

combining in-person and phone counseling might constitute ineffective duplication. Finally, the results provide insight into how intervention components work together (i.e. interact).

The only significant main effect was that preparation counseling improved abstinence rates at week 16. However, interaction effects revealed meaningful differences in component effectiveness depending on the levels of other components. In particular, the effects of cessation-phase counseling were enhanced by the use of pre-cessation NRT (Figs. 2a–c). That this pattern appeared with regard to both the patch and gum, and manifested at two time-points, suggests the robustness of this relation. Thus, while

prior data have yielded a mixed picture of the effectiveness of preparation pharmacotherapy [28–30], the current results suggest that NRT pre-treatment can be helpful, but its benefit depends on the nature of the cessation counseling that is provided, with intensive cessation-phase counseling providing more benefit than minimal counseling.

Conversely, some intervention components appeared to undermine each other's effects. For instance, there was evidence that the two intensive levels of counseling used together produced lower abstinence rates than when either was used without the other (i.e. at weeks 16 and 26, intensive cessation in-person and intensive cessation phone

Table 2 Main effects self-reported point-prevalence abstinence rates at 2, 16 and 26 weeks post-quit.

Factor	% Abstinent at 2 weeks		% Abstinent at 16 weeks		% Abstinent at 26 weeks	
	On	Off	On	Off	On	Off
Preparation patch	44.1	43.2	36.5	32.5	29.8	26.0
Preparation gum	43.4	44.0	36.3	32.6	29.8	25.8
Preparation counseling	44.5	42.8	38.2	30.9	30.3	25.6
Cessation in-person counseling	47.5	39.9	36.3	32.8	27.7	28.2
Cessation phone counseling	43.1	44.2	35.6	33.4	30.3	25.6
Medication duration	44.1	43.2	36.2	33.0	28.5	27.3

On = factor was present or at the intensive level or longest duration (e.g. intensive counseling, 16 weeks of medication). Off = factor was not present or was at the minimal level or shortest duration (e.g. minimal counseling, 8 weeks of medication).

Table 3 Logistic regression models for 2-, 16- and 26-week point-prevalence outcome.

Variable	2 weeks post-TQD				16 weeks post-TQD				26 weeks post-TQD			
	Unadjusted		Adjusted ^a		Unadjusted		Adjusted ^a		Unadjusted		Adjusted ^a	
	<i>b</i>	<i>P</i> -value	<i>b</i>	<i>P</i> -value	<i>b</i>	<i>P</i> -value	<i>b</i>	<i>P</i> -value	<i>b</i>	<i>p</i> -value	<i>b</i>	<i>P</i> -value
Intercept	−0.26	0.001	0.43	0.45	−0.70	< 0.001	−0.69	0.25	−1.04	< 0.001	−0.34	0.59
Preparation patch	0.01	0.87	0.04	0.66	0.08	0.34	0.11	0.22	0.09	0.34	0.11	0.24
Preparation gum	−0.01	0.95	−0.00	0.96	0.11	0.21	0.12	0.19	0.12	0.20	0.12	0.23
Preparation counseling	0.03	0.69	0.04	0.60	0.18	0.04	0.19	0.03	0.11	0.23	0.11	0.23
Cessation in-person counseling	0.14	0.10	0.15	0.07	0.05	0.54	0.06	0.48	−0.04	0.68	−0.03	0.80
Cessation phone counseling	−0.03	0.72	−0.03	0.75	0.05	0.59	0.06	0.54	0.12	0.21	0.12	0.20
Medication duration	0.02	0.78	0.01	0.91	0.08	0.39	0.07	0.46	−0.02	0.80	−0.03	0.73
Preparation patch × preparation gum	0.05	0.56	0.05	0.54	0.04	0.68	0.04	0.65	0.06	0.54	0.06	0.53
Preparation patch × preparation counseling	0.16	0.050	0.18	0.04	0.15	0.10	0.17	0.07	0.18	0.07	0.19	0.06
Preparation patch × cessation in-person counseling	0.14	0.09	0.15	0.08	0.19	0.03	0.20	0.03	0.22	0.02	0.22	0.02
Preparation patch × cessation phone counseling	0.20	0.01	0.23	0.01	0.18	0.047	0.20	0.03	0.13	0.18	0.15	0.14
Preparation patch × medication duration	−0.06	0.50	−0.07	0.43	0.00	0.97	−0.00	0.96	−0.01	0.95	−0.02	0.84
Preparation gum × preparation counseling	0.10	0.22	0.05	0.59	−0.06	0.52	−0.11	0.22	−0.05	0.61	−0.09	0.35
Preparation gum × cessation in-person counseling	0.11	0.18	0.12	0.15	0.20	0.02	0.21	0.02	0.22	0.02	0.22	0.02
Preparation gum × cessation phone counseling	−0.07	0.37	−0.08	0.37	−0.01	0.96	0.01	0.93	−0.06	0.51	−0.06	0.52
Preparation gum × medication duration	−0.00	0.99	−0.00	0.97	0.01	0.89	−0.00	0.96	−0.04	0.67	−0.05	0.60
Preparation counseling × cessation in-person counseling	−0.04	0.59	−0.03	0.68	−0.10	0.26	−0.10	0.26	−0.17	0.08	−0.16	0.09
Preparation counseling × cessation phone counseling	−0.01	0.95	0.00	1.00	−0.18	0.04	−0.19	0.04	−0.14	0.15	−0.14	0.14
Preparation counseling × medication duration	0.05	0.58	0.06	0.48	0.06	0.52	0.06	0.48	−0.11	0.29	−0.11	0.27
Cessation in-person counseling × cessation phone counseling	−0.05	0.56	−0.06	0.47	−0.28	0.002	−0.28	0.002	−0.23	0.02	−0.23	0.02
Cessation in-person counseling × medication duration	−0.06	0.46	−0.04	0.65	−0.13	0.15	−0.10	0.27	−0.08	0.40	−0.05	0.61
Cessation phone counseling × medication duration	−0.06	0.51	−0.06	0.52	0.03	0.78	0.04	0.66	0.02	0.87	0.02	0.81

^aModels were adjusted for gender, race (white versus non-white), age, education (high school or less versus at least some college), health-care system, Heaviness of Smoking Index and baseline carbon monoxide ($n = 631$ due to missing covariates). TQD = Target Quit Day.

counseling produced lower abstinence rates when used together than when used by themselves; Fig. 2d). This may be due to redundancy in treatment mechanism or to

participant burden—the content of the two counseling types were similar and were designed to last 15 (phone) to 20 (in-person) minutes.

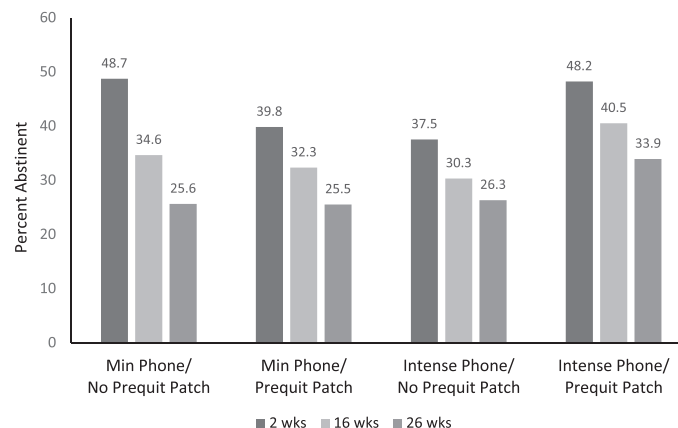
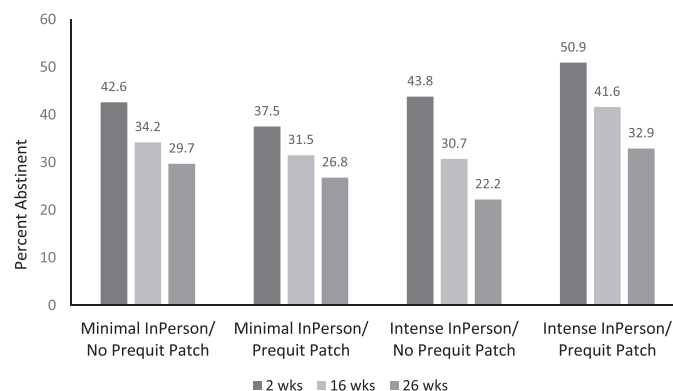
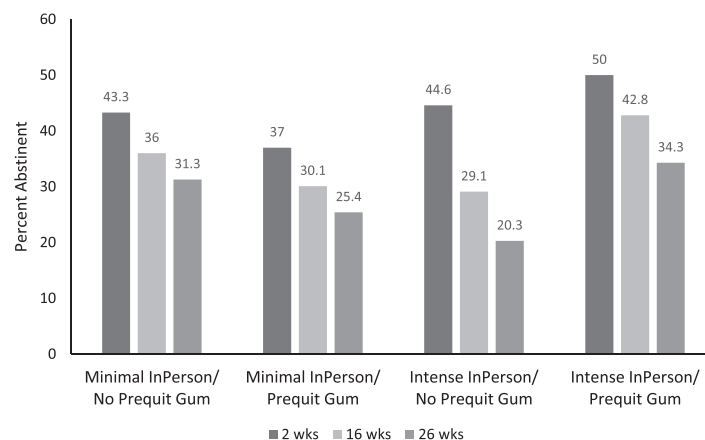
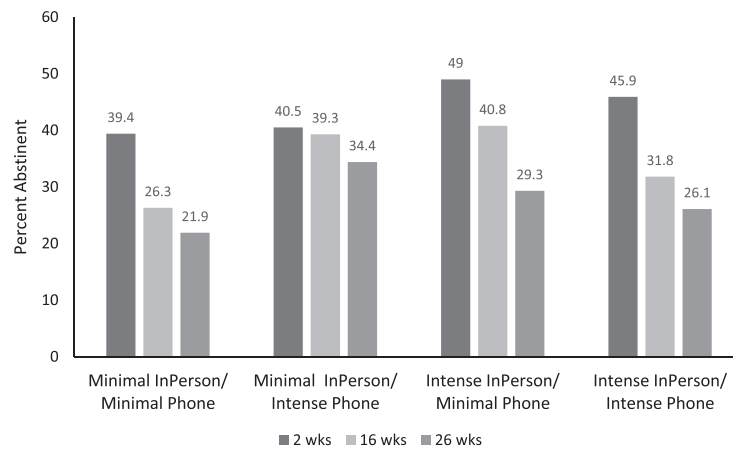
a. Preparation Patch x Cessation Phone Counseling – Significant at Weeks 2 and 16**b. Preparation Patch x Cessation In-Person Counseling – Significant at Weeks 16 and 26****c. Preparation Gum x Cessation In-Person Counseling – Significant at Weeks 16 and 26**

Figure 2 Significant interactions from the 7-day point-prevalence abstinence models. (a). Preparation patch × cessation phone counseling: significant at weeks 2 and 16. (b) Preparation patch × cessation in-person counseling: significant at weeks 16 and 26. (c) Preparation gum × cessation in-person counseling: significant at weeks 16 and 26. (d) Cessation in-person counseling × cessation phone counseling: significant at weeks 16 and 26. (e) Preparation counseling × cessation phone counseling: significant at week 16. (f) Preparation patch × preparation counseling: significant at week 2

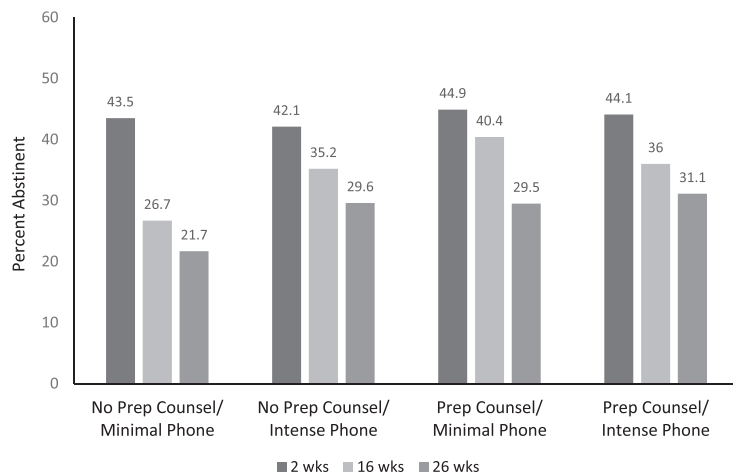
Three types of intervention components yielded promising effects—preparation NRT, preparation counseling and intensive cessation in-person counseling—based on patterns of effects observed across the three time-points. Preparation counseling produced a significant main effect at 16 weeks, and a significant synergistic interaction with

preparation patch at 2 weeks (Table 3). Preparation NRT (either patch or gum) and intensive cessation in-person counseling interacted synergistically at both 16 and 26 weeks. Cessation in-person counseling appears more promising than cessation phone counseling because it produced a somewhat stronger main effect at 2 weeks

d. Cessation In-Person Counseling x Cessation Phone Counseling – Significant at Weeks 16 and 26



e. Preparation Counseling x Cessation Phone Counseling – Significant at Week 16



f. Preparation Patch x Preparation Counseling – Significant at Week 2

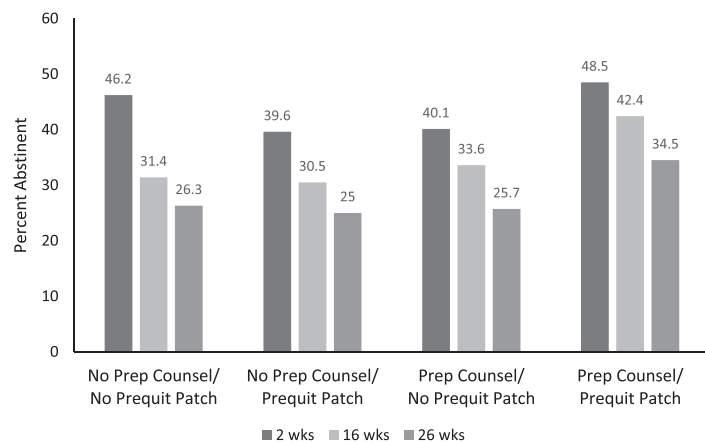


Figure 2 (Continued)

(although not significant: Table 3), and it participated uniquely in the synergistic interactions with preparation NRT at weeks 16 and 26. The data do not permit a clear-

cut decision as to whether preparation patch or gum would be superior. They produced similar synergistic interactions with cessation in-person counseling at both 16 and

26 weeks, and the two could not be distinguished based on their main effects (Tables 2 and 3).

However, the evidence supporting these three components is not wholly compelling. The main effect for preparation counseling occurred at only one time-point, and the promise of the other components is supported by interaction effects, which show that a component can be effective, but its effects are conditional on the presence of another component [70]. Another concern with interactions is that the cause of the interaction is unknown—does it occur because of antagonistic effects on change mechanisms, or because of some other factor such as perceived burden? These interactions involve factors that have been experimentally manipulated in a controlled fashion, which increases the likelihood of replicability. However, future research is required to identify the extent to which such interactions replicate, especially when they are not stipulated *a priori*.

The number of interaction effects, and the fact that they reflect both synergistic and antagonistic effects among components, illustrates the importance of evaluating intervention components with factorial designs before combining components into treatment packages [8]. One cannot extrapolate confidently the joint actions of intervention components based upon their individual effects or on their effects as elements of unvaried combinations of components as occurs in standard RCTs [7,9,10]. This highlights a potential value of factorial designs (as per MOST [8]), which uniquely permit the modeling of interaction effects.

The Phase-Based Model emphasizes the importance of examining component effectiveness over time. In fact, preparation NRT and cessation-phase counseling interactions were present at 16 and 26 weeks, but not at 2 weeks. This suggests that some treatment effects take time to appear—they may ‘incubate’. Thus, there may be no simple relation between temporal propinquity and sensitivity to treatment effects [14]; more research is needed to characterize the main and interactive effects of intervention components over time and to elucidate the mechanisms that account for observed patterns.

Additional research is also needed to confirm which intervention components are most effective at the three treatment phases targeted in this research and to assess the effects of components on other outcome criteria, both general (e.g. cost) and phase-relevant (e.g. does preparation-phase intervention reduce pre-quit smoking? [14]) criteria. In addition, our use of a fractional factorial design precluded the estimation of higher-order interactions; such interactions are assumed to be negligible relative to main effects and two-factor interactions, but we were unable to test this empirically. Further, this research examined intervention components that function primarily during the preparation and cessation phases; it is

possible that a longer duration of medication use would produce stronger maintenance-phase effects [13,71]. Finally, consistent with this experiment’s goal of hypothesis generation, it was not powered for simple effects tests; therefore, interactions were interpreted via an appraisal of consistent patterns of effects [11].

CONCLUSION

Using innovative, efficient strategies to investigate approaches for treating smokers recruited in primary care, this research identified three intervention components that demonstrated promising effects on abstinence: preparation NRT, preparation counseling and intensive cessation in-person counseling. Intensive cessation phone counseling and extended medication (16 versus 8 weeks of combination NRT) demonstrated less evidence of effectiveness. The multiple statistical interactions among the different intervention components support the use of factorial experiments to screen intervention components for their main and interactive effects, prior to assembling multi-component treatments. The promising intervention components identified in this research should undergo further evaluation, including an RCT that would determine their effects when they are used together as an integrated treatment.

Declaration of interests

This research was supported by grants 9P50CA143188 and 1K05CA139871 from the National Cancer Institute to the University of Wisconsin Center for Tobacco Research and Intervention and by the Wisconsin Partnership Program. L.M.C. is also supported by NIH grants P50DA10075 and R01DK097364. This work was carried out in part while T.R.S. was a Primary Care Research Fellow supported by a National Research Service Award (T32HP10010) from the Health Resources and Services Administration to the University of Wisconsin Department of Family Medicine. J.W.C. is also supported by Merit Review Award 101CX00056 from the US Department of Veterans Affairs. W.-Y.L. is also supported by NSF grant DMS-1305725. The authors have received no direct or indirect funding from, nor do they have a connection with, the tobacco, alcohol, pharmaceutical or gaming industries or anybody substantially funded by one of these organizations. W.-Y.L. is partially supported by a grant from Eli Lilly and Company for research that is unrelated to smoking or tobacco dependence treatment.

Acknowledgements

We would like to acknowledge the staff at Aurora Health Care, Deancare and Epic Systems Corporation for their collaboration in this research. We are very grateful to the staff

and students at the Center for Tobacco Research and Intervention in the University of Wisconsin School of Medicine and Public Health for their assistance with this research.

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Supporting information

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

Table S1. The 32 Experimental Conditions in the Fractional Factorial Design

Table S2. Overview of Preparation Phase Counseling

Table S3. Overview of Minimal Cessation Phase In-Person Counseling

Table S4. Overview of Intense Cessation Phase In-Person Counseling

Table S5. Overview of Minimal Cessation Phase Phone Counseling

Table S6. Overview of Intense Cessation Phase Phone Counseling

Table S8a. 16-Week Point-Prevalence Abstinence Model (Unadjusted) with Variable Missing Data Assumptions

Table S8b. 16 Week Point-Prevalence Abstinence Model (Adjusted) with Variable Missing Data Assumptions