Adherence to Varenicline and Associated Smoking Cessation in a Community-Based Patient Setting

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ABSTRACT

BACKGROUND: Varenicline, a selective α4β2 nicotinic acetylcholine receptor partial agonist, is a pharmacotherapy indicated for smoking cessation treatment. To our knowledge, no studies have described varenicline treatment adherence and efficacy from real-world treatment patterns in a U.S. primary care setting.

OBJECTIVE: To estimate adherence to varenicline prescription orders and subsequent quit rates among smokers in a primary care setting.

METHODS: In this retrospective cohort study, eligible patients were enrolled with Geisinger Health Plan, had an initial varenicline prescription written by a Geisinger provider between January 1, 2006, and December 31, 2009, and had a follow-up clinic visit within the subsequent 12 months. Adherence was derived from linking electronic prescriptions with adjudicated pharmacy claims. Smoking status was collected at each health care encounter.

RESULTS: Of the 1,477 eligible patients, 823 (55.7%) were primary nonadherent, having failed to initiate on the prescribed varenicline therapy. Of the remaining 654 patients, 359 (54.9%) were adherent, having completed a full 12-week course of therapy, and 295 (45.1%) were partially adherent, having initiated but not completed the full course of therapy. A total of 521 patients (35.3%) ceased smoking during the 12-month follow-up period: 182 (50.7%) of the adherent cohort, 82 (27.8%) of the partially adherent population, and 257 (31.2%) of the nonadherent cohort. No significant difference was found in quit rates between the partially adherent and nonadherent patient cohorts (adjusted HR 0.88 [95% CI = 0.69-1.13]). However, patients adherent to the varenicline regimen were almost twice as likely to succeed in quitting smoking compared with completely nonadherent patients (HR 1.93 [95% CI = 1.59-2.33]).

CONCLUSION: Smoking cessation occurred more often among individuals adherent to varenicline therapy; however, medication nonadherence was common. After prescribing varenicline, clinicians and payers could consider active patient follow-up to maximize adherence and optimize treatment outcomes.

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What this study adds

- Varenicline is an effective smoking cessation therapy that increases the odds of quitting smoking compared with placebo. Two large randomized, double-blind, placebo-controlled trials (Gonzales et al. 2006; Jorenby et al. 2006), each randomizing over 1,000 healthy adult smokers to treatment with varenicline, sustained-release (SR) bupropion, or placebo, reported abstinence rates after the 12-week treatment period of 44.0% for the varenicline groups. The benefit of varenicline has been confirmed in a Cochrane meta-analysis, which estimated that use of varenicline was associated with a two- to three-fold increase in the odds of quitting compared with pharmaceutically unassisted attempts.
- Owing to differences in populations and available levels of support to quit smoking, the results of randomized controlled trials in smoking cessation do not necessarily translate to those achieved in the real-world setting. Although the reported abstinence rates from observational studies have been encouraging, the results fall over a large range, and some studies report an underestimation of smoking status in groups such as pregnant women and those with respiratory disease.
- There is a gap in the literature on level of adherence to smoking cessation therapy and the impact that this has on abstinence rates. To our knowledge, there are no previously published studies of adequacy to smoking cessation pharmacotherapy in a real-world setting, and there is limited information information in clinical and observational trials.

What is already known about this subject

- Approximately 20% of Americans are addicted to smoking, and this addiction is responsible for nearly 445,000 deaths annually. Although 70% of smokers report that they want to quit, less than half attempt to quit, and only 4%-7% are successful.
Cigarette smoking remains the leading preventable cause of disease and death in the United States. As of 2009, the Centers for Disease Control and Prevention estimated that 46 million Americans were cigarette smokers. Reducing the number of smokers is therefore a national public health priority. The 2007 Institute of Medicine report “Ending the Tobacco Problem: A Blueprint for the Nation” recommends a comprehensive approach to reduce smoking, including the use of pharmacological agents. Randomized clinical trials have indicated that the use of pharmacological agents, namely nicotine replacement therapies (NRT), bupropion, and varenicline, significantly increase the odds of successfully quitting smoking compared with placebo.

However, treatment efficacy as measured in clinical trials does not automatically guarantee effectiveness when used in the real-world setting among the general smoking community. Clinical trial participants tend to receive more attention and more behavioral support than is typically offered to a primary care patient, and trial participants are often healthier and more motivated than their counterparts in the primary care setting. These differences may contribute to significantly lower medication adherence rates and, as a result, to lower rates of smoking cessation in primary care patients.

The objective of this research was to assess adherence to varenicline therapy and to estimate the association between medication adherence and smoking cessation rates in a community health care setting.

### Methods

This was a retrospective cohort study of medication adherence and self-reported smoking cessation. Potentially eligible study participants were identified from patients who had a Geisinger Clinic primary care physician and whose pharmacy insurance was provided by Geisinger Health Plan. Geisinger’s electronic health records (EHR) and Geisinger Health Plan’s administrative pharmacy claims database were the primary data sources for this study. The recording of smoking status was collected during the patient assessment and medication reconciliation process and was reported at all subsequent visits during the 12-month follow-up period.

Geisinger Clinic is a multispecialty practice that has 57 sites and 730 employed physicians and physician’s assistants. The patient population includes residents from central and northeastern Pennsylvania. Between 1996 and 2001, the Epic Systems Corporation EHR system was installed in all clinic community practice sites, medical centers, and specialty clinics. Although patients in the system have insurance coverage through a range of payers, all subjects in this study were members of the Geisinger Health Plan, which covers approximately 30% of patients seeing physicians in the system. Smoking status is assessed at all office visits as part of routine data gathering as per standard Geisinger Health System procedures and logged in the EHR. The study protocol was approved by the Geisinger Institutional Review Board.

To be eligible for inclusion, an individual must have had a prescription recorded in the EHR for an initial order for varenicline between January 1, 2006, and December 31, 2009, and at least 1 follow-up clinic visit within the subsequent 12-month period. Initial and continuing prescriptions were identified by the medication name or dose. Initial prescriptions were either named “CHANTIX STARTING MONTH PAK” or were written as 0.5 milligram (mg) tablet. Continuing prescriptions were either named “CHANTIX CONT MONTH PAK” or were written as a 1 mg tablet. Initial prescriptions were used to ensure that the patient was beginning a new course of varenicline. As of the index prescription order date, the participant must have been aged 18 years or older, enrolled with a Geisinger primary care physician, and had pharmacy insurance benefits provided through Geisinger Health Plan prior to the initial prescription order. The majority of subjects in the study had equivalent benefit coverage and out-of-pocket costs for smoking cessation treatments, including Chantix.

### Variables and Definitions

Data were extracted from both the EHR and paid pharmacy claims files. The following variables were selected from the EHR: demographics; encounter data (e.g., office visits); comorbidities; prescription dates; smoking status; and date of smoking cessation, if achieved. Smoking cessation success or failure was defined in this study based on subject response to querying about smoking status during office visits subsequent to, but within 12 months, of index date, as recorded in the EHR. Comorbidities were defined by an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code associated with 2 outpatient visits or listed on the problem list; comorbidities were compiled into the Charlson Comorbidity Index. All paid claims for smoking cessation medications,
including dates of purchase, days’ supply, and National Drug Code (NDC) number, were extracted from insurance pharmacy claims files.

A full course of varenicline therapy is routinely considered to comprise 1 full week of therapy before, and 12 weeks of therapy following, the initial smoking abstinence date. If smoking abstinence is maintained, an additional 12 weeks of treatment is recommended to increase the likelihood of sustained abstinence. Adherence metrics were derived through linking prescription order records to matching claims. Linking the medication prescriptions from the EHR to the pharmacy claims was performed by identifying all prescriptions in the EHR for varenicline and then looking for a pharmacy claim on or after the date of the prescription with an NDC for varenicline. Applying the definition of a full course of varenicline therapy described above, each participant was categorized as adherent, partially adherent, or nonadherent. Adherent individuals were those who purchased at least a 90-day supply during the 113 days following the index prescription fill. This definition required patients to complete the 3-month course of therapy with available drug on at least 80% of days. Individuals with drug available >0% to <80% of days were deemed partially adherent. Participants with no paid pharmacy claim for varenicline in the 12-month period following the prescription order were deemed nonadherent.

**Statistical Analysis**

Comparisons between adherence groups were conducted using the nonparametric Kruskal-Wallis test for continuous data and the Pearson chi-square test for categorical data. The association between adherence and smoking cessation was assessed using nonparametric Kaplan-Meier curves, which displayed the monthly cumulative incidence of smoking cessation following the varenicline order. Patients who did not achieve sustained smoking cessation by 12 months, including those who reported quitting in 1 visit and then reported smoking in a subsequent visit, were not considered censored for Kaplan-Meier curves until 1 year. Smoking cessation rates among the different adherence groups were compared using the log-rank test and Cox proportional hazards model controlling for potential confounding variables. Variables that differed significantly across adherence groups (P<0.10) were considered in the regression model. Model results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

All analyses were performed using the Statistical Analysis System (SAS) version 9.2 (SAS Institute Inc., Cary, NC). Two-sided P values were reported, and a P value of <0.05 was considered statistically significant.

**Results**

Subject disposition is shown in Figure 1. A total of 13,303 patients received a varenicline prescription during the enrollment period. Of these, 4,092 (30.8%) had eligible pharmacy insurance coverage, and 3,709 (27.9%) were starting pack orders, indicating that their prescriptions were intended to initiate therapy. A total of 1,477 (11.1%) individuals had at least 1 visit with an eligible provider during the 12-month follow-up period (and thus had smoking status re-assessed); 2,232 had no follow-up visit and were excluded.

The eligible study sample (n=1,477) was predominantly female (58.2%), Caucasian (98.4%), married (62.3%), had a mean age of 49.1 years, was overweight—with a median body mass index (BMI) of 28.3—and had average systolic and diastolic blood pressure readings of 124.1 and 74.7 mmHg, respectively (Table 1). The most common comorbid conditions were diabetes (13.9%), chronic obstructive pulmonary disease (9.4%), cardiovascular disease (8.6%), coronary artery disease (8.5%), and asthma (8.0%). The median number of packs of cigarettes smoked per day at baseline was 1.

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**FIGURE 1** Subject Disposition

- n=13,303 received prescription orders during enrollment phase
- n=4,092 (30.8%) with eligible pharmacy insurance
- n=3,709 (27.9%) initiated treatment order
- Eligible patients n=1,477 (11.1%) with visit within 12 months of starting treatment
  - Primary nonadherent patients n=823
  - Adherent patients n=359
  - Partially adherent patients n=295
  - Nonadherent patients who quit n=257 (31.2%)
  - Adherent patients who quit n=182 (50.7%)
  - Partially adherent patients who quit n=82 (27.8%)

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*a*January 1, 2006, and December 31, 2009.
*b*Geisinger Health Plan pharmacy coverage prior to varenicline order.
*c*Prescription order written for varenicline starting month pack.

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Subjects were classified as nonadherent if they had no visit within 12 months of the prescription order. Nonadherent patients were those who purchased at least a 90-day supply during the 113 days following the index prescription fill. This definition required patients to complete the 3-month course of therapy with available drug on at least 80% of days. Individuals with drug available >0% to <80% of days were deemed partially adherent. Participants with no paid pharmacy claim for varenicline in the 12-month period following the prescription order were deemed nonadherent.

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Compared with the 2,232 ineligible patients (who met all eligibility criteria except the requirement to have at least 1 clinic visit during the 12-month follow-up period), eligible patients were significantly more likely to be female (50.4% vs. 58.2%, respectively; \( P < 0.001 \)), older (44.2 vs. 49.1 years, respectively; \( P < 0.001 \)), and to have a higher BMI, higher systolic and diastolic blood pressure, and higher rates of comorbid health conditions. The 2 samples had comparable smoking histories. Eligible patients had higher rates of prior bupropion and NRT use (Table 1).

A total of 823 (55.7%) eligible patients were primary nonadherent, having failed to initiate prescribed varenicline therapy. Of the remaining 654 patients, 359 (54.9%) were adherent, having completed a full course of therapy, and 295 (45.1%) were partially adherent, having initiated but not completed the full course of therapy. The adherent, partially adherent, and nonadherent cohorts were similar on most baseline characteristics, with borderline significant differences in age, marital status, systolic blood pressure, and history of lung cancer (Table 2). Compared with nonadherent patients, the adherent cohort was significantly more likely to have a history of bupropion (0.5% vs. 17.6%, respectively; \( P < 0.001 \)) and NRT (0% vs. 3.3%, respectively; \( P < 0.001 \)) use.
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Overall, 521 (35.3%) participants ceased smoking during the 12-month follow-up period. Among the primary nonadherent cohort, nearly 31% reported quitting, a rate that was similar to that of the partially adherent cohort (28%). Among the fully adherent cohort, 50.7% reported cessation (P<0.001; Figure 2). The smoking cessation curves for the partially adherent and primary nonadherent cohorts were not significantly different (P=0.29), and each was different from the adherent cohort (both with P values of <0.001).

After adjustment for age, marital status, systolic blood pressure, and presence of lung cancer, the HR using the proportional hazards regression model for quitting was 1.93 (95% CI = 1.59-2.33; P<0.0001) and 0.88 (95% CI = 0.69-1.13; P = 0.3253) for the adherent and partially adherent cohorts, respectively, compared with the primary nonadherent cohort (Table 3).

### Discussion
Among the 1,477 eligible patients prescribed varenicline, only 24% were adherent to the recommended 3-month course of therapy. Fifty-six percent of patients did not initiate therapy, and 20% initiated therapy but discontinued before completing the recommended course. Twelve-month smoking cessation rates were similar between the nonadherent (31.2%) and partially adherent (27.8%) cohorts. The smoking cessation rate among the fully adherent cohort reached 50.7%.

To our knowledge, there are no published studies of primary nonadherence to smoking cessation pharmacotherapy. However, in a survey of 1,219 adults who reported recent use of smoking cessation medications, Balmford et al. (2011) reported that only 40% of individuals remained adherent for more than 8 weeks and that nonadherence was associated with medication side effects, lack of efficacy, and patient perception of the need for medication.

The abstinence rate among the 359 individuals who completed therapy is comparable with that reported in clinical trials. In a randomized, double-blind, placebo-controlled trial of 1,025 healthy adult smokers who were randomized to treatment with varenicline, bupropion SR, or placebo, Gonzales et al. (2006) reported an abstinence rate in those receiving varenicline of 44.0% after the 12-week treatment period, which decreased to 21.9% at 52 weeks. In a similarly designed trial, Jorenby et al. (2006) reported abstinence rates in varenicline users of 43.9% and 23% at weeks 12 and 52, respectively. Since our results pertain to individuals who sustained smoking abstinence during the 12-month follow-up period, our estimate of 50.7% indicates a comparable effectiveness rate among those who completed therapy in the community setting.

This study highlights the importance of initiating and completing the recommended treatment course of varenicline, subsequent to being motivated to succeed in a quit attempt. Individuals who completed the full course of therapy were 93% more likely to quit smoking than those who did not. This result is comparable with estimates reported in a recent meta-analysis of placebo-controlled smoking cessation trials, in which the odds of successful smoking cessation associated with varenicline use were 2.4 (95% CI = 1.9-3.1).

This study has numerous strengths. The study sample was large and involved over 1,000 primary care patients with experience of varenicline treatment. The limited exclusion criteria resulted in a study sample that was representative of a typical primary care population, with high comorbidity burdens and a diverse range of prior treatment histories, as opposed to the...
homogeneous and otherwise healthy populations enrolled in randomized trials. Finally, at Geisinger Clinic, smoking status is considered an essential measure, equivalent to height, weight, blood pressure, and pulse rate, and is recorded by trained nurses at every clinical visit, thereby minimizing the potential for recall bias.

**Limitations**
Because the present investigation was an observational study, outcomes were subject to selection bias, and associations between treatment and outcomes cannot be deemed causal. Though we detected few differences in measured characteristics between adherent and nonadherent cohorts, there is likely an association between adherence and unmeasured confounders, most notably participation in counseling or other behavioral interventions, and also with the patient’s general desire and readiness to quit smoking. As the data set comprised EHR and pharmacy claims data, but not medical claims, participation in these programs was not verifiable. Access to behavioral interventions provided by Geisinger, however, did not differ across the cohorts in this study. Polypharmacy for smoking cessation was also not examined as part of this study, as concomitant bupropion use levels were low (data not shown) and use of NRT purchased over the counter was not obtainable through pharmacy claims. There is also a known association between adherence and unmeasured confounders.

**Conclusion**
Primary medication nonadherence was high in this patient sample and was attributable primarily to patients electing not to initiate prescribed therapy. The HR for quitting smoking for individuals who adhered to varenicline therapy was 1.93 compared with those who failed to initiate therapy. Taking these findings into consideration, future research should focus on causal factors and on the development and implementation of early interventions to support medication adherence, particularly those interventions that monitor adherence and smoking cessation outcomes in near real time.

**AUTHORS**

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