A Double-Blind Randomized Placebo-Controlled Pilot Study of Neuropsychiatric Adverse Events in Abstinent Smokers Treated with Varenicline or Placebo

Dahlia Garza, Michael Murphy, Li-Jung Tseng, Henry J. Riordan, and Anjan Chatterjee

Background: Varenicline is an $\alpha 4\beta 2$ partial nicotinic agonist approved for smoking cessation. There have been spontaneous postmarketing reports of neuropsychiatric adverse events (NPAEs) in smokers without a history of psychiatric illness quitting with varenicline.

Methods: One hundred ten smokers without history of psychiatric illness (screened by Structured Clinical Interview for DSM-IV) were randomized to 12 weeks of varenicline 1 mg twice daily ($n = 55$) or placebo. Adverse events were solicited systematically. Depressive symptoms, anxiety, aggression, and irritability were measured at baseline and weekly using the Montgomery-Åsberg Depression Rating Scale (MADRS), the Hamilton Anxiety Scale (HAM-A), and the Overt Aggression Scale—Modified (OAS-M). The Profile of Mood States (POMS) was administered daily. Mixed-model analysis of repeated measures was conducted to compare mean changes in scores between groups across study periods.

Results: Participants' mean baseline characteristics were 33 years of age, 22 cigarettes/day and Fagerström Test for Nicotine Dependence score > 7. Reported NPAEs were similar between groups. No suicidal events were reported. There were no significant differences between groups for the MADRS (treatment difference vs. placebo $= .03$, 95% confidence interval [CI] $-.68$–$.73$; NS), HAM-A (treatment difference [TD] $= .14$, 95% CI $-.62$–$.90$; NS), OAS-M Aggression subscale (TD $= .5$, 95% CI -1.18–2.18; NS), OAS-M Irritability subscale (TD $= .08$, 95% CI $-.17$–$.34$; NS), and the POMS total scores (TD $= .5$, 95% CI $-.52$–1.53; NS).

Conclusions: There were no significant differences between groups on measures of depressive symptoms, anxiety, or aggression/hostility. Systematically solicited NPAEs were similar between the varenicline and placebo groups.

Key Words: Neuropsychiatric, nicotine withdrawal, psychiatric, safety, smoking cessation, varenicline

Varenicline, a selective partial agonist of $\alpha 4\beta 2$ subunits of nicotinic acetylcholine receptors, is approved in many countries as an aid for smoking cessation. Varenicline has demonstrated superior efficacy compared with placebo in multiple clinical trials (1–9), several of which were conducted before regulatory approval in 2006 in the United States and Europe. Common adverse events (AEs) reported for varenicline included nausea, vomiting, insomnia and sleep disturbances, headaches, vivid dreaming, flatulence, and constipation (1–9).

In clinical trials with varenicline, neuropsychiatric adverse events (NPAEs; including changes in behavior, agitation, depressed mood, and suicidal ideation and behavior) occurred infrequently and at a rate comparable to placebo (10). A recently published post hoc analysis of 10 placebo-controlled clinical trials of varenicline found that psychiatric AEs, except sleep disorders and disturbances, were uncommon in smokers with no current or recent history of psychiatric disorders (11). Specifically, the relative risk of varenicline versus placebo was .86 (95% confidence interval [CI] .67–1.12) for anxiety disorders, 1.42 (.96–2.08) for depressed mood disorders, 1.21 (.79–1.83) for mood disorders, and 1.70 (1.50–1.92) for sleep disorders and disturbances (11). A large, retrospective, cohort study of the UK General Practice Research Database found no clear evidence that people prescribed varenicline were at increased risk of depression, self-harm, or suicidal thoughts versus people taking bupropion or nicotine replacement therapies (12).

Since varenicline's regulatory approval, postmarketing pharmacovigilance reporting of various NPAEs—including anxiety, depression, irritability, anger, and hostility, as well as less commonly suicidal behavior and completed suicide—with varenicline's use have occurred. Although many of these AEs are similar to those experienced by smokers attempting to quit smoking with or without treatment, the absence of a comparator or control and the relative dearth of information in postmarketing reports make it hard to ascribe causality. Additionally, some of these reports have been from smokers without any reported medical history of psychiatric disorders.

The etiopathogenesis of reported NPAEs while attempting to quit using varenicline is unclear and may be multifactorial. Such events may represent part or whole of a nicotine withdrawal syndrome. Nicotine abstinence has been associated with a withdrawal syndrome in the published literature, and several withdrawal symptoms are neuropsychiatric in nature, most commonly irritability, depressed mood, anxiety, and aggression or hostility (13–17). Furthermore, an association has been found between smoking and suicidality (18–21). Moreover, smokers with past psychiatric history may experience relapse of psychiatric symptomatology related to stressful life events. Finally, varenicline may be hypothesized as having a direct pharmacologic effect in this regard. Therefore, any effort to understand these events needs to control for nicotine withdrawal and past psychiatric history in an effort to clarify the role of varenicline, if any.

The objective of this double-blind placebo-controlled study was to estimate and characterize NPAEs reported by smokers quitting smoking on either varenicline or placebo. The smoking population addressed here had no history of psychiatric disorders. Also, all participants were asked to abstain from smoking to remove any

Pfizer Pharmaceuticals Inc. (DG, L-JT, AC), New York, New York, and Medical and Scientific Affairs (MM, HJR), Worldwide Clinical Trials, King of Prussia, Pennsylvania.

Address correspondence to Dahlia Garza, M.D., Pfizer Pharmaceuticals Inc., 150 East 42nd Street (Mail Stop #150-3-03), New York, NY 10017; E-mail: dahlia.garza@pfizer.com.

Received Jul 1, 2010; revised Nov 22, 2010; accepted Dec 2, 2010.

0006-3223/$36.00
doi:10.1016/j.biopsych.2010.12.005

differential nicotine withdrawal symptoms between randomized groups.

Data on the quantity, quality, and natural history of neuropsychiatric symptoms in quitting smokers are sparse (15), and event rates as well as quantification of clinically meaningful differences are not readily available. These factors necessitated that the study design be an exploratory, unpowered preliminary examination of the events themselves.

Methods and Materials

Study Design and Participants

This randomized, double-blind, placebo-controlled pilot study enrolled smokers at a single United States Phase I investigational center from September 2008 to August 2009. The trial was conducted in accordance with the Declaration of Helsinki (22) and in compliance with the institutional review board for the study site (California IRB, Inc., Pasadena, California) and the International Conference on Harmonisation and Good Clinical Practice Guidelines (23).

Adult smokers (aged 18–75 years) who smoked an average of 10 or more cigarettes per day during previous year and with no period of abstinence greater than 3 months during this period were recruited. At screening, smokers had to have a Fagerström Test for Nicotine Dependence score greater than 5 (24).

Women of childbearing age were permitted if they consented to use approved birth control methods (oral, intrauterine, implantable, or injectable contraceptive for 1 month or more before study entry; barrier method [condom and/or diaphragm, with spermicide]) during the study and 30 days or more after study completion. All participants were required to understand and agree to all study procedures, and all provided written informed consent.

Participants were excluded if they had any current or past history of psychiatric illness as determined by the *Structured Clinical Interview for DSM* (for Axis I and II disorders) at screening (25,26) or present or past suicidal behavior, ideation, attempts as assessed by the Columbia Suicide Severity Rating Scale (27), or a response greater than 1 on Question 1 ("Have you ever thought about or attempted to kill yourself?") of the Suicidal Behaviors Questionnaire—Revised (28) at screening or baseline. Smokers were excluded if additionally, at screening or baseline, they scored more than 0 on Items 1 ("Apparent Sadness") or 2 ("Reported Sadness") of the Montgomery-Åsberg Depression Rating Scale (MADRS) (29) or a score of 2 or higher on Question 1 ("Anxious Mood") of the Hamilton Anxiety Scale (HAM-A) (30).

Smokers with unstable medical illness were also excluded (e.g., severe chronic obstructive pulmonary disease, clinically unstable cardiovascular disease within 6 months or less). In addition, past history of varenicline use, concurrent use of other smoking cessation medications, or concurrent enrollment in other clinical trials were exclusionary.

Randomization and Interventions

Fourteen days after screening, participants were randomized in a 1:1 ratio to receive either varenicline or placebo for a 12-week treatment period. Randomized treatment group assignments were obtained by the investigators through a drug management system accessed via the Internet or telephone. Investigators and participants were blind to treatment allocation, and the blind could only be broken in emergency situations for reasons of subject safety in which knowledge of the treatment assignment was necessary for clinical decision making. Investigators were to contact the trial sponsor before breaking the blind, and the process for breaking the blind was electronic.

During Week 1 of the treatment period, varenicline or placebo equivalents were administered at .5 mg once daily (first 3 days), then .5 mg twice daily (b.i.d., next 4 days), followed by 11 weeks of 1 mg b.i.d. During the treatment period, participants attended weekly outpatient clinic visits at Weeks 1 and Weeks 5 through 13 and were admitted to an inpatient facility from Days 14 through 28 (Figure 1). Because the half-life of varenicline is approximately 24 hours and steady-state conditions are reached within 4 days of repeated administration (31), the target quit date was set as Day 14, the day of inpatient admission. Participants were asked to continue with their current smoking habits unchanged during the first 2 weeks of treatment. The inclusion of a 2-week inpatient period in the study design was to allow observation of participants during complete smoking abstinence. The inpatient investigational facility was a completely nonsmoking building; however, if a participant insisted on smoking and could not be prevented from doing so through counseling, then he or she was escorted outside of the building and allowed to smoke.

During clinic visits and the inpatient period, investigators assessed AEs, vital signs and laboratory values, smoking and nicotine abstinence (confirmed by a nicotine use inventory, exhaled carbon monoxide, urine cotinine measurement, and patient-recorded smoking logs. Additionally, treatment compliance was measured by unused drug tablets) and subjects were administered the questionnaires and scales described subsequently in the Assessments section. Participants were contacted by telephone on Days 4 and 11, and 30 or more days after the end of treatment to assess AEs.

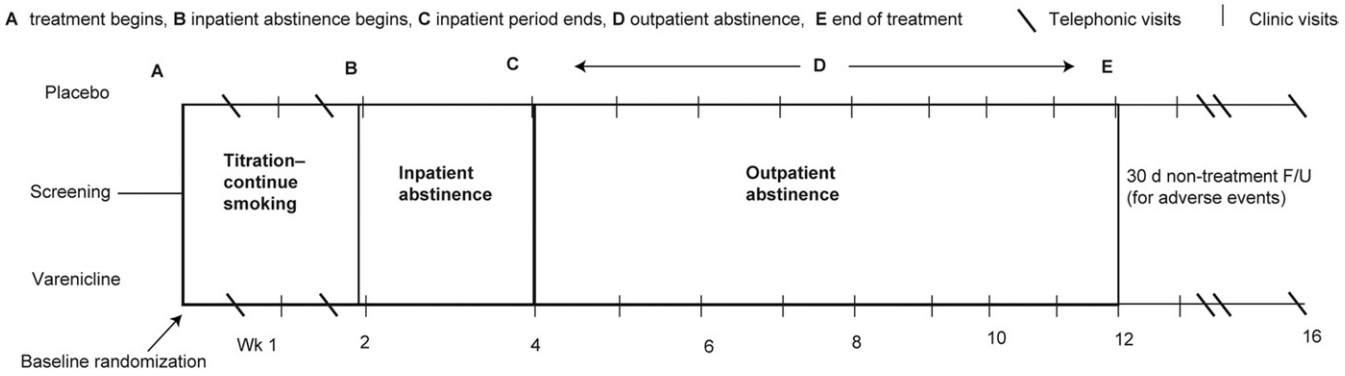

Figure 1. Study design. F/U, follow-up.