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Original Investigation

Adherence to Varenicline in the COMPASS Smoking Cessation Intervention Trial

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Abstract

Introduction: Patient adherence to smoking cessation medications can impact their effectiveness. It is important to understand the extent to which prescribed medications are actually taken by smokers, how this influences smoking cessation outcomes, and what factors may influence adherence.

Methods: Smokers recruited from a large health plan were randomized to receive different modes of cessation counseling in combination with varenicline (Swan, G. E., McClure, J. B., Jack, L. M., Zbikowski, S. M., Javitz, H. S., Catz, S. L., et al. 2010. Behavioral counseling and varenicline treatment for smoking cessation. *American Journal of Preventive Medicine*, 38, 482–490). One thousand one hundred and sixty-one participants were mailed a 28-day varenicline supply when they set a quit date and were able to request up to two refills from the health plan pharmacy at no cost. Pharmacy fill records were obtained and telephone surveys completed at baseline, 21 days, 12 weeks, and 6 months post target quit date.

Results: Good adherence to varenicline (≥80% of days taken) was associated with a twofold increase in 6-month quit rates compared with poor adherence (52% vs. 25%). Smokers were more likely than nonsmokers to stop varenicline early. Purposeful nonadherence was associated with smoking at 12 weeks and was predicted in multivariate analyses by age, gender, adherence self-efficacy, and initial medication side effect severity.

Conclusions: Innovative methods for increasing adherence to smoking cessation medications are needed, particularly early in the quit process. Simple metrics of adherence such as number of days cessation medication is taken can and should be routinely incorporated in effectiveness trials and reported to advance future attempts to understand and reduce nonadherence.

Introduction

Medication adherence, the extent to which medication-taking behavior corresponds with agreed recommendations from a health care provider, underlies the internal validity of all clinical efficacy trials and impacts real-world treatment effectiveness (World Health Organization, 2003). Even highly efficacious medications will not be maximally effective if taken by patients with insufficient consistency or duration to achieve positive therapeutic outcomes.

Varenicline (aka, Chantix) has been shown to be an efficacious smoking cessation medication. Varenicline is an α4β2 partial agonist that was specifically developed to aide cessation by reducing the effects of nicotine withdrawal while also temporarily reducing the reinforcing effects of nicotine through stimulation of the dopaminergic reward pathway. In clinical trials, it significantly increased abstinence rates compared with placebo, bupropion, and nicotine replacement therapy (NRT; Cahill, Stead, & Lancaster, 2008; Gonzales et al., 2006; Jorenby et al., 2006; Nides et al., 2006; Oncken, Cooney, Feinn, Lando, & Kranzler, 2007; Tonstad et al., 2006; Williams, Reeves, Billing, Pennington, & Gong, 2007). A meta-analysis showed that longer prescribed durations of varenicline use were associated with higher abstinence rates (Lee, Jones, Bybee, & O'Keefe, 2008). However, little is known about the actual length or patterns of varenicline use when smokers are prescribed a standard course of treatment.

Studies with other cessation pharmacotherapies have shown that the amount of NRT or bupropion actually used by people can be much less than recommended (Blondal, Franzon, & Westin, 1997; Garvey et al., 2000; Hajek et al., 1999; Hurt et al., 1997; Killen et al., 2004; Lam, Abdullah, Chan, Hedley, & Hong Kong Council on Smoking & Health Smoking Cessation Health Centre Steering Group, 2005). Moreover, higher levels of adherence to NRT or bupropion appear to be related to better smoking cessation outcomes (Killen et al., 2004; Mooney, Sayre,

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Hokanson, Stotts, & Schmitz, 2007; Schmitz, Stotts, Mooney, Delaune, & Moeller, 2007; Shiffman, Sweeney, Ferguson, Sembower, & Gitchell, 2008; Swan, Javitz, Jack, Curry, & McAfee, 2004). Because patient adherence to smoking cessation medications can impact their effectiveness, it is important to understand the extent to which all prescribed cessation medications are actually taken by smokers and how this influences smoking cessation outcomes. Since varenicline is relatively newer to the market, adherence to this medication has not been well described in real-world settings.

The first large adherence study to include varenicline investigated the predictors of adherence in two randomized controlled trials comparing varenicline, bupropion sustained release, and placebo (Hays, Leischow, Lawrence, & Lee, 2010). High rates of adherence were observed for all treatments, and three factors were shown to predict medication adherence: age, early 7-day point prevalence abstinence at Week 2, and number of cigarettes smoked per day. Presence of adverse events in the first thirty days of treatment and other baseline demographic and smoking history characteristics did not significantly predict adherence in these trials (Hays et al., 2010). The distinction made between purposeful and unintentional adherence in one smoking cessation study (Toll, McKee, Martin, Jatlow, & O'Malley, 2007) is important to note when considering potential predictors of adherence because the chronic disease adherence literature suggests that adherence-related motivation, beliefs, and attitudes that are amenable to change may be more likely to influence purposeful (also termed "intentional") adherence lapses and demographic factors such as age may be more likely to influence unintentional adherence lapses (e.g., forgetting; Clifford, Barber, & Horne, 2008; Wroe, 2002). For example, a study to explore attitudes about bupropion found that greater self-efficacy beliefs for using bupropion as indicated were associated with higher levels of electronically monitored bupropion adherence, a greater number of treatment sessions attended, and an increased likelihood of completing treatment (Fucito, Toll, Salovey, & O'Malley, 2009).

We report on adherence to a standard 12-week varenicline regimen that was mailed to all smokers who set quit dates in the COmprehensive Medication Program And Support Services (COMPASS) trial. This trial compared the effectiveness of three modalities of a behavioral smoking cessation program when combined with varenicline use among smokers seeking treatment at a large health care organization. When varenicline treatment was integrated with either Web-based counseling, proactive phone-based counseling, or integrated phone and Web counseling, no significant differences in 6-month abstinence rates were found (Swan et al., 2010). Abstinence rates in this real-world effectiveness study were high (31%–34%) and similar to rates seen in varenicline clinical trials when the medication was combined with in-person counseling (Swan et al., 2010).

The goals of this secondary analysis are to describe rates and patterns of adherence to varenicline, investigate the extent to which varenicline adherence impacts smoking cessation outcomes, and to identify modifiable factors associated with varenicline adherence that can be addressed in future integrated behavioral and pharmacotherapy smoking cessation interventions.

Methods

Setting and Participants

Group Health is a consumer-governed nonprofit health care organization that serves approximately 600,000 residents of Washington and Idaho. Group Health enrollees were recruited from October 2006 to October 2007 through brochures placed in health plan–owned clinics, physician referrals, and through the Quit For Life Program administered by Free & Clear, Inc. All protocols were reviewed and approved by the Institutional Review Boards of Group Health, SRI International, and Free & Clear, Inc. as well as by a study Data and Safety Monitoring Board.

Inclusion/Exclusion Criteria

Smokers were eligible for participation in the COMPASS trial (Swan et al., 2010) if they were at least 18 years old, smoked at least 10 cigarettes/day over the past year and 5 cigarettes/day within the past week, had dependable telephone and Internet access and were comfortable using the Internet, were eligible for smoking cessation services under current health plan coverage, and were medically appropriate for varenicline use. Individuals were excluded from participation in the COMPASS trial for any of the following reasons: current/planned pregnancy or breast feeding; self-report of poor health, severe chronic heart disease, or COPD; on dialysis or with certain kidney disease; current treatment for or self-report of schizophrenia, bipolar disorder, or mania; high-frequency alcohol use over the past six months (more than two drinks per day almost every day); and/or binge drinking two or more times in the last month, current use of bupropion, NRT, investigational or recreational/street drugs, or other drugs that could potentially interfere with renal clearance of varenicline (Leabman & Giacomini, 2003).

Measures

Eligible volunteers were interviewed by phone at baseline to assess smoking history, nicotine dependence (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), quitting history, motivation to quit, depression as measured by a modified Hopkins Symptom Checklist (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974; McClure et al., 2009), self-efficacy for taking varenicline (including items assessing self-efficacy for adhering despite nicotine withdrawal symptoms and for adhering despite medication side effects), treatment outcome expectations, and demographics. Telephone follow-up surveys were conducted by nonintervention study staff approximately 21 days, 12 weeks, and 6 months after the target quit date to collect information on quit attempts, smoking, and medication adherence. At 21 days and 12 weeks, participants were also asked if during the past month, they experienced any of a number of treatment-related symptoms including known medication side effects (e.g., nausea, vomiting, change in appetite) and nicotine abstinence effects (e.g., irritability, desire to smoke; Halperin et al., 2009; McClure et al., 2009). Severity of symptoms and side effects endorsed in the past month was rated by participants on a Likert scale from 1 (*very mild*) to 5 (*very severe*), with 0 on this scale signifying "*not present*."

Smoking abstinence was defined as the self-report of no smoking, not even a puff, within the past seven days (i.e., 7-day point-prevalent abstinence). Individuals who were not reached

for 6-month follow-up were considered to be smoking. The number of varenicline prescriptions filled during the approximately 6-month study period was obtained from pharmacy records, including study-prescribed medication and any additional varenicline prescribed by usual primary care providers.

Telephone follow-up surveys included four self-report adherence indices: total number of days varenicline was taken over the approximately 6-month study period, proportion of varenicline taken 7 days prior to quit date, proportion of varenicline taken 7 days post quit date (Mannheimer, Friedland, Matts, Child, & Chesney, 2002), and the Morisky Medication Adherence Questionnaire (MAQ) at 21 days and 12 weeks post quit date (Morisky, Green, & Levine, 1986). The MAQ has been validated with smokers and yields a total score and two subscales that measure purposeful nonadherence (e.g., purposefully stopping medication after feeling better or worse) and unintentional nonadherence (e.g., careless or forgetful in taking medication; Toll et al., 2007). Participants respond yes or no to four MAQ items assessing history of medication nonadherence. Items are scored 0 (*yes*) or 1 (*no*) and summed such that higher MAQ total or subscale scores reflect higher adherence/lower nonadherence (Morisky et al., 1986; Toll et al., 2007).

At each follow-up point, participants were asked if they were still taking varencline. Those participants who had stopped taking varenicline were asked to indicate "yes" or "no" for each reason for stopping: experienced side effects, felt it was not needed, and felt it was not working. Participants still taking the medication were assigned a "no" answer for each of these items.

Integrated Medication and Behavioral Interventions

All COMPASS trial participants received a prescription from a study physician for a 12-week supply of varenicline to be taken according to recommended guidelines (Fiore et al., 2008) starting one week prior to the target quit date. The study protocol was for the central Group Health pharmacy to mail a starter supply of varenicline and up to two 28-day prescription refills (upon request) to each participant who set a quit date at no charge to the participant.

Smokers (n = 1,202) were randomized to receive one of three delivery modes of cessation counseling (phone, Web, and integrated phone/Web), and all those who set a quit date (n = 1,161; 96.6%) received varenicline. We previously reported high cessation rates (33%) but no significant differences across study arms at 6 months (Swan et al., 2010). In this paper, the relationship of varenicline adherence to smoking abstinence at 6 months post quit date is examined for the 1,161 COMPASS participants who were mailed varenicline prescriptions, regardless of intervention arm assignment.

Statistical Analysis

Logistic regression analysis was used to evaluate the relationship of each medication adherence measure to smoking outcome at 6-month follow-up (Table 2). Chi-square analysis was used to compare the reasons for stopping varenicline given by smokers and nonsmokers (Table 3). For analysis of baseline and 12-week predictors of the numbers of days varenicline was taken during the 6-month study period and the extent of purposeful nonadherence, only those variables shown in Table 4 with univariate p-values less than .15 were included in the final multivariate linear regression models.

Results

Baseline characteristics for the sample can be found in Table 1.

Rates of Varenicline Adherence

For those who were mailed any study medication, the average total number of days varenicline was reported taken over the course of the approximately 6-month study period (range = 0–210, median = 77.0, M = 63.3, SD = 33.2) was less than the prescribed 84 days. According to pharmacy records, the mean number of varenicline prescriptions filled during the 6-month study period was 2.4 (range = 1–9, median = 3.0, SD = 1.1) and the average total days supply was 69.4 (median = 82, SD = 32.2). Pharmacy records reflect the number of 28-day varenicline prescriptions mailed to all participants, an estimate of medication adherence that was somewhat higher than what respondents to 12-week or 6-month follow-up surveys reported they had actually taken.

Initial adherence reports were also examined. Estimates from a self-report rating scale (Mannheimer et al., 2002) administered approximately four weeks after planned varenicline

Table 1. Baseline Characteristics of the Sample (Those Who Received Study Medication From Pharmacy)

Characteristic	Overall N = 1,161
Demographics	
Age in years, M (SD)	47.3 (10.9)
Gender (% female)	66.8
Race (% White)	89.6
Years of formal schooling, M (SD)	14.1 (2.2)
Marital status (% married)	64.0
Smoking history	
Cigarettes per day, M (SD)	19.7 (8.1)
FTND, M (SD)	5.0 (2.1)
Other smokers in home (% yes)	44.3
Quitting history	
Quit attempt past year (% yes)	48.2
Longest previous quit of 6 months or more (% yes)	36.5
Previous use of NRT (% yes)	83.0
Previous use of bupropion (% yes)	49.2
Psychosocial, M (SD)	
Depression scale	0.9 (0.7)
Medication attitudes, M (SD)	
Positive treatment outcome expectations	4.4 (0.6)
Negative treatment outcome expectations	2.2 (0.9)
Total varenicline adherence self-efficacy items	9.4 (0.6)
Stick to schedule if having severe withdrawal symptoms	8.1 (2.3)
Stick to schedule if having annoying side effects	7.5 (2.3)

Note. FTND = Fagerström Test for Nicotine Dependence; NRT = nicotine replacement therapy.

initiation (21 days post scheduled quit dates) suggested that the mean proportion of varenicline taken 7 days prior to (M = 92.5%, SD = 23.6%) and 7 days following (M = 91.6%, SD = 22.2%) scheduled quit dates was relatively high but variable. Overall scores on the Morisky MAQ at 21 days (M = 3.2, SD 0.8) and at 12 weeks postquit (M = 3.0, SD = 0.9) were indicative of good initial adherence that lessened over time (mean change = −0.25, t = −7.4, p < .0001).

Relation of Varenicline Adherence to 6-Month Smoking Abstinence

Table 2 compares the mean varenicline adherence of nonsmokers to smokers. Smoking status for these analyses was classified on the basis of 7-day point-prevalent smoking abstinence at 6 months post target quit date among those who received medication, with missing cessation status imputed as relapse. Odds of being a nonsmoker at 6-months were more than one and a half times greater for those requesting more refills of varenicline according to pharmacy records. Odds of being a nonsmoker at 6-month follow-up were also significantly greater for participants who reported taking more days of varenicline and for those who reported taking higher proportions of varenicline prior to and immediately following their quit date. Odds of being a nonsmoker were greater for those with higher total Morisky MAQ scores at 21 days but not at 12 weeks. As shown in Table 2, less purposeful nonadherence was significantly associated with smoking status at both of these assessment points, while unintentional nonadherence was not.

Good adherence, defined by convention as taking 80% or greater of the prescribed regimen (DiMatteo, Giordani, Lepper, & Croghan, 2002), was strongly associated with smoking cessation. More than half (52.2%) of those who reported good adherence were abstinent at 6-month follow-up, whereas only a quarter (25.4%) of those who reported taking varenicline for less than 80% of the days prescribed were abstinent at 6 months ($\chi^2_{(1)}$ = 73.1, p < .0001).

Reasons for Stopping Varenicline

Smokers were significantly more likely than nonsmokers to report having stopped taking varenicline at 21-day and 12-week follow-ups (see Table 3). Overall, the most frequently endorsed reasons for stopping varenicline early were side effects and perceived lack of need. The reasons for stopping varenicline given by smokers and nonsmokers are shown in Table 3. More than half of smokers (53%) and nonsmokers (52.8%) who were no longer taking varenicline at 21-day follow-up indicated they stopped due to side effects. By the 12-week follow-up, a significantly greater proportion of smokers (45.4%) than nonsmokers (29.2%) who were no longer taking varenicline reported side effects as a reason for stopping. A high proportion of nonsmokers who stopped varenicline indicated they felt it was not needed (27.8% at 21 days and 43.3% at 12 weeks), whereas few smokers indicated they stopped varenicline due to not needing it (13.7% at 21 days and 11.9% at 12 weeks). Relatively few participants no longer taking varenicline indicated they stopped due to feeling it was not working. However, the proportion of smokers who indicated they stopped varenicline due to the medication not working was higher (11.9%) than that of nonsmokers who endorsed this reason for stopping (3.2%).

Predictors of Varenicline Adherence

Univariate linear regression analyses were conducted to identify predictors of varenicline adherence as measured by the reported number of days varenicline was taken during the 6-month study period and by the purposeful nonadherence scale of the MAQ at 12 weeks post target quit date. Older age, greater baseline self-efficacy for adhering to varenicline, and less initial nicotine withdrawal symptom severity (at 21-day follow-up) were found to significantly predict both greater number of days varenicline was taken and less purposeful nonadherence (see Table 4). Gender and education were not significantly associated with varenicline days taken but were significant predictors of less purposeful nonadherence. Baseline measures of depression, treatment outcome expectations, presence of smokers in the home, and nicotine

Table 2. Comparison of Varenicline Adherence Among Smokers and Nonsmokers at 6 Months (Intent-to-Treat 7-day Point-Prevalent Abstinence)

Characteristic	Not smoking, *M* (*SD*)	Smoking, *M* (*SD*)	*OR*[a] (95% *CI*)	*p* value
Self-report at 21 days post quit date	*N* = 375	*N* = 605		
Adherence 7 days prior to quit date	0.94 (0.21)	0.91 (0.25)	1.15 (1.00–1.33)	.0479
Adherence 7 days following quit date	0.94 (0.18)	0.90 (0.25)	1.24 (1.07–1.4443)	.0043
Total MAQ adherence score	3.3 (0.7)	3.1 (0.9)	1.25 (1.09–1.44)	.0012
Less unintentional nonadherence[b]	1.4 (0.6)	1.4 (0.6)	1.06 (0.93–1.20)	.4018
Less purposeful nonadherence[b]	1.9 (0.3)	1.8 (0.5)	1.50 (1.28–1.76)	.0001
Self-report at 12 weeks post quit date	*N* = 374	*N* = 519		
Total MAQ adherence score	3.0 (0.9)	3.0 (1.0)	1.08 (0.94–1.24)	.2748
Less unintentional nonadherence [b]	1.3 (0.6)	1.4 (0.7)	0.93 (0.81–1.06)	.2526
Less purposeful nonadherence[b]	1.7 (0.5)	1.6 (0.6)	1.23 (1.07–1.41)	.0042
Self-report over 6-month study period	*N* = 396	*N* = 595		
Number of days varenicline taken	74.1 (28.7)	56.1 (34.1)	1.81 (1.56–2.09)	.0001
Pharmacy records over 6-month study period	*N* = 396	*N* = 765		
Number of varenicline prescriptions filled	2.7 (1.1)	2.2 (1.1)	1.66 (1.45–1.89)	.0001

Note. MAQ = Medication Adherence Questionnaire; *OR* = odds ratio.

[a]*OR*s for nonsmoking at 6 months are calculated for a pooled 1 *SD* increase in the independent variable.

[b]Higher values of MAQ unintentional and purposeful subscales are associated with less nonadherence (i.e., greater adherence).

Table 3. Reasons Varenicline was Stopped Early by Smokers and Nonsmokers

Reason for stopping, *N* (%)	Not smoking	Smoking	Chi square
Self-report at 21 days post quit date			
Still taking varenicline	341 (90.4)	476 (78.3)	$\chi^2_{(1)} = 24.3, p < .0001$
No longer taking varenicline	36 (9.6)	132 (21.7)	
Experienced side effects	19 (52.8)	70 (53.0)	$\chi^2_{(1)} = 0.0, p = .9785$
Felt it was not needed	10 (27.8)	18 (13.7)	$\chi^2_{(1)} = 4.0, p = .0458$
Felt it was not working	2 (5.9)	17 (12.9)	$\chi^2_{(1)} = 1.3, p = .2532$
Self-report at 12 weeks post quit date			
Still taking varenicline	155 (41.4)	172 (33.0)	$\chi^2_{(1)} = 6.7, p = .0098$
No longer taking varenicline	219 (58.6)	349 (67.0)	
Experienced side effects	64 (29.2)	158 (45.4)	$\chi^2_{(1)} = 14.8, p = .0001$
Felt it was not needed	95 (43.2)	41 (11.9)	$\chi^2_{(1)} = 71.7, p < .0001$
Felt it was not working	7 (3.2)	41 (11.9)	$\chi^2_{(1)} = 13.1, p = .0003$

dependence were not significant predictors of varenicline days taken; these baseline factors were similarly unrelated to purposeful nonadherence, with the exception of cigarettes per day. Medication side effect severity ratings at 21-day follow-up were also not found to predict number of days varenicline was taken but were found to predict less purposeful nonadherence.

As shown in Table 4, all variables with univariate *p*-values <.15 were entered into multivariate regression models predicting varenicline number of days varenicline was taken (r^2 = .0224, p = .0234, n = 854) and less purposeful nonadherence (r^2 = .0847, p = .0001, n = 830). Only age emerged as a significant independent predictor of the number of days varenicline was taken during the study period. Multivariate predictors associated with less purposeful nonadherence (i.e., greater adherence) at 12 weeks included older age, male gender, greater self-efficacy for varenicline adherence, and lower initial medication side effect severity (see Table 4).

Discussion

While many people took medication consistently, adherence to varenicline in this trial was less than optimal overall. On average, participants who received varenicline took this medication for about 63 of the prescribed 84 days. This overall adherence rate (75%) falls below the conventional 80% cutpoint for good adherence; however, it is similar to that reported for other nicotine addiction medications, such as bupropion and NRT. Adherence rates for these medications have ranged from 22% to 77%

Table 4. Univariate and Multivariate Predictors of Varenicline Adherence

	Number of days varenicline taken			Less purposeful nonadherence		
Outcome	Univariate		Multivariate	Univariate		Multivariate
Predictor	r^2	*p* value	*p* value	r^2	*p* value	*p* value
Older age at baseline	.0077	.0057	.0347	.0108	.0020	.0132
Male gender	−.0000	.8384		.0240	.0001	.0106
More years of formal schooling	.0027	.1017	.3186	−.0046	.0454	.0662
Fewer baseline cigarettes per day	.0003	.5661		−.0082	.0075	.0981
Lower baseline FTND	.0028	.1080	.2027	−.0009	.3785	
No other smokers in the home	.0025	.1181	.1957	.0002	.6742	
Lower baseline depression	.0023	.1315	.3693	.0043	.0522	.3215
Greater varenicline adherence self-efficacy	.0050	.0262	.1941	.0087	.0055	.0110
Less negative treatment outcome expectations	.0026	.1134	.6223	.0009	.3811	
More positive treatment outcome expectations	.0000	.9116		.0000	.9102	
Lower initial medication side effect symptom severity	.0036	.0666	.4343	.0470	.0001	.0001
Lower initial nicotine withdrawal symptom severity	.0076	.0082	.0896	.0216	.0001	.0774

Note. Multivariate models included all variables with a univariate *p* value <.15. Because of missing data, only $N = 854$ cases were used for the multivariate model of days taken (overall model $r^2 = .0224, p = .0234$) and 830 cases were used for the multivariate model of less purposeful nonadherence (overall model $r^2 = .0847, p < .0001$). Higher scores on the Medication Adherence Questionnaire purposeful nonadherence subscale reflect less purposeful nonadherence (i.e., greater adherence). FTND = Fagerström Test for Nicotine Dependence.

(Blondal et al., 1997; Garvey et al., 2000; Hajek et al., 1999; Hurt et al., 1997; Killen et al., 2004; Lam et al., 2005; Mooney et al., 2007; Schmitz et al., 2007; Shiffman et al., 2008). Adherence data for the COMPASS trial were collected prior to the Federal Drug Administration issuing a black box warning about possible neuropsychiatric symptoms associated with varenicline in 2009 and therefore may overestimate future adherence rates for this medication.

Our results demonstrate the importance of medication adherence to smoking abstinence. More than half of those who reported good adherence (≥80%; 67.2/84 days) to varenicline were nonsmokers 6 months after their target quit date. Moreover, the abstinence rate among those with the highest adherence was double that among those with poor adherence (52% vs. 25%). Thus, improving treatment adherence may be an important way to increase the effectiveness of smoking cessation interventions. COMPASS participants received basic instruction in how to use their medication and standard encouragement from quitline counselors to continue using the medication, but this may not have been adequate for many participants. If the COMPASS behavioral interventions had more specifically focused on improving adherence to varenicline, perhaps the abstinence rates among those who reported poor adherence could have been raised. In the absence of new cessation treatment options, improving adherence to existing treatments is an important avenue to explore in research trials and an important component to include in behavioral programs aimed at increasing cessation rates.

What might an enhanced adherence intervention look like? Like smoking cessation interventions (Fiore et al., 2008), adherence interventions that are multifaceted and include behavioral components are most likely to be effective (Haynes, Ackloo, Sahota, McDonald, & Yao, 2008). Adherence counseling could potentially be integrated into cessation counseling using common intervention approaches such as combining motivational enhancement with cognitive behavioral strategies. In many cases, similar techniques could be used to explicitly target medication adherence as well as cessation but would be applied somewhat differently. For example, when stimulus control strategies are applied to smoking cessation, smokers are taught how to decouple their smoking from learned environmental cues for this behavior. Applying stimulus control strategies to medication adherence entails teaching how to pair medication taking with a regularly occurring daily activity. Similarly, goal setting, self-monitoring, and improving self-efficacy for specific behavior change skills are effective cognitive–behavioral components that are commonly employed in both cessation and adherence interventions (Fiore et al., 2008; Haynes et al., 2008) and in theory should not be difficult to cross-train or deliver together.

Multiple adherence measures were used to evaluate varenicline adherence in the COMPASS trial, and all were associated with increased odds of being a nonsmoker at 6-month follow-up except for unintentional nonadherence. Consistent with findings from prior research that tested the validity of two Morisky MAQ subscales for use with other smoking cessation medications (Toll et al., 2007), purposeful nonadherence but not unintentional nonadherence was significantly associated with subsequent smoking status. The consistency of these findings suggest that effective strategies to address purposeful treatment nonadherence (e.g., stopping medication after feeling better or worse) are likely needed across smoking cessation medications and are not unique to varenicline. The most frequently endorsed reasons for stopping medication early in this study were side effects and perceived lack of need. This implies that purposeful nonadherence might be targeted in integrated behavioral and pharmacotherapy interventions by providing timely side effect management and coping strategies. Providing information about the greater likelihood of a successful quit with longer use of medication might also be helpful to bolster perceived treatment outcome expectations and the perceived importance of continued adherence. Specific interventions to encourage longer term use of medications should become a standard part of treatment protocols for smoking cessation pharmacotherapy.

The finding in multivariate analyses that age was a significant predictor of adherence is not surprising in this sample. Linear relationships between increasing age and greater adherence are more likely in general to be observed in adult samples that exclude adolescents and the very old, the two age groups with the lowest likely adherence rates (Bush & Iannotti, 1993; Park & Liu, 2007). In the context of a smoking cessation trial, it may be that age is a marker for greater experience with taking medications in general or with longer histories of making past quit attempts. Older participants in this study took relatively more prescription and nonprescription medications at baseline and had relatively longer past quit attempts.

Results of this study also have implications for how to measure adherence to cessation medications. Toll et al. (2007) recommended that a two-item measure of purposeful adherence be routinely administered as a screening tool for nonadherence. While this is a reasonable approach (and we unfortunately did not assess this construct at baseline), the assessment of multiple adherence indices at different timepoints during intended drug exposure in the COMPASS trial allows us to make somewhat broader recommendations. We suggest that simple metrics of cessation medication adherence be routinely used and reported in efficacy trials, effectiveness trials, and in evaluating programs in usual-care settings. Self-reported number of days varenicline was used had a robust relationship to cessation outcomes and appeared to yield more detailed and accurate information than estimating medication adherence from prescription refill records in this trial. Routinely asking smokers how many days they have taken a particular smoking cessation medication is pragmatic and could be accomplished with a single question that yields several useful indices of adherence including classification of early medication stoppers, good and poor medication adherers, and a continuous measure estimating the proportion of prescribed medication taken.

In sum, medication adherence was a significant driver of treatment outcome in the COMPASS trial. Our data suggest that good adherence was associated with a twofold increase in quit rates compared with poor adherence. Thus, in the absence of newer and more effective treatments for nicotine dependence, it is important to better understand the drivers of medication nonadherence and how to maximize treatment utilization in order to maximize abstinence rates. Researchers are encouraged to more systematically collect and report data that will inform these issues.

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Declaration of Interests

Dr. SMZ and Ms. MD are employed by Free & Clear, Inc. The authors have no other potential conflicts of interest to report.

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