Brief report

Predictors of Varenicline Adherence Among Cancer Patients Treated for Tobacco Dependence and its Association With Smoking Cessation

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Abstract

Introduction: The degree to which smokers adhere to pharmacotherapy predicts treatment success. The development of interventions to increase adherence requires identification of predictors of treatment adherence, particularly among specific clinical populations.

Methods: Using data from a 12-week open-label phase of a clinical trial of varenicline for tobacco dependence among cancer patients ($N = 207$), we examined: (1) the relationship between self-reported varenicline adherence and verified smoking cessation and (2) demographic and disease-related variables, and early changes in cognition, affect, withdrawal, the reinforcing effects of smoking, and medication side effects, as correlates of varenicline adherence.

Results: At the end of 12 weeks, 35% of the sample had quit smoking and 52% reported taking $\geq 80\%$ of varenicline. Varenicline adherence was associated with cessation ($p < .001$): 58% of participants who were adherent had quit smoking versus 11% of those who were not. Participants who experienced early reductions in depressed mood and satisfaction from smoking and experienced an increase in the toxic effects of smoking, showed greater varenicline adherence ($p < .05$); the relationship between greater adherence and improved cognition, reduced craving, and reduced sleep problems and vomiting approached significance ($p < .10$).

Conclusions: Among cancer patients treated for tobacco dependence with varenicline, adherence is associated with smoking cessation. Initial changes in depressed mood and the reinforcing effects of smoking are predictive of adherence.

Implications: The benefits of varenicline for treating tobacco dependence among cancer patients may depend upon boosting adherence by addressing early signs of depression and reducing the reinforcing dimensions of cigarettes.

Introduction

Varenicline is an effective treatment for tobacco dependence¹ among smokers with and without medical and psychiatric comorbidities.^{2,3} The 2014 Surgeon General Report underscored the importance of providing effective tobacco-dependence treatment to cancer patients,⁴ since continued smoking postdiagnosis is causally associated with poor cancer-related outcomes. Unfortunately, about 50% of cancer patients who smoked prior to their diagnosis continue to smoke, leading to calls from scientific and advocacy organizations and the National Cancer Institute to implement tobacco-dependence treatment within the oncologic context.

There is a growing recognition that adherence to treatment determines clinical success. Varenicline adherence—commonly defined as self-reported use of $\geq 80\%$ of prescribed pills—rarely exceeds 64%⁵ and nonadherence significantly reduces the likelihood of cessation.⁶ Few studies, however, have examined predictors of adherence to develop interventions to increase varenicline adherence.⁷ The limited literature indicates that lower varenicline adherence is associated with female gender,⁸ younger age,^{5,9} less education,⁵ nonwhite race,^{5,9} higher nicotine dependence,¹⁰ and increased side effects.¹¹ However, mechanisms through which varenicline affects cessation, including the reinforcing effects of smoking, nicotine craving or withdrawal, negative affect, and cognition, have not been examined as correlates of varenicline adherence. Furthermore, factors unique to clinical populations like cancer patients, including disease-related characteristics (eg, cancer stage) and common side effects (eg, nausea) have not been assessed as correlates of adherence.

Thus, with the goal of informing the design of an intervention to address adherence, this study examined the rate of varenicline adherence among cancer patients; assessed the relationship between varenicline adherence and cessation; and examined demographic and disease-related variables, as well as early changes in cognition, affect, withdrawal, the reinforcing effects of smoking, and medication side effects, as correlates of varenicline adherence.

Methods

This study used data from a clinical trial that randomized cancer patients to 12 weeks of varenicline (open-label) followed by either 12 weeks of placebo or 12 weeks of varenicline; all participants received 5 smoking cessation counseling sessions (NCT01756885). For the present analyses, only data up to 12 weeks were used. Participants were identified from electronic databases at cancer centers in Philadelphia and Chicago; patients were screened, initially by telephone, and then in-person, for study interest and eligibility.

Participants

Participants were required to be ≥ 18 years of age, received a cancer diagnosis or cancer treatment within the past 5 years, reported smoking ≥ 5 cigarettes per day, and reported an interest in quitting smoking. Additional eligibility criteria and exclusion criteria can be found elsewhere.³

Procedures

Institutional Review Boards at the University of Pennsylvania and Northwestern University approved the study. Participants provided written informed consent. If eligible and willing to enroll, participants received 12 weeks of open-label varenicline according to FDA guidelines. Participants received a 60-min in-person counseling

session when they began medication at Week 0 and then four counseling sessions at Weeks 1, 4, 8, and 12. Assessments were conducted and carbon monoxide breath samples were collected in-person at Weeks 0, 4, and 12.

Measures

Demographic and Disease Characteristics and Smoking History

Demographic data (eg, age), disease-related characteristics (eg, tumor site), smoking history (eg, cigarettes per day; CPD), and the Fagerström Test for Cigarette Dependence (FTCD)¹² were assessed at intake.

Smoking Variables

The Cigarette Evaluation Scale (CES)¹³ assessed the reinforcing effects of cigarettes (ie, satisfaction, psychological benefits, toxicity). The brief Questionnaire of Smoking Urges (QSU-B)¹⁴ measured an individual's urge to smoke using two subscales: Anticipation of Reward and Relief from Negative Affect. The Shiffman-Jarvik Withdrawal Form (SJWF)¹⁵ measured withdrawal symptoms.

Affect and Cognition

The Positive and Negative Affect Schedule (PANAS)¹⁶ assessed positive (eg, enthusiastic) and negative (eg, distressed) affect. The Hospital Anxiety and Depression Scale (HADS)¹⁷ assessed current depression and anxiety. The FACT-Cog Version 2 (FACT-2)¹⁸ assessed Cognitive Deficits (eg, mental acuity), Consequences of Cognitive Deficits (eg, functional interference), and Cognitive Capabilities (eg, positively framed items reflecting higher functioning). Depression and anxiety symptoms were also included on the side effects checklist.

Side Effects

Using an established checklist, participants rated the severity of specific varenicline-related side effects (eg, nausea), based on how much it interfered with their daily activities, as 0 (none), 1 (mild), 2 (moderate), or 3 (severe).

Varenicline Adherence

As in previous studies, varenicline adherence was defined as taking $\geq 80\%$ of study medication across 12 weeks.⁹ Pill count data were collected through self-report using a timeline follow-back method (TLFB) and used blister packs. Any discrepancy between TLFB data and used blister packs were resolved by relying on blister pack data. We have shown that self-reported 12-week pill count data are associated with salivary varenicline levels.⁵

Smoking Cessation

Daily smoking rate was collected through TLFB and Week 12 cessation was defined as no smoking for the 7 days prior to Week 12 and a breath carbon monoxide (CO) reading of < 10 parts per million (ppm).

Analyses

We used descriptive statistics to determine the rate of varenicline adherence and smoking cessation at 12 weeks and to characterize the sample. A chi-square test evaluated the relationship between adherence and cessation. ANOVA (for continuous measures) and chi-square (for categorical measures) evaluated differences in demographic and disease factors and smoking history between adherent

and nonadherent participants, which identified covariates for subsequent models. Multivariate logistic regression models were examined to assess change scores from Week 0 to 4 in smoking characteristics (eg, reinforcing effects of cigarettes, withdrawal, craving), affect and cognition (eg, depression, anxiety, cognitive function), and side effects (eg, nausea, vomiting, sleep problems, headache) in relation to varenicline adherence. The significance of measures was assessed using odds ratios and 95% confidence intervals.

Results

Sample Characteristics

Of 770 individuals screened, 201 were ineligible at phone screen and 59 were ineligible at intake. The primary reasons for ineligibility were suicidal ideation or a lifetime suicide attempt ($N = 29$, 11.2%);

bipolar disorder ($N = 26$, 10.0%); smoking <5 CPD ($N = 20$, 7.7%); consuming >25 alcoholic drinks/week ($N = 19$, 7.3%); and having no cancer diagnosis or treatment in the past 5 years ($N = 19$, 7.3%). Of the 569 participants eligible after phone screen, 283 (49.7%) attended the intake session and 207 enrolled. There were no significant differences between eligible participants who enrolled versus declined enrollment. Table 1 shows the sample characteristics.

Rate of Varenicline Adherence and Association with Smoking Cessation

At Week 12, 73 participants (35.3%) had quit smoking and 107 participants (51.7%) reported taking $>80\%$ of the medication. Adherence was significantly associated with smoking cessation: 62 of the participants who were adherent (58%) had quit smoking versus 11 of those who were not adherent (11%) had quit smoking

Table 1. Characteristics of Sample

Characteristic	Adherent ($N = 107$)	Nonadherent ($N = 100$)	Total ($N = 207$)	p
Sex				.53
Female	52 (48.6%)	53 (53.0%)	105 (50.7%)	
Male	55 (51.4%)	47 (47.0%)	102 (49.3%)	
Race				.28
White	78 (72.9%)	66 (66%)	144 (69.6%)	
People of color	29 (27.1%)	34 (34%)	63 (30.4%)	
Ethnicity				.25
Hispanic/Latino	3 (2.8%)	6 (6.1%)	9 (4.4%)	
Not Hispanic/Latino	104 (97.2%)	92 (93.9%)	196 (95.6%)	
Marital status				.53
Married	56 (52.3%)	48 (48.0%)	104 (50.2%)	
Not married	51 (47.7%)	52 (52.0%)	103 (49.8%)	
Education				.34
Below college graduate	66 (61.7%)	68 (68.0%)	134 (64.7%)	
College graduate or beyond	41 (38.3%)	32 (32.0%)	73 (35.3%)	
Income				.22
$<20\,000$	22 (20.6%)	22 (22.7%)	44 (21.6%)	
$20\,000$ to $75\,000$	43 (40.2%)	48 (49.5%)	91 (44.6%)	
$>75\,000$	42 (39.2%)	27 (27.8%)	69 (33.8%)	
Employment				.85
Employed	51 (47.7%)	49 (49.0%)	100 (48.3%)	
Not employed	56 (52.3%)	51 (51.0%)	107 (51.7%)	
Tumor type				.85
Head and neck	7 (7.9%)	2 (2.6%)	9 (5.5%)	
Lung	14 (15.7%)	14 (18.7%)	28 (17.1%)	
Hematological	8 (9.0%)	8 (10.7%)	16 (9.7%)	
Breast	18 (20.2%)	18 (24.0%)	36 (21.9%)	
Gastrointestinal	5 (5.6%)	3 (4.0%)	8 (4.9%)	
Genitourinary	24 (27.0%)	18 (24.0%)	42 (25.6%)	
Skin	10 (11.2%)	8 (10.7%)	18 (11.0%)	
Kidney, pancreas, and liver	3 (3.4%)	4 (5.3%)	7 (4.3%)	
Cancer stage				.06
Stage 0–1	11 (10.3%)	15 (15.0%)	26 (12.6%)	
Stage 2	10 (9.3%)	5 (5.0%)	15 (7.2%)	
Stage 3–4	16 (15.0%)	29 (29.0%)	45 (21.7%)	
Remission	26 (24.3%)	18 (18.0%)	44 (21.3%)	
Not specified	44 (41.1%)	33 (33.0%)	77 (37.2%)	
Age (Mean, SD)	59.83 (8.48)	57.03 (10.21)	58.48 (9.44)	.03
Cigarettes per day (Mean, SD)	14.64 (7.66)	15.30 (8.23)	14.96 (8.23)	.57
FTCD (Mean, SD)	4.43 (2.05)	4.57 (2.23)	4.50 (2.13)	.66
CO at intake (Mean, SD)	16.45 (9.28)	16.10 (10.34)	16.28 (9.79)	.80
Age started smoking (Mean, SD)	16.72 (5.33)	16.69 (4.79)	16.71 (5.06)	.97
Years smoked (Mean, SD)	41.64 (10.56)	39.13 (11.99)	40.43 (11.32)	.11

FTCD = Fagerström Test for Cigarette Dependence; CO = carbon monoxide.

Table 2. Separate Logistic Regression Analyses of Affective and Cognitive Variables, Smoking-Related Variables, and Side Effects, From Baseline to Week 4, Predicting Adherence

Affective and cognitive variables	Odds ratio	95% CI	<i>p</i>
Constant	0.39	0.04 to 4.24	.438
Age at initial screening	1.03	0.99 to 1.08	.127
HADS anxiety	1.09	0.90 to 1.31	.383
HADS depression	1.23	0.99 to 1.52	.056
PANAS positive	1.05	0.97 to 1.13	.240
PANAS negative	0.95	0.86 to 1.06	.348
FACT-2: Cognitive deficits	1.02	0.96 to 1.09	.475
FACT-2: Consequences of cognitive deficits	0.92	0.84 to 1.01	.078
FACT-2: Cognitive capabilities	0.99	0.94 to 1.04	.762
SEC: Depressed mood	0.38	0.17 to 0.84	.016
SEC: Anxiety	0.64	0.31 to 1.31	.223
Smoking variables	Odds ratio	95% CI	<i>p</i>
Constant	0.002	<0.001 to 0.70	.038
Age at initial screening	1.11	1.01 to 1.22	.030
SJWS (withdrawal symptoms)	0.92	0.85 to 1.01	.077
CES: satisfaction from smoking	0.49	0.26 to 0.93	.029
CES: psychological well-being	1.02	0.44 to 2.38	.955
CES: toxic effects of smoking	4.73	1.44 to 15.56	.010
QSU-B: Anticipation of reward	1.11	0.95 to 1.29	.206
QSU-B: Relief from negative affect	1.24	0.96 to 1.59	.098
Side effects	Odds ratio	95% CI	<i>p</i>
Constant	0.21	0.02 to 2.03	.176
Age at initial screening	1.04	1.00 to 1.08	.039
SEC: Nausea	0.74	0.44 to 1.23	.242
SEC: Sleep problems	0.69	0.46 to 1.05	.083
SEC: Vomiting	0.51	0.23 to 1.12	.092
SEC: Headache	0.80	0.43 to 1.48	.467

HADS = Hospital Anxiety and Depression Scale; PANAS = Positive and Negative Affect Schedule; FACT-2 = FACT-Cog Version 2; SEC = Side Effects Checklist; SJWS = Shiffman-Jarvik Withdrawal Form; CES = Cigarette Evaluation Scale; QSU-B = Brief Questionnaire of Smoking Urges.

($\chi^2[1] = 53.8, p < .001$). When the analysis used a cutoff of <5 ppm, the relationship between adherence and cessation remained: 53% of adherent participants quit smoking versus 14% of nonadherent participants ($\chi^2[2] = 32.6, p < .001$).

Multivariate Models Examining Predictors of Varenicline Adherence

Age was included as a covariate in the three models predicting adherence (see Table 2). In Model 1, examining affect and cognition, depressed mood as reported on the SEC was a significant predictor of adherence ($OR = 0.38, 95\% CI = 0.17$ to $0.84, p = .016$). For adherent participants, there was almost no change in depressive symptoms from Week 0 ($M = .12, SD = .03$) to Week 4 ($M = .13, SD = .05$), but for nonadherent participants, depressive symptoms increased significantly from Week 0 ($M = .13, SD = .05$) to Week 4 ($M = .38, SD = .07$). Compared with adherent participants, nonadherent participants also showed an increase in depressive symptoms measured by the HADS and greater increase in the consequences of cognitive deficits (FACT-2) from Week 0 to Week 4, but these comparisons approached significance ($p < .10$).

In Model 2, examining smoking-related variables, decreases in the satisfaction from smoking ($OR = 0.49, 95\% CI = 0.26$ to $0.93, p = .03$) and increases in the toxic effects of smoking ($OR = 4.73, 95\% CI = 1.44$ to $15.56, p = .01$) measured by the CES predicted greater varenicline adherence. Adherent participants reported a significantly greater decrease in the satisfaction from smoking from

Week 0 ($M = 4.49, SD = .29$) to Week 4 ($M = 2.63, SD = .29$), versus nonadherent participants from Week 0 ($M = 4.05, SD = .30$) to Week 4 ($M = 3.3, SD = .29$). For adherent participants, there was a significant increase in toxic effects of smoking from Week 0 ($M = 1.60, SD = .19$) to Week 4 ($M = 2.07, SD = .17$), whereas there was a decrease in toxic effects of smoking from Week 0 ($M = 1.58, SD = .20$) to Week 4 ($M = 1.43, SD = .17$) for nonadherent participants. Compared with adherent participants, nonadherent participants also reported a greater decrease from Week 0 to Week 4 in nicotine withdrawal and craving relief from negative affect from Week 0 to Week 4, but these comparisons approached significance ($p < .10$).

In Model 3, examining side effects, two changes in side effects approached significance ($p < .10$). Nonadherent participants reported a greater increase in vomiting from Week 0 ($M = .03, SD = .04$) to Week 4 ($M = .26, SD = .07$), versus adherent participants from Week 0 ($M = .07, SD = .03$) to Week 4 ($M = .08, SD = .05$). Additionally, nonadherent participants reported a greater increase in sleep problems from Week 0 ($M = .38, SD = .09$) to Week 4 ($M = .60, SD = .09$), versus adherent participants from Week 0 ($M = .50, SD = .06$) to Week 4 ($M = .43, SD = .07$).

Multivariate models were re-run using 12-week pill count as a continuous measure of adherence and linear regression. In Model 1, depression measured by the checklist approached significance and positive affect was a significant predictor; in Model 2, the CES subscales were no longer significant; and in Model 3, increased vomiting was significant.

Discussion

This study examined the rate of adherence among cancer patients receiving varenicline for tobacco dependence and evaluated potential predictors of adherence. First, ~50% of patients were nonadherent. This rate, albeit high, is consistent with other studies across the general population of smokers,⁵ indicating that the issue of nonadherence to varenicline is no worse among cancer patients. Similarly, the end-of-treatment quit rate among adherent patients (58%) is more than five times the quit rate for nonadherent patients (11%). This result fits with other studies and highlights the clinical relevance of varenicline adherence.

Second, we found that varenicline adherence was related to a participant's change in depressed mood and experience of cigarette smoking reward. These results suggest that two proposed mechanisms through which varenicline promotes smoking cessation are critical to ensuring that smokers continue to take their medication. Symptoms of depression help to maintain tobacco dependence¹⁹ and reduce the efficacy of varenicline,²⁰ which allows the reinforcing effects of nicotine to maintain dependence. Our results suggest that initial changes in these processes may be important to determining varenicline's efficacy by influencing whether or not smokers continue to use the medication.

Finally, unlike previous studies, our results did not support the role of demographic or disease-related variables in determining varenicline adherence. Only age predicted adherence, with older smokers more adherent. Further, although there was a trend towards varenicline-related side effects correlating with lower adherence, the results were not statistically significant. It is plausible that because cancer patients frequently experience these symptoms related to their diagnosis, the effects of these symptoms on adherence are muted.

The limitations of this study should be considered. First, although we used a definition of varenicline adherence as done previously, self-report measures of varenicline adherence may not be ideal. We have previously shown that 12-week pill count is associated with biological levels of varenicline, but the association is relatively weak and may overestimate adherence.⁵ Second, although our study used prospective assessments, we cannot determine causality between varenicline adherence and its correlates due to the open-label design and lack of a control group. Third, the small sample size limits the study power, which may be responsible for some of the study's negative results. Finally, our findings may not apply to all smokers with cancer since patients with certain characteristics and comorbidities were excluded.

Nevertheless, this study presents novel findings of the importance of adherence to varenicline for determining the efficacy of this medication for treating tobacco dependence among cancer patients and identifies potential predictors of varenicline adherence among treatment-seeking smokers with cancer. These results have implications for intervention development. Mood management interventions early in treatment may mitigate the effect of depression symptoms on adherence, whereas a longer pre-cessation phase with varenicline may be needed to mitigate the effect of nicotine reward on adherence. Future studies should examine the benefits of such targeted adjunctive treatment modalities on varenicline adherence.

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Declaration of Interests

RS and BH receive medication and placebo free from Pfizer and have provided consultation to Pfizer. RS and RK have provided consultation to GlaxoSmithKline.

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