ORIGINAL INVESTIGATION

Enhancing Tobacco Quitline Effectiveness: Identifying a Superior Pharmacotherapy Adjuvant

Stevens S. Smith PhD[1,2], **Paula A. Keller** MPH[3], **Kate H. Kobinsky** MPH[2], **Timothy B. Baker** PhD[1,2], **David L. Fraser** MS[2], **Terry Bush** PhD[4], **Brooke Magnusson** MA[4], **Susan M. Zbikowski** PhD[4], **Timothy A. McAfee** MD, MPH[5], **Michael C. Fiore** MD, MPH, MBA[1,2]

[1]*Department of Medicine, University of Wisconsin School of Medicine and Public Health (UWSMPH), Madison, WI;* [2]*Center for Tobacco Research and Intervention, UWSMPH, Madison, WI;* [3]*Cessation Programs, ClearWay Minnesota, Minneapolis, MN;* [4]*Alere Wellbeing (formerly Free & Clear, Inc.), Seattle, WA;* [5]*Office on Smoking and Health, Centers for Disease Control and Prevention, Atlanta, GA*

Corresponding Author: Stevens S. Smith, PhD, UW Center for Tobacco Research and Intervention, 1930 Monroe St., Suite 200, Madison, WI 53711, USA. Telephone: 608-262-7563; Fax: 608-265-3102; E-mail: sss@ctri.medicine.wisc.edu

Received April 22, 2012; accepted July 8, 2012

ABSTRACT

Introduction: Telephone tobacco quitlines are effective and are widely used, with more than 500,000 U.S. callers in 2010. This study investigated the clinical effectiveness and cost-effectiveness of 3 different quitline enhancements: combination nicotine replacement therapy (NRT), longer duration of NRT, and counseling to increase NRT adherence.

Methods: In this study, 987 quitline callers were randomized to a combination of quitline treatments in a 2×2 × 2 factorial design: NRT duration (2 vs. 6 weeks), NRT type (nicotine patch only vs. patch plus nicotine gum), and standard 4-call counseling (SC) versus SC plus medication adherence counseling (MAC). The primary outcome was 7-day point-prevalence abstinence (PPA) at 6 months postquit in intention-to-treat (ITT) analyses.

Results: Combination NRT for 6 weeks yielded the highest 6-month PPA rate (51.6%) compared with 2 weeks of nicotine patch (38.4%), odds ratios [*OR*] = 1.71 (95% confidence interval [*CI*]:1.20–2.45). A similar result was found for 2 weeks of combination NRT (48.2%), *OR* = 1.49 (95% *CI*: 1.04–2.14) but not for 6 weeks of nicotine patch alone (46.2%), *OR* = 1.38 (95% *CI*: 0.96–1.97). The MAC intervention effect was nonsignificant. Cost analyses showed that the 2-week combination NRT group had the lowest cost per quit ($442 vs. $464 for 2-week patch only, $505 for 6-week patch only, and $675 for 6-week combination NRT).

Conclusions: Combination NRT for 2 or 6 weeks increased 6-month abstinence rates by 10% and 13%, respectively, over rates produced by 2 weeks of nicotine patch when offered with quitline counseling. A 10% improvement would potentially yield an additional 50,000 quitters annually, assuming 500,000 callers to U.S. quitlines per year.

INTRODUCTION

In 2010, more than half-a-million U.S. smokers called a state telephone quitline for information or help quitting smoking (North American Quitline Consortium [NAQC], 2011). In fact, smokers are 4 times more likely to use a quitline than face-to-face cessation counseling (Kaufman, Augustson, Finney-Rutten, & Davis, 2010; McAfee, Sofian, Wilson, & Hindmarsh, 1998). Quitlines also have the potential to reach underserved populations—for example, the elderly, persons living in rural areas, African Americans, and persons of lower socioeconomic status—populations that often have limited access to in-person cessation treatments (Lichtenstein, Zhu, & Tedeschi, 2010; NAQC, 2009).

Quitline counseling is both clinically effective and cost-effective (Abrams, Graham, Levy, Mabry, & Orleans, 2010; CDC, 2004, 2007; Fiore et al., 2008; Lichtenstein et al., 2010; McAfee, 2007; NAQC, 2009; Stead, Perera, & Lancaster, 2006; Zhu et al., 2002). The U.S. Public Health Service (PHS) Clinical Practice Guideline *Treating Tobacco Use and Dependence* in both 2000 (Fiore et al., 2000) and the *2008 Update* (Fiore et al., 2008) reported that quitline counseling was significantly more effective than minimal interventions. This collective evidence led the U.S. Department of Health and Human Services in 2004 to establish a national smoking cessation quitline network linking state quitlines via a single portal—1–800-QUIT-NOW.

In the United States in 2010, all state quitlines (including the District of Columbia, Guam, and Puerto Rico) offered counseling and 39 states offered free cessation medications (NAQC, 2011) with nicotine replacement therapy (NRT)

doi:10.1093/ntr/nts186
Advance Access publication September 19, 2012

being the most common. Other services include quit guides and various community and eHealth resources. While there is evidence that free cessation medication increases quitline calls (McAfee, 2007) and may boost cessation outcomes (Fiore et al., 2008; Hughes, Peters, & Naud, 2011), little is known about which pharmacotherapy strategies (e.g., length of treatment, combination vs. single agent) will optimize cessation outcomes when offered as part of quitline treatment.

It is vital to determine the optimal constituents of quitline interventions because of their potential reach (Campbell, Lee, Haugland, Helgerson, & Harwell, 2008). Meta-analyses of telephone counseling reported in the *Cochrane Database of Systematic Reviews* showed that increased counseling intensity (more proactive calls) only modestly and inconsistently boosts abstinence outcomes (Stead et al., 2006; cf. Carlin-Menter et al., 2011). Because of these mixed findings for quitline counseling intensity, the surest route to enhancing quitline effectiveness may be to optimize adjuvant pharmacotherapies.

Unfortunately, few quitline studies have directly compared the effectiveness of different pharmacotherapy adjuvants and extant results are inconsistent. For example, one study showed that 8 weeks of nicotine patches yielded significantly higher 6-month abstinence rates than did 2 weeks of patches when both were offered to uninsured quitline callers (McAfee et al., 2008). However, a study of callers to the New York State Smokers' Quit Line showed no significant differences in 7-month abstinence rates among those receiving either 2, 4, or 6 weeks of nicotine patches (Cummings et al., 2011). More recently, Ferguson et al. (2012) examined the effect of offering free NRT (vs. no NRT) with either standard or more intensive counseling in a 2 × 2 factorial design that recruited 2,591 smokers via the English national quitline. Neither the free NRT nor the more intensive counseling improved cessation rates at 6 months postquit. However, treatment assignment only modestly affected treatment exposure. Actual counseling utilization was similar in the two counseling groups; also, only about half the participants in the NRT group actually obtained the NRT and some participants not offered NRT obtained and used NRT on their own. Thus, the lack of significant effects may be due to functionally similar treatments as well as other methodological differences between studies (McAFee, Fellows, & Zbikowski, 2012).

No studies have addressed the relative efficacy of single-agent NRT versus combination NRT among quitline callers. Longer duration NRT and combination NRT boost cessation outcomes in nonquitline studies (Fiore et al., 2008; Piper et al., 2009; Smith et al., 2009; Stead, Perera, Bullen, Mant, & Lancaster, 2008); however, differences between quitline and face-to-face intervention contexts (e.g., differences in participants, intensity of counseling, and barriers to counseling and research participation) limit generalization of such findings. Moreover, recent data have cast doubt on the effectiveness of cessation pharmacotherapies in real-world use (e.g., Alpert, Connolly, & Biener, 2013; Ferguson et al., 2012), increasing the need to demonstrate effects in conditions that approach such use contexts.

There is strong evidence that nonadherence to cessation medication is common among smokers, especially in real-world effectiveness studies (Ossip, Abrams, Mahoney, Sall, & Cummings, 2009; Schmitz, Sayre, Stotts, Rothfleisch, & Mooney, 2005; Wiggers et al., 2006) and is associated with reduced clinical success (Catz et al., 2011; Lam, Abdullah, Chan, & Hedley, 2005; Shiffman, Sweeney, Ferguson, Sembower, & Gitchell, 2008). Therefore, this research tested a medication adherence intervention that was designed to address problematic beliefs or knowledge about NRT that might adversely affect appropriate use of the pharmacotherapies. Thus, the current study tested combination NRT (vs. nicotine patch only), longer duration of NRT (6 vs. 2 weeks), and the medication adherence intervention (vs. standard counseling [SC]). We hypothesized that each of these enhancements would independently increase abstinence rates.

METHODS

Setting

This study was conducted by the Center for Tobacco Research and Intervention (CTRI) at the University of Wisconsin-Madison (UW-Madison) School of Medicine and Public Health, in collaboration with the State of Wisconsin's tobacco cessation quitline vendor, Free & Clear, Inc. (now called Alere Wellbeing), Seattle, WA. Institutional Review Board (IRB) approval for the study was granted by the UW-Madison Health Sciences IRB.

Study Design

Participants were randomly assigned to conditions in a 2 × 2 × 2 fully crossed factorial design that tested NRT duration (2 vs. 6 weeks), NRT type (nicotine patch only vs. nicotine patch + nicotine gum), and standard 4-call counseling (SC) versus SC plus medication adherence counseling (MAC). The 2 × 2 × 2 design yielded eight possible treatment combinations; participants were randomly assigned to the eight treatment combinations via a list of randomized numbers generated by SAS Proc Plan (SAS Institute Inc., Cary, NC). Each participant had a 50% chance of being assigned to each level of a treatment.

Participant Recruitment

Adult smokers who called the Wisconsin Tobacco Quit Line (WTQL) from April 1, 2010 to June 15, 2010 were invited to participate in the study; no advertising or targeted recruitment was utilized. Eligibility criteria included the following: age ≥18 years, English speaking, smoking ≥10 cigarettes/day, and willing to set a quit date within the next 30 days. Exclusion criteria included the following: pregnant or lactating, medical contraindications for study medications (e.g., past 30 days, heart attack or stroke; past 6 months, serious or worsening angina, very rapid or irregular heartbeat requiring medication), and unwillingness to use study medications. After initial phone screening by quitline registration staff, participants were transferred to a Quit Coach® (trained cessation counselor) at the quitline who completed consent, a baseline survey, enrollment, randomization to treatment, and provision of prequit counseling; the Quit Coach also arranged for study medication and a quit guide to be mailed to the participant.

Counseling Interventions

WTQL Quit Coaches provided study participants with four counseling sessions including a prequit counseling session usually on the day of the initial call by the smoker. Subsequent

counseling sessions occurred during three proactive calls; call 2 was timed to be made on or close to the participant's quit date and calls 3 and 4 scheduled to occur about 2 and 4 weeks, respectively, after the quit day. Study participants could make ad hoc calls to the WTQL for additional assistance. Quit Coaches made multiple attempts on different days to reach a participant for each of the proactive calls. All study participants also received a standard quit guide in the mail, access to recorded medication information (via phone), and access to Web Coach®, an online cessation program maintained by the quitline.

Standard Counseling

All participants received standard cessation counseling consistent with recommendations in the 2008 PHS Guideline (Fiore et al., 2008). During call 1, Quit Coaches discussed smoking history, prior quit attempts, problem-solving and coping strategies, social support, and appropriate use of cessation medications; also, a target quit date was set during this first call. Call 2 occurred on or close to the quit date and focused on management of withdrawal symptoms, appropriate use of medications, strategies to maintain abstinence in high-risk situations, and early relapse prevention. Calls 3 and 4 also addressed relapse prevention but counseling was tailored to address concerns and questions raised by the participant.

Standard Counseling Plus MAC

One half of study participants were randomized to receive MAC during all counseling calls in addition to SC. The MAC protocol was developed by study investigators and involved the following: (a) prequit assessment of beliefs that might undermine NRT adherence, (b) ongoing medication adherence assessment by Quit Coaches, and (c) tailored coaching based on the ongoing assessments. (See Supplementary Appendix A for details of the MAC intervention.)

Study Medications

Each participant received an initial supply of open-label NRT in standard packaging (with package insert) from the WTQL via mail consistent with randomization (patches only or patches plus gum) about 7–10 days after call 1. Medications for participants receiving only 2 weeks of NRT arrived in one shipment. Participants randomized to receive 6 weeks of NRT were sent an initial shipment of 4 weeks of NRT; they were sent an additional 2 weeks of NRT after completing a subsequent call and indicating interest in receiving additional NRT (72% requested the additional NRT). In addition to Quit Coach instructions on NRT use, participants had 24-hr access to automated phone recordings on proper medication use. Quit Coaches and a quitline physician were available at all times to address any medical issues.

Data Collection and Measures

During registration, quitline staff collected sociodemographic information, current and past tobacco use, prior cessation attempts, and basic health information. After enrollment, participants were transferred to a Quit Coach who administered the Wisconsin-Beliefs Assessment on Smoking and Cessation (WI-BASC), a new eight-item measure of beliefs about the use and effectiveness of cessation medications used in the MAC intervention. (See Supplementary Appendix A for more details about the WI-BASC and MAC.)

Outcome data were collected at 2, 6, 12, and 26 weeks postquit by university-based research staff not affiliated with the WTQL. A minimum of 10 attempts were made to reach each participant for each follow-up call. During each follow-up call, study participants were asked about tobacco use in the past 7 days, motivation to quit (or stay quit), confidence in quitting, and use of cessation medications and other cessation interventions. During the week 2 and 6 calls, more detailed data were collected about medication use. Participants received up to $50 total for completing follow-up assessments.

Study Outcomes and Hypotheses

As specified in the original study protocol, the primary outcome was self-reported 7-day point-prevalence abstinence (PPA) at the 6-month follow-up (not biochemically confirmed) analyzed. Consistent with recommendations of the NAQC (2009), we also report 30-day PPA at the 6-month follow-up. We hypothesized that combination NRT, longer duration of NRT, and MAC would each independently increase abstinence rates. Because there was little or no research on which to base predictions about interactions among the three interventions, we did not make a priori predictions about specific interactions of the treatments. Secondary outcomes included number of proactive counseling calls completed and total minutes of counseling.

To test medication adherence, we assessed the number of days of NRT use (patch and gum assessed separately) in the first 2 weeks as reported at the week 2 follow-up and the total number of weeks of NRT use as reported at the week 6 follow-up. We predicted that the MAC intervention would increase the use of NRT.

Analysis Plan and Statistical Methods

Chi-square (χ^2) tests and univariate analyses of variance (ANOVAs) were used to test group differences in baseline measures as well as sample representativeness; all tests were two-tailed with $\alpha = .05$. Univariate ANOVAs were also used to test continuous outcomes such as weeks of medication use and total minutes of phone counseling; in these analyses of continuous outcome data, only responder data were used.

Hierarchical logistic regression (HLR) analysis with effects coding for main and interactive effects of NRT duration, NRT type, and MAC was used to test the primary outcome, 7-day PPA at 6 months in intention-to-treat (ITT) analyses. To evaluate the joint effects of NRT duration and type on ITT 7-day PPA at 6 months, we tested focused pairwise comparisons for the four combinations of duration and type in which 2 weeks of patch only (least intensive) was the reference condition. The other three pharmacotherapy conditions (2 weeks combination NRT, 6 weeks patch only, and 6 weeks combination NRT) were contrasted with 2 weeks patch only via 3 dummy-coded variables (Aguinis, 2004; Cohen, Cohen, West, & Aiken, 2003) that were entered as a set in HLR analyses, with and without MAC treatment as a covariate.

For all ITT analyses of abstinence at 6 months, missing smoking status was coded as smoking. However, several authors have questioned the appropriateness of the "missing = smoking" approach (e.g., Barnes, Larsen, Schroeder,

Hanson, & Decker, 2010; Hedeker, Mermelstein, & Demirtas, 2007; Nelson, Partin, Fu, Joseph, & An, 2009). Due to space limitations, we address missing data and analytic issues in Supplementary Appendix B including presentation of analyses of missing data, rationale for using the "missing = smoking" approach, and comparative results for ITT and responder-only analyses of the primary outcome (7-day PPA rate at 6 months).

For cost analyses, we computed the costs of intervention per caller, the cost per quit based on the 6-month ITT 7-day PPA, and the incremental cost-effectiveness ratio (ICER; Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005). Intervention costs included direct costs associated with registration, provision of NRT and counseling (standard and MAC), and mailing of a quit guide (all participants) and a MAC information sheet (MAC participants only). Facility space, supplies, and physician supervision time were included in the call costs; research-related costs were excluded.

We also computed secondary analyses of potential moderators including gender and race in order to meet requirements for National Institutes of Health (NIH)-funded clinical trials (Dickerson, Leeman, Mazure, & O'Malley, 2009). The evaluation of moderators was accomplished with moderated logistic regression (MLR; Jaccard, 2001), in which gender or racial subgroup served as moderators. These MLR models included the dummy-coded variables for NRT group (with 2 weeks of patch as the reference condition), the moderator (e.g., gender), and two-way interactions of each NRT group dummy variable and the moderator (Kraemer, Wilson, Fairburn, & Agras, 2002). We also tested smoking heaviness as a potential moderator given its robust association with abstinence (e.g., Hyland et al., 2004). Race was coded as White versus non-White; smoking heaviness was coded as light smoking (≤15 cigarettes/day) versus heavy smoking (>15 cigarettes/day).

The study was originally powered to detect at least a 6.4% increase in the abstinence rate due to an enhanced intervention (e.g., using combination NRT); this effect size was based on prior quitline studies, and we predicted that 7-day PPA rates at 6 months would be approximately 12% in a standard intervention versus 18.4% in an enhanced intervention.

RESULTS

Participant Characteristics, CONSORT Diagram, and Sample Representativeness

Table 1 provides descriptive statistics for baseline variables by treatment group (main effects of NRT duration, NRT type, and MAC); groups did not differ on any of these variables. On average, participants smoked one pack of cigarettes per day; approximately 85% smoked their first cigarette within the first 30 min after waking, indicating significant nicotine dependence (Baker et al., 2007).

The study CONSORT diagram is shown in Figure 1. Overall, 76% of study participants completed the 6-month follow-up assessment; the completion rate did not differ by treatment groups. There were no serious adverse events (SAEs) or deaths during the study.

To assess the sample's representativeness, we compared enrollees with adult quitline callers seeking cessation assistance who did not enroll in the study (but who met basic inclusion–exclusion criteria) during the period of study enrollment. Enrollees and nonenrollees were compared on gender, race, education, age, cigarettes per day, and time to first cigarette after waking. There were no significant group differences on any of the measures.

PPA Outcomes

Table 2 provides 7-day and 30-day PPA rates at each of the postquit follow-up end points. HLR analysis of the primary outcome, 7-day PPA at 6 months, which included all main effects and interaction effects in the 2 × 2 × 2 design, yielded a statistically significant effect only for the NRT type main effect (patch only vs. combination NRT); no other main effects or interactions were significant. More specifically, a higher rate of abstinence was observed for combination NRT (49.9%) versus nicotine patch only (42.3%), odds ratio (*OR*) = 1.36 (95% *CI*: 1.06–1.75). Contrary to prediction, there was no significant difference between groups for 6 weeks of NRT (48.9%) versus 2 weeks of NRT (43.3%), *OR* = 1.26 (95% *CI*: 0.98–1.61); similarly, there was no difference in abstinence rates between groups for the MAC treatment (44.6%) versus no MAC treatment (47.6%), *OR* = 0.89 (95% *CI*: 0.69–1.14). As shown in Table 2, 30-day PPA rates were lower than 7-day PPA rates. HLR results for the 30-day PPA rates were similar to the 7-day PPA rates except that the main effect of NRT type approached significance, $p = .079$.

Because NRT is prescribed in real-world use both in terms of duration of treatment (e.g., up to 12 weeks as per labeling) and type (e.g., patch, gum, or both), we conducted analyses that evaluated the joint effects of duration and type. Specifically, the 2-week patch-only group was used as the reference group against which 2 weeks of combination NRT, 6 weeks of patch only, and 6 weeks of combination NRT were compared. As shown in Table 2, participants receiving 2 weeks of patch only achieved the lowest abstinence rate (38.4%) at 6 months. Participants receiving combination NRT for 2 or 6 weeks achieved statistically significantly higher rates of abstinence (48.2% and 51.6%, respectively) compared with 2 weeks of patch only. Participants receiving 6 weeks of nicotine patch only achieved a 7-day PPA rate of 46.2% that was not significantly higher than 38.4%. Inclusion of the MAC effect in the models did not change the results.

Cost Analyses

The 2-week combination NRT group showed both the lowest cost per quit ($442) and the lowest ICER ($357) relative to the 2-week patch-only group (Table 2). The highest ICER was observed in the 6-week combination NRT group ($1290); the 6-week patch-only group showed an intermediate ICER value of $712.

Medication Adherence/Use

Table 2 provides means and standard deviations for medication use measures including number of days of patch use (all participants) and gum use (combination NRT condition only) in the first 2 weeks and number of weeks of patch use and gum use reported at the 6-week follow-up.

Each of these measures was analyzed in 2 × 2 × 2 ANOVAs for patch use and 2 × 2 ANOVAs for gum use. Contrary to prediction, no significant main or interaction effects were

Table 1. Participant Characteristics by Treatment Condition[a]

Characteristic	Total no. of participants, *n* (% or *M* ± *SD*)	Duration of NRT		Type of NRT		MAC	
		Two weeks (n = 490)	Six weeks (*n* = 497)	Nicotine patch only (*n* = 494)	Nicotine patch + gum (*n* = 493)	No (*n* = 485)	Yes (*n* = 502)
Gender							
Female	569 (57.6)	54.9	60.4	57.3	58.0	58.4	57.0
Male	418 (42.4)	45.1	39.6	42.7	42.0	41.6	43.0
Age (*M* ± *SD*, year)	987 (41.9 ± 13.0)	42.0 ± 12.2	41.9 ± 13.7	42.7 ± 13.3	41.2 ± 12.5	42.0 ± 13.0	41.9 ± 12.9
Race							
White	747 (76.4)	76.5	76.2	77.7	75.1	74.1	78.6
Black	176 (18.0)	18.9	17.1	17.4	18.6	19.0	17.0
American Indian/ Alaska Native	17 (1.7)	1.6	1.8	1.6	1.8	2.3	1.2
Asian	5 (0.5)	0.0	1.0	0.4	0.6	0.6	0.4
Other	33 (3.4)	2.9	3.9	2.9	3.9	3.9	2.8
Hispanic							
No	944 (96.1)	96.5	95.7	95.9	96.3	96.1	96.2
Yes	38 (3.9)	3.5	4.3	4.1	3.7	3.9	3.8
Education							
Less than HS	171 (17.4)	16.6	18.1	17.8	16.9	16.1	18.6
HS Degree/GED	378 (38.4)	38.0	38.7	36.7	40.0	38.8	38.0
Post-HS schooling	436 (44.3)	45.4	43.1	45.4	43.1	45.2	43.4
Type of health insurance							
Commercial	187 (19.6)	18.5	20.6	19.5	19.6	20.0	19.2
Medicare	125 (13.1)	12.6	13.5	13.4	12.7	12.4	13.8
Medicaid	314 (32.9)	33.7	32.1	33.0	32.8	33.8	31.9
Uninsured	329 (34.5)	35.2	33.8	34.0	34.9	33.8	35.1
Cigarettes/day (*M* ± *SD*)	987 (20.7 ± 9.6)	20.4 ± 9.9	20.9 ± 9.3	21.0 ± 10.1	20.3 ± 9.1	20.4 ± 9.3	20.9 ± 9.9
Time to first cigarette after waking							
Within 5 min	515 (52.4)	51.4	53.3	50.9	53.9	52.6	52.2
6–30 min	329 (33.5)	34.2	32.7	34.5	32.4	34.2	32.8
31–60 min	89 (9.1)	8.4	9.7	9.5	8.6	8.3	9.8
>60 min	50 (5.1)	5.9	4.2	5.1	5.1	5.0	5.2
Number of previous quit attempts							
0	74 (7.7)	7.2	8.3	8.1	7.3	7.4	8.1
1	199 (20.8)	19.2	22.4	21.1	20.5	21.3	20.3
2–5	529 (55.3)	59.2	51.5	54.7	55.9	54.9	55.7
6+	166 (16.2)	14.5	17.8	16.1	16.3	16.5	15.9

Note. GED = General Educational Development certificate; HS = high school; MAC = medication adherence counseling; NRT = nicotine replacement therapy.

[a]Values expressed as number (percentage) unless otherwise indicated. Groups did not differ on any of the variables.

found for MAC plus SC intervention versus SC only for any of the medication use measures. The only significant effect in the analyses was NRT duration, which was a consistent and strong main effect for all four medication use outcomes. Participants randomized to receive 6 weeks of NRT used their patches and/or gum for more days in the first 2 weeks as well as for more weeks in the first 6 weeks relative to those randomized to receive only 2 weeks of NRT (see Table 2).

Quitline Counseling Utilization

Nearly 60% of study participants completed at least three proactive counseling calls; 18.4% completed only one counseling call (see Table 2). Chi-square (χ^2) analyses revealed no significant main effects (i.e., NRT duration, NRT type, and MAC) on this variable. A 2×2 × 2 ANOVA on total minutes of counseling showed only two significant effects: 6-week NRT produced longer counseling duration (65.3 min) than the 2-week group mean (61.9; $F(1,979) = 4.4$, $p < .05$), and a MAC main effect ($F(1,979) = 18.8$, $p < .001$) with MAC counseling adding about 7 min to SC.

Moderation Analyses of 7-Day PPA at 6 Months: Gender, Race, and Smoking Heaviness

Supplementary Table 1 provides ITT 7-day PPA rates at 6 months postquit by NRT group and the 3 moderators. For gender and race, there were no significant moderator × treatment interactions. Inspection of abstinence rates suggests possible gender and race subgroup differences in response to NRT treatment, but it is likely that the study was underpowered to detect reliable moderator effects. For smoking heaviness, there

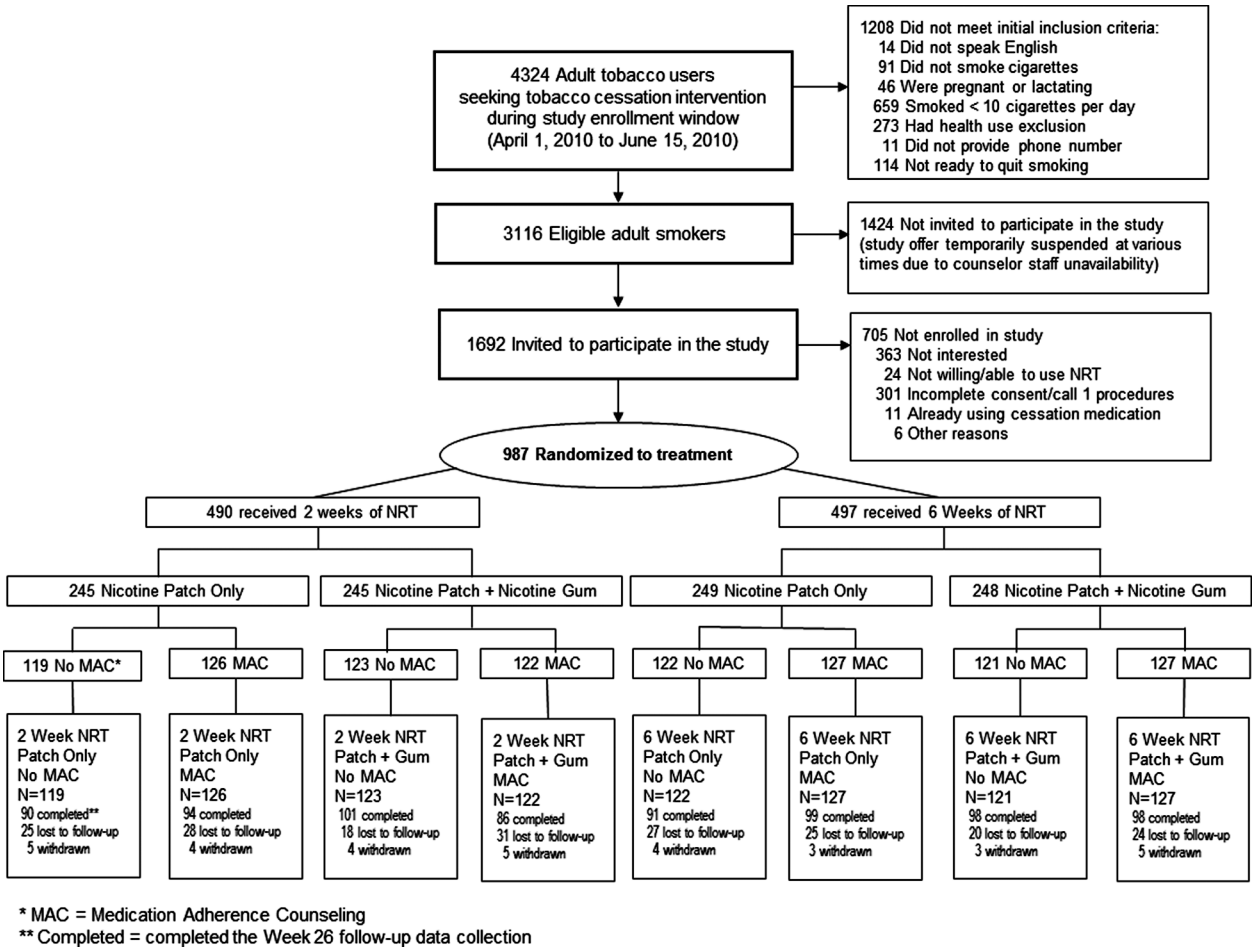

Figure 1. CONSORT diagram.

was a significant moderator × treatment interaction such that lighter smokers in the group receiving 2 weeks of combination NRT had a higher 7-day PPA rate at 6 months (57.4% vs. 34.9% for 2 weeks of patch only) than heavier smokers (42.4% vs. 40.3% for 2 weeks of patch only), interaction $p = .030$.

DISCUSSION

This real-world study was designed to identify the optimal medication adjuvants to tobacco cessation quitline counseling. Results showed that combination NRT for 2 or 6 weeks yielded significantly higher 6-month abstinence rates (48.2% and 51.6%, respectively) than did 2 weeks of nicotine patch only (38.4%), when each served as an adjuvant to quitline counseling. In addition, cost analyses showed that 2 weeks of combination NRT provided the most cost-effective cessation medication strategy both in terms of cost per quit and ICER. Contrary to predictions, MAC did not enhance abstinence outcomes.

Given the reach of quitlines, and existing funding constraints (Barry, Saul, & Bailey 2010), it is critical to identify the most clinically effective and cost-effective forms of quitline intervention. The current study supports the use of combination NRT as a quitline adjuvant but does not clearly distinguish which duration of combination NRT, 2 versus 6 weeks, is optimal (neither the tests of the main effect nor focused pairwise comparisons of NRT duration were statistically significant, $p = .071$). The 2-week combination NRT treatment was the most cost-effective intervention combination and achieved similar 6-month abstinence rates as the 6-week combination NRT intervention. Importantly, both the 2- and 6-week combination NRT treatments boosted 6-month abstinence rates by at least 10%, an increase that has the potential to yield an additional 50,000 quitters annually assuming 500,000 callers to U.S. quitlines per year and a comparable minimum service offering.

Combination NRT may have improved abstinence outcomes for several reasons. For example, prior research has demonstrated that combination NRT is more effective than single NRTs in reducing nicotine withdrawal severity (Bolt, Piper, Theobald, & Baker, 2011) and in improving cessation success in smokers with more severe nicotine dependence (Loh et al., 2012). In addition, combination NRT may increase success because the patch provides relatively steady dosing of nicotine for more than 24 hr with the option of using the nicotine gum on an "as-needed" basis in response to challenges such as spikes in craving or stressors. Although combination NRT is not currently FDA approved, it is recommended in the 2008 PHS Clinical Practice Guideline (Fiore et al., 2008) and its safety has been demonstrated in prior research (Piper et al., 2009) and in the current study (no SAEs).

Table 2. Primary Abstinence Outcomes, Medication Use, and Counseling Utilization by Treatment Main Effects

		Duration of NRT		Type of NRT		Medication adherence counseling	
Outcome	Total no. of participants, *n* (% or *M* ± *SD*	Two weeks (*n* = 490)	Six weeks (*n* = 497)	Nicotine patch only (*n* = 494)	Nicotine patch + gum (*n* = 493)	No (*n* = 485)	Yes (*n* = 502)
IIT 7-day PPA (%)							
2 weeks postquit	987	36.9	42.9	37.0	42.8	39.4	40.0
6 weeks postquit	987	42.4	51.1	45.5	48.1	46.4	47.2
12 weeks postquit	987	41.6	47.5	42.7	46.5	45.6	43.6
26 weeks postquit	987	43.3	48.9	42.3	49.9	47.6	44.6
ITT 30-day PPA (%)							
6 weeks postquit	987	29.4	35.8	30.4	34.9	30.9	34.3
12 weeks postquit	987	34.9	38.8	34.8	38.9	37.5	36.3
26 weeks postquit	987	35.1	39.0	34.4	39.8	37.5	36.7
Number of days of nicotine patch use in the first 2 weeks, *M* (*SD*)	799	9.07 (5.22)	10.75 (4.63)	9.62 (5.22)	10.26 (4.73)	9.8 (4.91)	10.0 (5.07)
Number of days of nicotine gum use in the first 2 weeks, *M* (*SD*)	392	5.97 (5.44)	8.00 (5.33)	—	7.03 (5.47)	7.01 (5.40)	7.05 (5.55)
Number of weeks of nicotine patch use in the first 6 weeks, *M* (*SD*)	716	3.22 (2.03)	4.48 (1.92)	3.78 (2.11)	3.95 (2.03)	3.76 (2.00)	3.96 (2.13)
Number of weeks of nicotine gum use in the first 6 weeks, *M* (*SD*)	346	2.72 (2.21)	3.94 (2.35)	—	3.36 (2.36)	3.44 (2.27)	3.27 (2.45)
% Proactive quitline counseling calls completed							
1 Call	182 (18.4%)	20.8	16.1	18.0	18.9	18.6	18.3
2 Calls	214 (21.7%)	22.7	20.7	19.6	23.7	22.9	20.5
3 Calls	248 (25.1%)	24.1	26.2	25.9	24.3	23.9	26.3
4 Calls	343 (34.8%)	32.4	37.0	36.4	33.1	34.6	34.9
Total minutes of quitline counseling, *M* (*SD*)	987	61.9 (23.9)	65.3 (26.2)	63.0 (25.5)	64.2 (24.8)	60.1 (23.9)	67.0 (25.8)

Note. ITT = intention-to-treat; NRT = nicotine replacement therapy; PPA = point-prevalence abstinence.

Table 3. Intent-to-Treat (ITT) 7-Day Point-Prevalence Abstinence (PPA) at 6 Months Postquit and Cost Analyses by Nicotine Replacement Therapy (NRT) Group

	ITT 7-day PPA (%)	Odds ratio (95% *CI*) for comparison with 2 weeks of nicotine patch only	Cost per caller	Cost per quit (based on 6-month ITT 7-day PPA)	ICER[a]
NRT group					
Two weeks nicotine patch only	38.4	—	$178	$464	—
Two weeks patch plus nicotine gum	48.2	1.49 (1.04–2.14)	$213	$442	$357
Six weeks nicotine patch only	46.2	1.38 (0.96–1.97)	$233	$505	$712
Six weeks patch plus nicotine gum	51.6	1.71 (1.20–2.45)	$348	$675	$1290

Note. [a]ICER = incremental cost-effectiveness ratio is a measure of the added cost per added quit for two treatments. ICER was computed as the cost difference between the least-intensive treatment group (2 weeks of nicotine patch only) and a more intensive comparison group divided by the difference in the quit rates of the two groups being compared; for example, the ICER for the group that received 2 weeks of nicotine patch and nicotine gum = (213 − 178)/(0.482 − 0.384) = $357.

A limitation of the current study is that self-reported abstinence rates were not biochemically confirmed. Although the Society for Research on Nicotine and Tobacco (SRNT) Subcommittee on Biochemical Verification (2002) did not recommend such verification for studies that collect data via telephone, mail, or Internet, it is possible that misreporting of true smoking status in the current study may have resulted in overestimates of abstinence success. The abstinence rates in the current study are substantially higher than rates reported in some other quitline studies (Cummings et al., 2011; McAfee et al., 2008; NAQC, 2009). This difference might be due to misreporting of true smoking status or other factors (e.g., study enrollment occurred just prior to the start of Wisconsin's "smoke-free" law on July 5, 2010). Although the effect of no biochemical verification in the current study cannot be determined, it is worth noting that the 7-day PPA rate of 38.4% at 6 months for participants in the least-intensive NRT condition (2 weeks of nicotine patch only) is very similar to the 7-month follow-up ITT 7-day PPA rate in a separate UW-CTRI quitline study. In this unpublished, nonrandomized study, 500 callers to the WTQL (March–May, 2009) received 2 weeks of nicotine patch and 4 proactive phone counseling sessions. At the 7-month follow-up (83% response rate), the ITT 7-day PPA rate was 36%. Thus, the abstinence rates in the current study would appear to be consistent with the success rates achieved in another WTQL study conducted a year prior to the current study.

Few quitline studies have included biochemical verification that would allow examination of misreporting of smoking status but existing studies suggest that misreporting may range between 10% and 30% (Ferguson et al., 2012; Walker et al., 2011; Zhu et al., 1996). Assuming misreporting of 20% in the current study, 6-month abstinence rates would be 32% and 31% for the 6- and 2-week combination NRT groups, respectively, versus 25% for the 2-week patch-only group. In this scenario, the 6% improvement with 2 weeks of combination NRT would potentially result in an additional 33,000 annual quits nationwide. Thus, there would still be strong public health benefit associated with combination NRT even if substantial misreporting occurred. However, we cannot determine whether misreporting varied with type of treatment and this limits the strength of inferences that can be made.

Another limitation is that the current study may have been underpowered to detect certain effects given that actual 6-month rates were substantially higher (>38%) than we predicted (approximately 18% for an enhanced intervention). The study was powered to detect a 6.4% increase due to an enhanced intervention (e.g., 18.4% vs. 12% in a standard intervention) but power to detect such an effect size (6.4% increase) is substantially reduced as proportions approach 50% (given the same sample size). Such a reduction in power likely accounts for the nonsignificant main effect for NRT duration and the failure to detect any interaction effects.

In summary, the current study shows that combination NRT for either 2 or 6 weeks significantly boosts abstinence rates when used along with other tobacco quitline interventions (counseling, online support, etc.), with 2 weeks of combination NRT being the most cost-effective intervention tested. Combination NRT as a quitline adjuvant has the potential to produce significant public health benefit if widely used, with an estimated 30,000–50,000 additional quitters in the United States each year.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 and Supplementary Appendices A and B can be found online at www.ntr.oxfordjournals.org

FUNDING

National Cancer Institute (NCI) grant 1RC1CA144382 to S.S.S.; T.B.B. was supported by NCI grant K05CA139871. Clinical Trial Registry: clinicaltrials.gov Identifier: NCT01087905; registered March 15, 2010 (prior to enrollment of study participants).

DECLARATION OF INTERESTS

S.S.S. *has served in the past 5 years as a coinvestigator on research studies at the University of Wisconsin–Madison that were funded wholly or in part by GlaxoSmithKline and Pfizer. T.B.B. has served as an investigator in the past 5 years on research studies at the University of Wisconsin–Madison that were funded in part by GlaxoSmithKline. T.B., B.M., and S.M.Z. are employees at Alere Wellbeing and also own stock in Alere Wellbeing (formerly Free & Clear, Inc.), an organization providing quitline services in Wisconsin.*

T.A.M. was employed by and owned stock in Free & Clear prior to being appointed Director of the Office on Smoking and Health, CDC, in September 2010. He was also an unpaid member of the Board of Directors of the nonprofit North American Quitline Consortium. T.A.M. has no current financial disclosures. M.C.F. has served in the past 5 years as an investigator on research studies at the University of Wisconsin-Madison that were funded wholly or in part by Pfizer, GlaxoSmithKline, and Nabi. From 1997 to 2010, M.C.F. held a University of Wisconsin named Chair for the Study of Tobacco Dependence, made possible by a gift to the university from GlaxoWellcome. P.A.K., K.H.K., and D.L.F. have no financial disclosures.

ACKNOWLEDGMENTS

We thank the following staff at the Center for Tobacco Research and Intervention at the University of Wisconsin School of Medicine and Public Health for their help with this research: Paul Kohn, Sandy Keller, Jared Holzhuter, Samantha Neymark, and Emily Gelber. In addition, we thank the staff at the Wisconsin Tobacco Quit Line for assistance with the study.

REFERENCES

Abrams, D. B., Graham, A. L., Levy, D. T., Mabry, P. L., & Orleans, C. T. (2010). Boosting population quits through evidence-based cessation treatment and policy. *American Journal of Preventive Medicine*, *38*(Suppl. 3), S351–S363. doi:10.1016/j.amepre.2009.12.011

Aguinis, H. (2004). *Regression analysis for categorical moderators*. New York, NY: Guilford Press.

Alpert, H. R., Connolly, G. N., & Biener, L. (2013). A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tobacco Control*, *22*(1), 32–37. doi:10.1136/tobaccocontrol-2011-050129

Baker, T. B., Piper, M. E., McCarthy, D. E., Bolt, D. M., Smith, S. S., Kim, S. Y., …Toll, B. A.; Transdisciplinary Tobacco Use Research Center (TTURC) Tobacco Dependence Phenotype Workgroup. (2007). Time to first cigarette in the morning as an index of ability to quit smoking: Implications for nicotine dependence. *Nicotine & Tobacco Research*, *9*(Suppl. 4), S555–S570. doi:10.1080/14622200701673480

Barnes, S. A., Larsen, M. D., Schroeder, D., Hanson, A., & Decker, P. A. (2010). Missing data assumptions and methods in a smoking cessation study. *Addiction*, *105*, 431–437. doi:10.1111/j.1360-0443.2009.02809.x

Barry, M. B., Saul, J., & Bailey, L. A. (2010). *U.S. quitlines at a crossroads: Utilization, budget, and service trends 2005–2010. Special report from the North American Quitline Consortium*. Retrieved from www.naquitline.org/resource/resmgr/reports_2010/100407_special-report.pdf (accessed October 13, 2011).

Bolt, D. M., Piper, M. E., Theobald, W. E., & Baker, T. B. (2012). Why two smoking cessation agents work better than one: Role of craving suppression. *Journal of Consulting and Clinical Psychology*, *80*, 54–65. doi: 10.1037/a0026366

Carlin-Menter, S., Cummings, K. M., Celestino, P., Hyland, A., Mahoney, M. C., Willett, J., & Juster, H. R. (2011). Does offering more support calls to smokers influence quit success? *Journal of Public Health Management and Practice*, *17*, E9–E15. doi:10.1097/PHH.0b013e318208e730

Campbell, S. L., Lee, L., Haugland, C., Helgerson, S. D., & Harwell, T. S. (2008). Tobacco quitline use: Enhancing benefit and increasing abstinence. *American Journal of Preventive Medicine*, *35*, 386–388. doi:10.1016/j.amepre.2008.06.032

Catz, S. L., Jack, L. M., McClure, J. B., Javitz, H. S., Deprey, M., Zbikowski, S. M. …Swan, G. E. (2011). Adherence to varenicline in the COMPASS smoking cessation intervention trial. *Nicotine & Tobacco Research*, *13*, 361–368. doi:10.1093/ntr/ntr003

Centers for Disease Control and Prevention (CDC). *Telephone quitlines: A resource for development, implementation, and evaluation*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Final Edition, September 2004. Retrieved from www.cdc.gov/tobacco/quit_smoking/cessation/quitlines/pdfs/quitlines.pdf (accessed December 2, 2011).

Centers for Disease Control (CDC). *Best practices for comprehensive tobacco control programs—2007*. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. Retrieved from www.cdc.gov/tobacco/stateandcommunity/best_practices/pdfs/2007/bestpractices_complete.pdf (accessed October 13, 2011).

Cohen, J., Cohen, P., West, S., & Aiken, L. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Mahwah, NJ: Erlbaum.

Cummings, K. M., Hyland, A., Carlin-Menter, S., Mahoney, M. C., Willett, J., & Juster, H. R. (2011). Costs of giving out free nicotine patches through a telephone quit line. *Journal of Public Health Management and Practice*, *17*, E16–E23. doi:10.1097/PHH.0b013e3182113871

Dickerson, D. L., Leeman, R. F., Mazure, C. M., & O'Malley, S. S. (2009). The inclusion of women and minorities in smoking cessation clinical trials: A systematic review. *American Journal on Addictions*, *18*, 21–28. doi: 10.1080/10550490802408522

Drummond, M. F., Sculpher, M. J., Torrance, G. W., O'Brien, B. J., & Stoddart, G. L. (2005). *Methods for the economic evaluation of health care programmes* (3rd ed.). New York, NY: Oxford University Press.

Ferguson, J., Docherty, G., Bauld, L., Lewis, S., Lorgelly, P., Boyd, K. A., …Coleman, T. (2012). Effect of offering different levels of support and free nicotine replacement therapy via an English national telephone quitline: Randomised controlled trial. *BMJ*, *344*, e1696. doi:10.1136/bmj.e1696

Fiore, M. C., Bailey, W. C., Cohen, S. J., Dorfman, S. F., Goldstein, M. G., Gritz, E. R., …Wewers, M. E. (2000). *Treating tobacco use and dependence. Clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service. Retrieved from www.ahrq.gov/path/tobacco.htm

Fiore, M. C., Jaen, C. R., Baker, T. B., Bailey, W. C., Benowitz, N. L., Curry, S. J., …Wewers, M. E. (2008). *Treating tobacco use and dependence: 2008 update. Clinical practice guideline*. Rockville, MD: U.S. Department of Health and Human Services, Public Health Service. Retrieved from www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf

Hall, S. M., Delucchi, K. L., Velicer, W. F., Kahler, C. W., Ranger-Moore, J., Hedeker, D., … Niaura, R. (2001). Statistical analysis of randomized trials in tobacco treatment: Longitudinal designs with dichotomous outcome. *Nicotine & Tobacco Research*, *3*, 193–202. doi:10.1080/14622200110050411

Hedeker, D., & Gibbons, R. D. (2006). *Longitudinal data analysis*. Hoboken, NJ: John Wiley & Sons.

Hedeker, D., Mermelstein, R. J., & Demirtas, H. (2007). Analysis of binary outcomes with missing data: Missing

= smoking, last observation carried forward, and a little multiple imputation. *Addiction*, *102*, 1564–1573. doi:10.1111/j.1360-0443.2007.01946.x

Hughes, J. R., Peters, E. N., & Naud, S. (2011). Effectiveness of over-the-counter nicotine replacement therapy: A qualitative review of nonrandomized trials. *Nicotine & Tobacco Research*, *13*, 512–522. doi:10.1093/ntr/ntr055

Hyland, A., Li, Q., Bauer, J. E., Giovino, G. A., Steger, C., & Cummings, K. M. (2004). Predictors of cessation in a cohort of current and former smokers followed over 13 years. *Nicotine & Tobacco Research*, *6*(Suppl. 3), S363–S369. doi:10.1080/14622200412331320761

Jaccard, J. J. (2001). *Interaction effects in logistic regression*. Newbury Park, CA: Sage.

Kaufman, A., Augustson, E., Finney-Rutten, L., & Davis, K. (2010). Awareness and use of tobacco quitlines: Evidence from the Health Information National Trends Survey. *Journal of Health Communication*, *15*(Suppl. 3), 264–278. doi:10.1080/10810730.2010.526172

Kraemer, H. C., Wilson, G. T., Fairburn, C. G., & Agras, W. S. (2002). Mediators and moderators of treatment effects in randomized clinical trials. *Archives of General Psychiatry*, *59*, 877–883. doi:10.1001/archpsyc.59.10.877

Lam, T. H., Abdullah, A. S., Chan, S. S., & Hedley, A. J.; Hong Kong Council on Smoking and Health Smoking Cessation Health Centre (SCHC) Steering Group. (2005). Adherence to nicotine replacement therapy versus quitting smoking among Chinese smokers: A preliminary investigation. *Psychopharmacology*, *177*, 400–408. doi:10.1007/s00213-004-1971-y

Lee, J- H., Herzog, T. A., Meade, C. D., Webb, M. S., & Brandon, T. H. (2007).The use of GEE for analyzing longitudinal binomial data: A primer using data from a tobacco intervention. *Addictive Behaviors*, *32*, 187–193. doi:10.1016/j.addbeh.2006.03.030

Liang, K. Y., & Zeger, S. L. (1986). Longitudinal data analysis using generalizing linear models. *Biometrika*, *73*, 13–22. doi:10.1093/biomet/73.1.13

Lichtenstein, E., Zhu, S. H., & Tedeschi, G. J. (2010). Smoking cessation quitlines: An underrecognized intervention success story. *The American Psychologist*, *65*, 252–261. doi:10.1037/a0018598

Loh, W. Y., Piper, M. E., Schlam, T. R., Fiore, M. C., Smith, S. S., Jorenby, D. E., … Baker, T. B. (2012). Should all smokers use combination smoking cessation pharmacotherapy? Using novel analytic methods to detect differential treatment effects over 8 weeks of pharmacotherapy. *Nicotine & Tobacco Research*, *14*, 131–141. doi:10.1093/ntr/ntr147

McAfee, T. A. (2007). Quitlines a tool for research and dissemination of evidence-based cessation practices. *American Journal of Preventive Medicine*, *33*(6 Suppl.) S357–S367. doi:10.1016/j.amepre.2007.09.011

McAfee, T. A., Bush, T., Deprey, T. M., Mahoney, L. D., Zbikowski, S. M., Fellows, J. L., & McClure, J. B. (2008). Nicotine patches and uninsured quitline callers. A randomized trial of two versus eight weeks. *American Journal of Preventive Medicine*, *35*, 103–110. doi:10.1016/j.amepre.2008.04.017

McAfee, T., Fellows, J., & Zbikowski, S. M. (2012). Re: Effect of offering different levels of support and free replacement therapy via an English national telephone quitline: Randomised controlled trial. *BMJ*, *344*:e1696. doi:10.1136/bmj.e1696 [Rapid Response Letter to the Editor; Retrieved from www.bmj.com/content/344/bmj.e1696/rr/584897; accessed June 14, 2012].

McAfee, T., Sofian, N. S., Wilson, J., & Hindmarsh, M. (1998). The role of tobacco intervention in population-based health care: A case study. *American Journal of Preventive Medicine*, *14*(3 Suppl.), 46–52. doi:10.1016/S0749-3797(97)00051-2

Nelson, D. B., Partin, M. R., Fu, S. S., Joseph, A. M., & An, L. C. (2009). Why assigning ongoing tobacco use is not necessarily a conservative approach to handling missing tobacco cessation outcomes. *Nicotine & Tobacco Research*, *11*, 77–83. doi:10.1093/ntr/ntn013

North American Quitline Consortium (NAQC). (2009). *Tobacco cessation quitlines: A good investment to save lives, decrease direct medical costs and increase productivity*. *North American Quitline Consortium, 2009*. Retrieved from www.naquitline.org/resource/resmgr/docs/naqc_issuepaper_tobaccocessa.pdf (accessed October 13, 2011).

North American Quitline Consortium (NAQC). (2011). *Results from the 2010 NAQC annual survey of quitlines*. *North American Quitline Consortium, 2011*. Retrieved from www.naquitline.org/resource/resmgr/2010_survey/0714final2010surveyresults.ppt (accessed December 6, 2011).

Ossip, D. J., Abrams, S. M., Mahoney, M. C., Sall, D., & Cummings, K. M. (2009). Adverse effects with use of nicotine replacement therapy among quitline clients. *Nicotine & Tobacco Research*, *11*, 408–417. doi:10.1093/ntr/ntp005

Piper, M. E., Smith, S. S., Schlam, T. R., Fiore, M. C., Jorenby, D. E., Fraser, D., & Baker, T. B. (2009). A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Archives of General Psychiatry*, *66*, 1253–1262. doi:10.1093/ntr/ntp005

Robins, J. M., Rotnitzky, A., & Zhao, L. P. (1995). Analysis of semiparametric regression models for repeated outcomes in the presence of missing data. *Journal of the American Statistical Association*, *90*, 106–121. doi: 10.2307/2291134

Schmitz, J. M., Sayre, S. L., Stotts, A. L., Rothfleisch, J., & Mooney, M. E. (2005). Medication compliance during a smoking cessation clinical trial: A brief intervention using MEMS feedback. *Journal of Behavioral Medicine*, *28*, 139–147. doi:10.1007/s10865-005-3663-4

Schneider, K. L., Hedeker, D., Bailey, K. C., Cook, J. W., & Spring, B. (2010). A comment on analyzing addictive behaviors over time. *Nicotine & Tobacco Research*, *12*, 445–448. doi:10.1093/ntr/ntp213

Shiffman, S., Sweeney, C. T., Ferguson, S. G., Sembower, M. A., & Gitchell, J. G. (2008). Relationship between adherence to daily nicotine patch use and treatment efficacy: Secondary analysis of a 10-week randomized, double-blind, placebo-controlled clinical trial simulating over-the-counter use in adult smokers. *Clinical Therapeutics*, *30*, 1852–1858. doi:10.1016/j.clinthera.2008.09.016

Smith, S. S., McCarthy, D. E., Japuntich, S. J., Christiansen, B., Piper, M. E., Jorenby, D. E., …Jackson, T. C. (2009). Comparative effectiveness of 5 smoking cessation pharmacotherapies in primary care clinics. *Archives of Internal Medicine*, *169*, 2148–2155. doi:10.1001/archinternmed.2009.426

Smolkowski, K., Danaher, B. G., Seeley, J. R., Kosty, D. B., & Severson, H. H. (2010). Modeling missing binary outcome data in a successful web-based smokeless tobacco cessation program. *Addiction*, *105*, 1005–1015. doi:10.1111/j.1360-0443.2009.02896.x

SRNT Subcommittee on Biochemical Verification. (2002). Biochemical verification of tobacco use and cessation. *Nicotine & Tobacco Research*, *4*, 149–159. doi:10.1080/14622200210123581

Stead, L. F., Perera, R., Bullen, C., Mant, D., & Lancaster, T. (2008). Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews (Online)*, Issue 1, CD000146. doi: 10.1002/14651858.CD000146.pub3

Stead, L. F., Perera, R., & Lancaster, T. (2006). Telephone counselling for smoking cessation. *Cochrane Database of Systematic Reviews (Online)*, Article Number CD002850. doi:10.1002/14651858.CD002850.pub2

Walker, N., Howe, C., Bullen, C., Grigg, M., Glover, M., McRobbie, H., …Rodgers, A. (2011). Does improved access and greater choice of nicotine replacement therapy affect smoking cessation success? Findings from a randomized controlled trial. *Addiction*, *106*, 1176–1185. doi:10.1111/j.1360-0443.2011.03419.x

Wiggers, L. C., Smets, E. M., Oort, F. J., Storm-Versloot, M. N., Vermeulen, H., van Loenen, L. B., … Legemate, D. A.(2006). Adherence to nicotine replacement patch therapy in cardiovascular patients. *International Journal of Behavioral Medicine*, *13*, 79–88. doi:10.1207/s15327558ijbm1301_10

Zhu, S. H., Anderson, C. M., Tedeschi, G. J., Rosbrook, B., Johnson, C. E., Byrd, M., & Gutiérrez-Terrell, E. (2002). Evidence of real-world effectiveness of a telephone quitline for smokers. *New England Journal of Medicine*, *347*, 1087–1093. doi:10.1056/NEJMsa020660

Zhu, S. H., Stretch, V., Balabanis, M., Rosbrook, B., Sadler, G., & Pierce, J. P. (1996). Telephone counseling for smoking cessation: Effects of single-session and multiple-session interventions. *Journal of Consulting and Clinical Psychology*, *64*, 202–211. doi:10.1037/0022-006X.64.1.202