Published in final edited form as:

Psychopharmacology (Berl). 2018 July ; 235(7): 2065–2075. doi:10.1007/s00213-018-4903-y.

Can We Increase Smokers' Adherence to Nicotine Replacement Therapy and Does This Help Them Quit?

Tanya R. Schlam,

Center for Tobacco Research and Intervention, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison

Jessica W. Cook,

Center for Tobacco Research and Intervention, Division of General Internal Medicine, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison and William S. Middleton Memorial Veterans Hospital, Madison, Wisconsin

Timothy B. Baker,

Center for Tobacco Research and Intervention, Division of General Internal Medicine, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison

Todd Hayes-Birchler,

Center for Tobacco Research and Intervention, School of Medicine and Public Health, University of Wisconsin-Madison

Daniel M. Bolt,

Department of Educational Psychology, University of Wisconsin-Madison

Stevens S. Smith,

Center for Tobacco Research and Intervention, Division of General Internal Medicine, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison

Michael C. Fiore, and

Center for Tobacco Research and Intervention, Division of General Internal Medicine, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison

Megan E. Piper

Center for Tobacco Research and Intervention, Division of General Internal Medicine, Department of Medicine, School of Medicine and Public Health, University of Wisconsin-Madison

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All authors can be reached at: Center for Tobacco Research and Intervention, University of Wisconsin-Madison, 1930 Monroe Street, Suite 200, Madison, WI 53711. Correspondence concerning this article should be addressed to Tanya Schlam, Center for Tobacco Research and Intervention, University of Wisconsin-Madison, Madison, WI 53711. Phone: 608-262-4149. FAX: 608-265-3102. trsclam@ctri.wisc.edu.

The primary smoking cessation outcomes from this experiment were reported previously in Schlam et al. (2016). A poster and a talk with a preliminary version of some of the findings in this paper were presented at the Society for Research on Nicotine and Tobacco annual convention in 2016, and a talk was presented at the annual convention in 2018.

Clinical Trial Registration: [ClinicalTrials.gov](https://clinicaltrials.gov) NCT01120704

Compliance with Ethical Standards

The study was approved by the University of Wisconsin Health Sciences Institutional Review Board, and all participants gave written informed consent.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Abstract

Objective: To examine the effects of five intervention components on smokers' adherence to combined nicotine patch and nicotine gum during a quit attempt and assess whether adherence is related to cessation.

Method: Smokers interested in quitting ($N=513$; 59% female; 87% White) received nicotine patch plus nicotine gum and participated in a $2 \times 2 \times 2 \times 2$ randomized factorial experiment (i.e., 32 treatment conditions) evaluating five intervention components: 1) Medication Adherence Counseling versus None; 2) Automated Medication Adherence Calls versus None; 3) Electronic Medication Monitoring with Feedback and Counseling versus e-Monitoring Alone; 4) 26 versus 8 Weeks of Nicotine Patch plus Nicotine Gum; and 5) Maintenance Counseling versus None. Adherence was assessed over the first 6 weeks post-target quit day via timeline follow-back (nicotine patch) and electronic medication dispenser (gum).

Results: In the first 6 weeks post-quit day, 12% of participants used no patches or gum, and 40% used the patch every day. Only 1.4% used both patch and gum adherently every day in the 6 weeks post-target quit day. E-Monitoring Counseling increased gum use (from 1.9 to 2.6 pieces/day; $p < .001$) but did not increase abstinence. More adherent patch and gum use in the first 6 weeks were each associated with higher point-prevalence abstinence rates through 1 year.

Conclusions: This large experiment with electronic monitoring of nicotine gum adherence showed that e-Monitoring Counseling increased gum use but not abstinence. Adherence to nicotine patch and to gum were each strongly related to abstinence, but it is unclear whether adherence increases abstinence, or relapse causes medication discontinuation.

Keywords

smoking cessation; tobacco dependence; medication adherence; electronic medication monitoring; nicotine replacement therapy

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Smoking is the top preventable cause of death in the U.S. (Danaei et al. 2009), yet the percentage of smokers who successfully quit in a given quit attempt remains stubbornly low. Smokers who use smoking cessation medication to help them quit can double or triple their likelihood of successfully quitting: e.g., from ~5% attaining long-term abstinence in an unaided quit attempt to ~10-30% in an aided one (Fiore et al. 2008, Hughes et al. 2004). These figures may, however, underestimate the potential benefit of cessation pharmacotherapy because, in both research studies and in real-world use, people tend to use considerably less cessation medication than recommended (Lam et al. 2005, Mooney et al. 2007, Schmitz et al. 2005, Shiffman et al. 2008, Wiggers et al. 2006).

Studies have found adherent use of medications is strongly related to increased likelihood of abstinence (Catz et al. 2011, Lam et al. 2005, Ma et al. 2016, Mooney et al. 2005, Shiffman et al. 2008). This strong correlation suggests that increasing adherence causes increased abstinence rates (e.g., Cropsey et al. 2017). Of course, relapse may also cause nonadherence (the correlation could, for example, reflect decreased use of medication once a lapse or relapse occurs during a quit attempt). Unfortunately, few studies have manipulated cessation medication adherence as a way to both improve clinical outcomes and inform causal

inference (although cf. Mooney et al. 2007, Smith et al. 2013). Moreover, while some studies have used real-time or daily self-report assessments of medication adherence (Hollands et al. 2013, Ma et al. 2016, Mooney et al. 2007, Schmitz et al. 2005, Shiffman et al. 2008), such studies are the exception, generally comprise only small numbers of participants, and have not yielded strong evidence that adherence can be substantially improved so as to increase abstinence rates.

In this paper, we present what are, to the best of our knowledge, the most comprehensive data to date on cessation medication adherence. These data were derived from real-time, electronically monitored acute nicotine replacement (nicotine gum) use, meaning that they are less subject to bias related to self-report and forgetting. These data were collected as part of a factorial experiment testing three intervention components we hypothesized would each increase medication adherence (to both nicotine patch and nicotine gum) and long-term abstinence, along with two intervention components we hypothesized would increase long-term abstinence (see Schlam et al. 2016 for primary cessation outcomes and details of study methods). These data allow us to: 1) characterize patterns of self-reported patch use and electronically recorded nicotine gum use, 2) identify baseline individual difference variables predictive of medication adherence, 3) examine the effects of five different intervention components (including three adherence intervention components) on medication adherence and abstinence, and 4) sensitively assess whether medication adherence is related to cessation success.

Method

Participants

Recruitment took place in 11 primary care clinics from two southern Wisconsin healthcare systems from 2010 to 2013. Adult smokers attending any clinic outpatient visit were invited by a medical assistant (prompted by a modified electronic health record) to participate in a research program to help smokers quit smoking or cut down on their smoking (Fraser et al. 2013, Piper et al. 2013). Patients interested in quitting in the next month were assessed by study staff by phone for eligibility including: smoking ≥ 5 cigarettes per day over the past 6 months; not using varenicline or bupropion; and having no medical contraindications to nicotine replacement therapy (NRT). Those eligible were asked to return to their clinic to provide written informed consent and begin treatment. Case managers (bachelor's level study staff supervised by a licensed clinical psychologist) delivered the treatment in patients' primary care clinics.

Participants in the final analysis sample ($N = 513$) were a mean of 46.2 years old ($SD = 12.8$) and smoked a mean of 18.6 cigarettes per day ($SD = 8.8$). The sample was 59% female, 87% White, and 10% African American; 4% were Hispanic and 13% had a college degree.

Assessments

At baseline (1 week pre-target quit day; TQD), participants completed questionnaires assessing sociodemographic variables, lifetime psychiatric history (e.g., ever diagnosed with

or treated for depression? Anxiety?), motivation to quit (how motivated are you to quit smoking?), self-efficacy (how likely is it that 1 year from now you will be a non-smoker?), and past and current smoking. Participants completed adherence questionnaires, including the 4-item Trait Adherence Questionnaire, which assesses difficulty adhering to medication in general (yes=1; no=0; responses are summed; Morisky et al. 1986; Cronbach's alpha in this sample = .56), and the 9-item Wisconsin Beliefs Assessment on Smoking and Cessation (WI-BASC; Schlam et al. 2016, based on a questionnaire developed by Smith et al. 2013; Cronbach's alpha in this sample = .74), which assesses misconceptions about smoking cessation medication (i.e., stop-smoking medicine is: addictive, dangerous, hard to use, likely not efficacious, not needed if withdrawal symptoms are gone or if you are smoking, not needed in the recommended amounts, and less important than willpower; see Online Resource 1 for items). WI-BASC response options range from 1 (strongly disagree) to 7 (strongly agree), and the total score is the mean of the 9 items. The Trait Adherence Questionnaire and the WI-BASC were modestly, but significantly correlated ($r = .14$, $p = .001$). Daily smoking status was assessed using timeline follow-back (Robinson et al. 2014) at study visits (Weeks 1, 4, 8) and in follow-up calls (Weeks 16, 26, 39, 52) and was used to determine self-reported 7-day point-prevalence abstinence. Adverse events were assessed during active medication use.

Medication Adherence Measures

Daily patch use data were collected during study visits via timeline follow-back. All participants were given nicotine gum and an electronic medication dispenser, the *Helping Hand* available from Bang & Olufsen Medicom (De Bleser et al. 2010). Participants were instructed to put a new blister pack of gum into the dispenser every day and to carry the dispenser with them so it could electronically record the date and time the gum blister pack was removed from the dispenser. Data from the gum dispenser were downloaded at each study visit.

Study Design

This study was a $2 \times 2 \times 2 \times 2$ fully crossed factorial experiment (i.e., there were 32 treatment conditions) testing the effects of the five two-level factors described below (Schlam et al. 2016). Half of the participants were randomized to each level of each factor; i.e., to a more intense ("On") level or to a less intense or absent ("Off") level. In addition, all participants received a base cessation treatment (8 weeks of nicotine patch plus nicotine gum, and a total of 50 minutes of counseling across four contacts starting at Week -1 pre-TQD and ending at Week 2). For those participants randomized to adherence counseling (described below), that counseling occurred immediately after any base cessation counseling.

1. **Medication Adherence Counseling (MAC).** Half of participants were assigned to two 10-minute in-person MAC sessions (Weeks -1 and 1) that provided information tailored to correct misconceptions regarding cessation medication based on a participant's WI-BASC questionnaire responses (Smith et al. 2013). The other half of participants did not receive MAC.
2. **Automated Adherence Calls.** Half of participants were assigned to brief automated medication reminder calls (6 automated calls in the first 6 weeks; a

total of 7 calls for the 8-week medication group and 11 calls for the 26-week medication group). The calls offered information, tips, and praise to encourage using the medication as recommended (May et al. 2003, World Health Organization 2003). The other half of participants received no adherence calls.

3. **Electronic Medication Monitoring with Feedback and Counseling (e-Monitoring Counseling).** All participants were asked to carry a medication dispenser. One-half of participants were given printouts showing their daily gum use (as electronically recorded by the dispenser; see Online Resource 2) along with 10-minute counseling sessions focused on the printouts and increasing adherence via collaborative problem solving. In the first 6 weeks, there were five such counseling sessions. The 26-week medication group had four additional later sessions. The other half of participants received no gum use printouts or associated counseling.
4. **Extended Medication.** All participants were given nicotine patches plus nicotine gum to use beginning on the TQD for 8 weeks. Half were randomized to receive study medication for a full 26 weeks (for dosing see Schlam et al. 2016). Participants were told to use the medication even if they were smoking. Participants were told to use the gum every 1-2 hours and to use at least 5 pieces a day during the first 6 weeks. Participants who experienced side effects were instructed to use fewer pieces of gum or to discontinue use if necessary.
5. **Maintenance Counseling.** Half of participants were randomized to Maintenance Counseling designed to prevent relapse and encourage new quit attempts as needed (three brief calls in the first 6 weeks; eight calls total through Week 22). The other half of participants had no Maintenance Counseling.

Analytic Plan

Adherence variables.—Adherence variables were computed for the first 6 weeks of medication use which was immediately prior to nicotine gum use tapering among participants randomized to only 8 weeks of medication. We examined adherence only on days when the participant should have provided medication use data (i.e., the participant had a working medication dispenser, had not been told to discontinue the medication due to side effects, and had not withdrawn from the study). As in Hollands et al. (2013), analyzable days with no medication use data recorded (where data were missing) were set to zero use based on the notion that participants with missing medication use data had most likely returned to smoking, and stopped using the medication and attending study visits. It should be noted gum use downloads were cumulative so if participants attended any later study visits, they would have downloaded their gum use data for the entire study period up until that moment.

Participants were included in analyses if they had 14 days of both nicotine gum and patch use data in the first 6 weeks post-TQD ($N = 513$; 94% of the 544 randomized participants; Schlam et al. 2016). The remaining participants had <14 days of medication use data due to: being advised not to use one or both medications in the first 2 weeks post-TQD ($n = 16$); withdrawing from the study in the first 2 weeks post-TQD ($n = 9$); never receiving an e-

monitoring device ($n = 1$); and a programming error that interfered with patch data collection ($n = 5$). Participants in the final analysis sample ($N = 513$) had analyzable patch use data on a mean of 41.1 ($SD = 4.1$) days and analyzable gum use data on a mean of 40.9 ($SD = 4.5$) days (range for both variables: 14 to 42 days; median and mode for both variables: 42). We calculated the percentage of days participants used the patch (range: 0.00-100.00%) and mean pieces of gum per day in the first 6 weeks of the quit attempt using the number of analyzable use days as the denominator. Finally, we calculated the percentage of days participants were adherent to both medications (i.e., the percentage of days where participants used both a patch and four or more pieces of gum, which is attainment of 80% of the recommended goal of five or more pieces/day; range: 0.00-100.00%).

Overview of the analyses.—Descriptive statistics were used to characterize the sample, overall adherence patterns, and baseline adherence beliefs. We examined relations between patch and gum use via correlations, and we examined baseline predictors of medication use with Student's t -tests and correlations. General linear models were used to examine the effect of treatment on medication use with models that included the five intervention component main effects and all interactions. Significant interactions were graphed for interpretation. A general linear model was then used to examine the effect of treatment on self-reported point-prevalence abstinence at 26 weeks post-TQD (this model was an intent-to-treat analysis that assumed missing equals smoking; this analysis model is identical to one reported in Schlam et al. 2016, except it uses the current sample so results may differ). Finally, we used logistic regression to examine the relations between medication use and self-reported 7-day point-prevalence abstinence at Weeks 8, 26, and 52. Relations between medication use and abstinence were then examined in an effort to identify an optimal level of medication use. All results are shown using the traditional $p < .05$ cut-off for statistical significance; we used the Benjamini-Hochberg (B-H) procedure (Benjamini and Yekutieli 2001) to control the false discovery rate within families of analyses with conceptually similar types of predictors and the same dependent variable.

Results

Adherence and Beliefs About Adherence

During the first 6 weeks of the quit attempt, participants used the patch a mean of 66.6% of days ($SD = 40.7$); 17.3% reported using no patches ($n = 89$), while 39.8% ($n = 204$) reported using a patch every day. There was no difference in 6-week patch use between the 8- and 26-week medication groups ($M = 65.3\%$ of days used the patch [$SD = 40.8$] vs. $M = 68.0\%$ of days [$SD = 40.6$], respectively; $t(511) = -.77$, $p = .44$). Participants with patch use data for the full 6 weeks (94% of the sample) reported using a mean of 4.76 patches a week ($SD = 2.81$). In the first 6 weeks, participants used a mean of 2.27 ($SD = 2.16$; range 0-12.57) pieces of nicotine gum per day; 15.6% used no gum ($n = 80$). There was no significant difference in 6-week gum use between the 8- and 26-week medication groups ($M = 2.14$ pieces of gum [$SD = 2.16$] vs. $M = 2.39$ pieces of gum [$SD = 2.16$], respectively; $t(511) = -1.31$, $p = .19$; Online Resource 3).

The percentage of days the patch was used and mean pieces of gum/day were strongly correlated ($r = .58, p < .001$); 61 participants (11.9%) did not use any patches or gum. Participants who used no patches or gum and those who used at least some study medication did not differ in age, gender, education (up to a high school diploma vs. more than high school), race (White vs. member of a racial minority), number of self-reported psychiatric diagnoses (0, 1, or >1), Trait Adherence score, or WI-BASC score (p 's $> .05$). It is important to note, however, that representation of some of these demographic or person factors in the "used no patches or gum" group is sparse given the small size of this group. Based on the distribution of the variable "percentage of days used the patch" we created three categories: used the patch $<25\%$ of days in the first 6 weeks (26.5% of the sample); 25-94% of days (23.4% of the sample); and 95% of days (50.1% of the sample). Participants in these three patch use categories used the following mean pieces of gum/day in the first 6 weeks: low adherence to patch group: 0.47 pieces/day ($SD = 0.86$); moderate adherence to patch group: 1.80 pieces of gum/day ($SD = 1.69$); high adherence to patch group: 3.44 pieces of gum/day ($SD = 2.10$).

We next examined adherence to the combination medication. Participants were classified as adherent (i.e., used a patch each day and used 4 pieces of gum/day) in the first 6 weeks on a mean of 28.8% of days ($SD = 32.6$; range 0-100%). Almost one-third of the sample (32.0%) were adherent to both medications on 0% of days in the first 6 weeks. Another 32.3% of the sample were adherent between 1% and 33% of days; 17.2% were adherent between 34% and 66% of days; 17.1% were adherent between 67 and 99% of days; and only 1.4% were adherent to both medications every day in the first 6 weeks.

In terms of medication adherence beliefs, at baseline, participants' WI-BASC scores ($M = 2.96, SD = 0.92$; range 1-6.11) indicated that they disagreed slightly with dysfunctional adherence beliefs such as "I'm concerned about becoming addicted to the stop-smoking medicine." However, the belief "Quitting smoking depends more on willpower than on taking medicine," received relatively strong endorsement ($M = 5.17, SD = 1.55$; range 1-7). On the Trait Adherence Questionnaire, participants' fairly low scores ($M = 1.18, SD = 1.18$; range 0-4) indicated relatively good trait adherence. However, 99 participants (19.5%) reported they are "careless at times" about taking their medicine.

Baseline Predictors of Adherence

We examined baseline predictors of the percentage of days participants used the patch and mean pieces of gum/day in the first 6 weeks. We obtained similar results when we examined predictors of joint adherence to patch plus gum (not reported). Patch and gum use were significantly, but modestly, negatively correlated with baseline total scores on the Trait Adherence Questionnaire (r 's magnitude $< .12$) but uncorrelated with the WI-BASC total score which assessed misconceptions about cessation medication. We then examined the following potential predictors: demographics (gender, race [White vs. member of a racial minority], age, and education [up to a high school diploma vs. more than high school]); psychiatric variables (history of depression, anxiety, and past-year binge drinking); and smoking variables (living with someone who smokes, motivation to quit, number of previous serious quit attempts, cigarettes per day, and smoking 30 minutes after waking). Unless

noted, the results discussed here were significant with the B-H correction for the 12 predictors for each dependent variable.

Student's *t*-tests and correlations revealed no significant relations between medication use and: education, history of depression or past-year binge drinking, living with a smoker, cigarettes per day, or time to first cigarette. There were gender and race differences, however. Men used more patches and gum than did women (percentage of days used the patch: Men = 72.5% [*SD* = 38.1] vs. Women = 62.5% [*SD* = 41.9], $t = -2.80$, $p = .005$, $d = -0.25$; mean pieces of gum/day: Men = 2.56 [*SD* = 2.29] vs. Women = 2.07 [*SD* = 2.04], $t = -2.50$, $p = .01$, $d = -0.22$, not significant with B-H correction). White smokers used more patches and gum than smokers from racial minority groups (percentage of days used the patch: White = 68.9% [*SD* = 39.6] vs. racial minority = 53.6% [*SD* = 44.0], $t = -2.85$, $p = .005$, $d = -0.35$; mean pieces of gum/day: White = 2.38 [*SD* = 2.19] vs. racial minority = 1.61 [*SD* = 1.87], $t = -2.92$, $p = .004$, $d = -0.36$). There was a positive correlation between age and both percentage of days using the patch ($r = .16$, $p < .001$) and pieces of gum/day ($r = .11$, $p = .01$, not significant with B-H correction). Participants who reported a history of anxiety (17.2% of the sample) used more gum per day (History of Anxiety = 2.78 [*SD* = 2.58] vs. No History = 2.17 [*SD* = 2.05] mean pieces of gum/day, $t = -2.09$, $p = .04$, $d = -0.25$, not significant with B-H correction) but did not use the patch on a greater percentage of days than those without such a history. Baseline motivation to quit ($M = 8.8$, $SD = 1.4$ on a scale from 1 [*not at all*] to 10 [*extremely*]) was positively related to gum use ($r = .09$, $p = .046$, not significant with B-H correction) but not patch use ($r = .08$, $p = .06$). Similarly, number of prior quit attempts ($M = 4.2$, $SD = 7.4$) was positively related to gum use ($r = .09$, $p = .04$; not significant with B-H correction), but not patch use ($r = .07$, $p = .10$).

Side Effects and Adherence

We examined whether adverse experiences with medication were associated with medication adherence. No participants reported serious adverse events (AEs) related to using the medications. Participants randomized to the 26- and 8-week medication durations reported the following as the most common AEs, respectively: vivid dreams (16% and 19%) and skin rash (23% and 19%; for additional details see Schlam et al. 2016). Participants reported a mean of 1.22 AEs ($SD = 1.92$; range 0 to 14) during the first 6 weeks post-TQD. The total number of AEs reported in the first 6 weeks was correlated with percentage of days of patch use ($r = .19$, $p < .001$) and with mean pieces of gum/day ($r = .11$, $p = .01$) such that those who used the medication on more days reported more AEs. However, the number of AEs reported was not significantly related to abstinence at 8, 26, or 52 weeks post-TQD.

The Effects of Treatment on Adherence

Table 1 presents the general linear model results of treatment effects on medication use. Only one effect was significant across all three medication adherence variables (patch, gum, and patch plus gum): the 3-way interaction of Maintenance Counseling $\times$ MAC $\times$ e-Monitoring Counseling (p 's = .01-.02; not significant with B-H correction). Patch and gum use were each highest when participants were assigned to the "on" condition of all three intervention components (Figures 1a and b). The combined effect of the three intervention components was especially striking for gum use (the target for e-Monitoring Counseling).

This pattern is consistent with the main effect of e-Monitoring Counseling on mean gum use/day (Table 1); participants used 2.61 pieces/day ($SD = 2.40$) with e-Monitoring Counseling vs. 1.92 pieces/day ($SD = 1.83$) without it ($p < .001$, $d = 0.18$, 95% confidence interval (CI) [0.002, 0.35]). Figure 1b shows neither MAC nor Maintenance Counseling consistently helped increase gum use.

E-Monitoring Counseling also had a main effect on combined patch and gum use. Participants who received such counseling were adherent to both medications a mean of 4.6 more days (of the 42 assessed) than were those not receiving it (i.e., they were adherent 34.28% of days [$SD = 35.92$] versus 23.27% of days [$SD = 27.77$]; $p < .001$, $d = 0.19$, 95% CI [0.01, 0.36]). However, this effect was driven by the effect of e-monitoring counseling on gum use since e-monitoring counseling did not increase patch use.

We analyzed additional models to test the robustness of these findings for the patch-based outcomes to account for the metric used (percentages) and the relative non-normality of distributions. More specifically, the patch use outcome had a bimodal distribution (over the first 6-weeks, 17.3% used the patch on no days while 39.8% used the patch every day), whereas the combined patch plus gum use outcome had a right-skewed distribution (32.0% had no days on which they were adherent to both medications). We therefore computed beta regression models (Ferrari and Cribari-Neto 2004) with the outcome transformed to address the extreme scores (Smithson and Verkuilen 2006). The pattern of significant findings in these alternative models remained essentially the same as in the linear regression models presented in Table 1.

The Effects of Medication Adherence Treatment on Abstinence

Paralleling analyses reported previously (Schlam et al., 2016 with an $N = 544$; in this paper's analyses $N = 513$), none of the adherence intervention components yielded a main effect on 26-week abstinence (although 26 vs. 8 weeks of nicotine patch plus nicotine gum increased abstinence; $b = .28$, $p = .007$, $d = .60$, 95% CI [0.42, 0.77]). There were 4 interactions that affected 26-week abstinence: MAC $\times$ Adherence Calls ($b = .24$, $p = .02$); Maintenance Counseling $\times$ MAC $\times$ e-Monitoring Counseling ($b = .33$, $p = .001$); MAC $\times$ Adherence Calls $\times$ e-Monitoring Counseling ($b = -.22$, $p = .03$); and Extended Medication $\times$ Maintenance Counseling $\times$ MAC $\times$ e-Monitoring Counseling ($b = -.21$, $p = .04$).

Only the Maintenance Counseling $\times$ MAC $\times$ e-Monitoring Counseling effect on 26-week abstinence was significant with B-H correction, and only this interaction was related to all three medication adherence variables (patch, gum, and combined use). Unpackaging this interaction (Online Resource 4) suggested that participants had the highest abstinence rate when they received Maintenance Counseling without MAC and e-Monitoring Counseling (50.0% abstinent); the abstinence rate was slightly lower when participants received all three components (47.2% abstinent). The benefits of Maintenance Counseling were not, however, consistently apparent. When Maintenance Counseling was used in combination with only one of the adherence components, the combination produced fairly low abstinence rates (31.8 and 33.8%).

The Association of Medication Adherence with Abstinence

Using logistic regression, the percentage of days participants used the patch was associated with self-reported 7-day point-prevalence abstinence at 8 weeks ($b = .018$, $p < .001$; odds ratio [OR] = 1.019, 95% CI [1.013, 1.024]). This demonstrates that for each 10 percentage point increase in the percentage of days participants used the patch, the relative odds of abstinence increases by a factor of $(1.019)^{10} = 1.21$. Effects with regard to patch use were also significant at 26 and 52 weeks (26 weeks: $b = .023$, $p < .001$; $OR = 1.023$, 95% CI [1.017, 1.029]; 52 weeks: $b = .023$, $p < .001$; $OR = 1.023$, 95% CI [1.016, 1.029]). Similarly, the mean number of pieces of gum/day was associated with abstinence at 8 weeks ($b = .33$, $p < .001$; $OR = 1.39$, 95% CI [1.27, 1.53]). This demonstrates that for every additional piece of gum participants used daily over 6 weeks, the relative odds of abstinence increases by a factor of 1.39. Effects with regard to gum use were also significant at 26 and 52 weeks (26 weeks: $b = .27$, $p < .001$; $OR = 1.31$, 95% CI [1.20, 1.43]; 52 weeks: $b = .26$, $p < .001$; $OR = 1.30$, 95% CI [1.19, 1.42]). In exploratory sensitivity analyses, the six analyses described above were repeated with two covariates: baseline motivation in one set of analyses and baseline self-efficacy in the other. In all 12 sensitivity analyses, adherence to the patch or gum remained significantly associated with abstinence and the magnitude of the relation remained very similar.

When patch use was treated categorically (<25% of days; 25-94% of days; 95-100% of days), there was a significant relation between patch use and abstinence at 8 weeks ($\chi^2 = 50.59$, $\phi = .31$, $p < .001$); 26 weeks ($\chi^2 = 69.37$, $\phi = .37$, $p < .001$); and 52 weeks ($\chi^2 = 55.00$, $\phi = .33$, $p < .001$; see Figure 2a). When gum use was divided into 5 categories (used 0 pieces of gum; >0 and <2; 2 to <4; 4 to <6; and used 6 or more pieces a day), there was a significant relation between gum use and abstinence at 8 weeks ($\chi^2 = 66.39$, $\phi = .36$, $p < .001$); 26 weeks ($\chi^2 = 46.79$, $\phi = .30$, $p < .001$); and 52 weeks after the TQD ($\chi^2 = 35.01$, $\phi = .26$, $p < .001$). Figure 2b illustrates a linear trend in the relation between gum use and cessation up to <6 pieces per day; using at least 4 pieces of gum a day (and fewer than 6) was associated with the highest abstinence rates. We also examined mean pieces of gum used in the first 2 weeks (to minimize the influence of relapsers discontinuing the gum) divided into the same 5 use categories, and the relation between gum use and cessation was similar (data not shown).

Discussion

This research found fairly low cessation medication adherence among primary care smokers during the first 6 weeks of a quit attempt collected via self-report (nicotine patch) and real-time, electronically monitored nicotine gum use. Only 40% of participants reported using a patch every day. Participants used a mean of 2.3 versus the recommended 5 pieces of nicotine gum a day, and use decreased over time. Adherent conjoint use of the patch and gum was rare, with only 1.4% of participants remaining adherent to both agents over the 6 weeks; one-third of participants were adherent to both agents on no days. This suggests conclusions about the effectiveness of smoking cessation pharmacotherapies must be made with the recognition that, even with motivated individuals and strong efforts to promote medication use, only a minority will use the intended dose.

Cessation medication misconceptions (as assessed by WI-BASC total score) were not associated with using less medication. The MAC intervention, designed to correct these misconceptions, did not have a main effect on either adherence or abstinence. In general, these findings and others suggest that adherence-related beliefs may be less important determinants of medication use than has been assumed (Kerr et al. 2004, Mooney et al. 2006, Neame and Hammond 2005, Smith et al. 2013).

We hypothesized that each of the three adherence intervention components (MAC, Automated Adherence Calls, and e-Monitoring Counseling) would increase both gum and patch use via main effects. However, in fact, only e-Monitoring Counseling produced a main effect on gum use. This accords with a recent review that concluded that, for a variety of medical conditions, integrating e-monitoring devices into health care (e.g., providers giving patients adherence feedback) was more frequently associated with greater adherence than simply having patients interface with e-monitoring devices (Checchi et al. 2014). However, in the current study, while e-Monitoring Counseling increased gum use, it did not have a main effect on abstinence. In fact, none of the adherence intervention components produced main effects on abstinence. These findings accord with Mooney et al.'s (2005) findings that contingency management plus corrective information about nicotine gum increased gum use but not abstinence. The findings also accord with a Cochrane review of high quality studies of adherence interventions; such interventions typically had little effect on adherence or disease outcomes (Nieuwlaat et al. 2014). We may have not yet developed an intervention that increases cessation medication adherence enough to also increase abstinence rates. It may be, however, that, as in Mooney et al. (2005), even under optimal conditions significant increases in adherence will not boost abstinence; naturally occurring medication use patterns may already approach the optimal medication benefit.

Participants who received a combination of Maintenance Counseling, MAC, and e-Monitoring Counseling used more nicotine gum (1.2 pieces/day more) than those who received none of those intervention components (but the interaction was not significant with B-H correction). The interaction involving these components also influenced abstinence. These effects did not, however, provide clear evidence that the adherence intervention components boosted abstinence; the highest 6-month abstinence rate (50%) was produced by Maintenance Counseling unaccompanied by either adherence component. In sum, it appears to be difficult to substantially increase the use of prn or "as needed" cessation medication given that it took the conjoint effects of three intervention components to increase mean gum use by more than one additional piece a day. This increase in adherence was paralleled by a higher abstinence rate, possibly suggesting a causal relation between adherence and abstinence. However, although participants were randomly assigned to the intervention conditions, the variation in medication adherence was not due solely to the intervention components, making other explanations possible.

Adherence in general, not just the portion related to treatment, was strongly related to abstinence, as found previously (Lam et al. 2005, Ma et al. 2016, Mooney et al. 2007, Shiffman et al. 2008). Using the patch on 95-100% of days in the first 6 weeks of treatment was associated with markedly higher abstinence rates through 1-year (~20 percentage points higher than rates of those using the patch 25-94% of days). Using 4-5 (but not 6 or more)

pieces of gum/day was associated with the highest long-term abstinence rates. Such strong relations are consistent with other findings suggesting adherence causally affects abstinence: e.g., compared to placebo, active cessation medication typically decreases the risk of full relapse following a lapse (Ferguson et al. 2012, Japuntich et al. 2011, Shiffman et al. 2006), and discontinuing subjects' active medication (vs. placebo) as per experimental protocol tends to produce a bump in relapse (Medioni et al. 2005). A review of studies that examined NRT adherence among non-relapsed participants concluded there is modest support for the idea that non-adherence contributes to relapse (Raupach et al. 2014). However, while there is strong evidence that greater adherence is associated with increased abstinence, it is also likely that substantial nonadherence is caused by participants' return to smoking (Burns and Levinson 2008). More research is needed to elucidate the potentially reciprocal influences between adherence and smoking status. In addition, more research is needed to examine the potential influence of third variables that might account for the relation between NRT adherence and abstinence. The current findings suggest that the relation between NRT adherence and abstinence is independent of baseline motivation and self-efficacy but other variables and time-varying effects should be explored.

Future research should further explore the determinants of nonadherence (e.g., genetic factors; although see Tyndale et al. 2015; see Pacek et al. 2017 for a review of correlates of cessation medication nonadherence). It would also be helpful to obtain better data on the proximal causes of nonadherence. In two studies (Balmford et al. 2011, Burns and Levinson 2008), smokers attributed their NRT nonadherence to going back to smoking, side effects, feeling NRT was not helping them quit, or having already quit. However, it is important to gather more proximal and longitudinal real-time data on nonadherence that addresses such mechanisms and perhaps others (e.g., forgetting medication).

Some study limitations should be noted. First, there were assessment limitations. Both smoking status and patch use were assessed via timeline follow-back, which can be prone to recall bias. Also, abstinence was not biochemically confirmed, which likely resulted in higher quit rates than would have been found if biochemical confirmation had been required. In addition, we did not assess use of non-cigarette tobacco products or electronic cigarettes, which might have substituted for smoking medications or affected abstinence rates. Second, some participants may not have used the e-monitoring medication dispenser correctly thus compromising the accuracy of their gum use data. Finally, use of the medication dispenser may have created reactive effects such that the device either increased gum use (e.g., due to knowing medication use was monitored) or decreased it (e.g., due to the inconvenience of carrying the dispenser). Estimated nicotine gum use rates are lower in this study than in some studies using only self-report data (Etter et al. 2009, Shiffman et al. 2003). This may be due to biases in retrospective self-report (a tendency to inflate adherence in self-report; Stirratt et al. 2015), sample differences, or the burden imposed by dispenser use in this study.

In summary, we found a substantial portion of participants were markedly non-adherent to both the nicotine patch and nicotine gum, even though participants were motivated to quit, had volunteered for an intensive treatment program, and efforts were made to enhance adherence. Adherence to the patch and gum were both strongly related to abstinence, but the causal basis of this relation is unclear (e.g., whether adherence increases abstinence, or

lapsing and relapsing cause medication discontinuation). Counseling based on real-time, electronic monitoring of nicotine gum use increased gum use modestly (<1 additional piece/day) but did not increase abstinence rates. Only the interaction of three intervention components significantly increased both adherence to the nicotine patch and gum and abstinence, perhaps reflecting a causal relation but also reflecting the refractoriness of adherence to treatment. At present, it seems likely that markedly increasing adherent use of NRT would require highly intensive, perhaps multicomponent, intervention efforts, or new approaches (e.g., Cropsey et al. 2017). Future analyses with this data set will explore temporal ordering (whether non-adherence precedes lapsing or vice-versa) in order to shed more light on causality. The strong relations observed between adherence and abstinence underscore the importance of elucidating the causal relations between these two variables.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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 help with this research.

Funding: This research was supported by grants 9P50CA143188, 1P01CA180945, and 1K05CA139871 from the National Cancer Institute to the University of Wisconsin Center for Tobacco Research and Intervention and by the Wisconsin Partnership Program. Dr. Cook is also supported by Merit Review Award 101CX00056 from the United States Department of Veterans Affairs.

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Fig 1. Maintenance Counseling $\times$ Medication Adherence Counseling (MAC) $\times$ Electronic Monitoring (e-Monitoring) with Counseling interacted in predicting (a) percentage of days used the nicotine patch in the first 6 weeks of the quit attempt and (b) mean pieces of nicotine gum used per day in the first 6 weeks

Fig 2.

Seven-day point-prevalence abstinence rates at 8, 26, and 52 weeks after the target quit day by (a) percentage of days used the nicotine patch in the first 6 weeks of the quit attempt (with patch use treated categorically: <25% of days; 25-94% of days; 95-100% of days), and (b) mean pieces of nicotine gum used a day in the first 6 weeks (with gum use divided into 5 categories: used 0 pieces of gum; >0 and <2; 2 to <4; 4 to <6; and used 6 or more pieces a day)

Table 1

General Linear Models Examining the Effect of Treatment on Use of the Nicotine Patch, Nicotine Gum, and Combined Nicotine Patch and Gum in the First 6 Weeks of the Quit Attempt

Variable	Percentage of Days Used the Nicotine Patch		Mean Daily Nicotine Gum Use		Percentage of Days Adherent to Both Nicotine Patch and Gum	
	<i>b</i>	<i>p</i> -value	<i>b</i>	<i>p</i> -value	<i>b</i>	<i>p</i> -value
Extended Medication	1.24	.48	.15	.11	2.61	.06
Maintenance Counseling	.89	.61	.07	.48	.63	.65
Medication Adherence Counseling (MAC)	−1.09	.53	.007	.94	−.03	.98
Automated Adherence Calls	−.62	.72	.06	.53	1.01	.47
e-Monitoring Counseling	−1.02	.56	.38	<.001	6.08	<.001
Extended Medication × Maintenance Counseling	−.99	.57	.01	.88	.98	.48
Extended Medication × MAC	−5.20	.003 [†]	−.14	.14	−1.76	.21
Extended Medication × Adherence Calls	.92	.60	.18	.05	3.23	.02 [†]
Extended Medication × e-Monitoring Counseling	.80	.65	.08	.42	2.08	.13
Maintenance Counseling × MAC	.91	.60	.11	.23	1.43	.30
Maintenance Counseling × Adherence Calls	.99	.57	.14	.12	1.78	.20
Maintenance Counseling × HH Counseling	1.87	.28	.04	.65	.60	.66
MAC × Adherence Calls	3.44	.048 [†]	.01	.88	−.29	.84
MAC × e-Monitoring Counseling	−.23	.90	.11	.22	.93	.50
Adherence Calls × e-Monitoring Counseling	.17	.92	−.002	.99	−.61	.66
Extended Medication × Maintenance Counseling × MAC	−2.96	.09	−.02	.80	−.36	.80
Extended Medication × Maintenance Counseling × Adherence Calls	−2.51	.15	−.07	.45	−1.60	.25
Extended Medication × Maintenance Counseling × e-Monitoring Counseling	1.81	.30	−.05	.63	−.22	.88
Extended Medication × MAC × Adherence Calls	−1.64	.35	−.04	.69	−.57	.68
Extended Medication × MAC × e-Monitoring Counseling	2.02	.25	.04	.65	.98	.48
Extended Medication × Adherence Calls × e-Monitoring Counseling	4.09	.02 [†]	.15	.10	2.29	.10
Maintenance Counseling × MAC × Adherence Calls	.89	.61	.08	.41	.82	.55
Maintenance Counseling × MAC × e-Monitoring Counseling	4.35	.01 [†]	.21	.02 [†]	3.20	.02 [†]
Maintenance Counseling × Adherence Calls × e-Monitoring Counseling	1.93	.27	−.10	.27	−.87	.53
MAC × Adherence Calls × e-Monitoring Counseling	−1.38	.43	−.05	.58	.15	.92
Extended Medication × Maintenance Counseling × MAC × Adherence Calls	.32	.85	.12	.19	2.13	.13
Extended Medication × Maintenance Counseling × MAC × e-Monitoring Counseling	−1.08	.53	−.03	.71	−.36	.79
Extended Medication × Maintenance Counseling × Adherence Calls × e-Monitoring Counseling	−.40	.82	.06	.52	1.03	.46

Variable	Percentage of Days Used the Nicotine Patch		Mean Daily Nicotine Gum Use		Percentage of Days Adherent to Both Nicotine Patch and Gum	
	<i>b</i>	<i>p</i> -value	<i>b</i>	<i>p</i> -value	<i>b</i>	<i>p</i> -value
Extended Medication × MAC × Adherence Calls × e-Monitoring Counseling	−1.51	.39	.01	.91	−.26	.85
Maintenance Counseling × MAC × Adherence Calls × e-Monitoring Counseling	1.86	.29	.20	.03 [†]	2.74	.048 [†]
Extended Medication × Maintenance Counseling × MAC × Adherence Calls × e-Monitoring Counseling	2.38	.17	.12	.21	1.52	.27

[†] Not significant with the Benjamini-Hochberg correction.