

## Trials that Matter: Varenicline: A Designer Drug to Help Smokers Quit

Two things are very clear to physicians and smokers alike: Smoking is bad for your health, and it is devilishly hard to quit (1, 2). Not surprisingly, therefore, many clinicians are pessimistic, even cynical, about treating smokers. “Why should I spend my limited time on this problem, when I know I am doomed to fail?” Actually, the rejoinders to this view—that smoking rates are at a historic low, that ex-smokers now outnumber current smokers, and that over 70% of smokers want to quit—are compelling. Physicians and smokers should also welcome the news that the FDA has approved a new drug, varenicline, for smoking cessation treatment. Varenicline, a partial nicotine agonist, has become the third pharmacologic agent approved by the FDA, following nicotine replacement therapy (currently available as patches, gum, lozenges, nasal spray, and an inhaler) and the psychoactive drug bupropion, approved in 1997 (3). Thus, after almost a decade, the FDA has had an opportunity to approve a new class of drug to treat the most important preventable health risk.

The development of varenicline reflects new understanding of how nicotine acts to increase craving for cigarettes. Receptors in the mesocorticolimbic area of the brain, which is targeted by most drugs of abuse, become desensitized through long-term exposure to nicotine, which subsequently reduce dopamine release. Nicotine receptors are ion channels that are activated by endogenous acetylcholine and by nicotine. The ion channel has at least 12 subunits that can combine in various ways to form many subtypes of ion channels. We now know that a particular nicotine receptor subtype ( $\alpha 4\beta_2$ ) is both necessary and sufficient to cause nicotine-induced sensitization, reward, and tolerance. These discoveries focused attention on specific inhibitors of the  $\alpha 4\beta_2$ -receptor subtype, starting with cytisine, a natural plant alkaloid, and leading to varenicline, a high-affinity  $\alpha 4\beta_2$ -receptor partial agonist whose effects include dopamine release and blocking the binding of nicotine to the  $\alpha 4\beta_2$  receptor, thereby reducing cravings for nicotine.

Recently, the *Journal of the American Medical Association* published 3 randomized, controlled trials of varenicline (4–6). We describe 1 of the 2 studies of quitting (4) and the study of maintenance of abstinence (6). Gonzales and coworkers reported a multicenter randomized, double-blind, placebo-controlled trial that compared varenicline with placebo and with bupropion SR. The researchers used media advertising to recruit adults who smoked at least 10 cigarettes per day and wanted to stop. They screened 1483 patients; 458 were excluded. Random assignment was stratified by center. After a brief up-titration phase, patients took twice-daily varenicline 0.5 mg, bupropion SR 150 mg, or placebo for 12 weeks. The target quit date was 8 days after starting treatment. All 3 groups received a smoking cessation self-help booklet and brief

weekly counseling sessions during the 12 weeks of active treatment. The primary end point was self-report of no use of any nicotine product during the 9th through the 12th week of treatment, confirmed by a negative test for exhaled carbon monoxide. After the active phase of treatment, participants had regular contact in person or by telephone for a total of 52 weeks.

The authors included all 1025 randomly assigned patients in the intention-to-treat analysis. Study completion rates were 60%, 56%, and 54% for varenicline, bupropion SR, and placebo, respectively. At baseline, patients smoked an average of 21 cigarettes per day and had smoked for an average of 24 years. Continuous abstinence rates from weeks 9 to 12—the primary endpoint—were 44.0%, 29.5%, and 17.7% for varenicline, bupropion SR, and placebo, respectively. By this measure, varenicline was superior to bupropion SR and placebo. Continuous abstinence rates for week 9 through week 52 were 21.9%, 16.1%, and 8.4%, by which measure varenicline was superior to placebo but not bupropion SR. Compared with placebo, bupropion SR and varenicline both reduced some symptoms of withdrawal, cigarette craving, and smoking reinforcement. The varenicline and placebo groups had the same rates of stopping treatment because of side effects; the rate for bupropion SR was higher. The results of the other quitting trial were essentially identical (5), although varenicline was superior to bupropion through the posttreatment phase.

The third trial addressed preventing relapse after quitting (6). Although 50% of smokers can achieve abstinence for several weeks, 50% to 60% of quitters resume smoking within 1 year. The authors screened 2416 patients and assigned 1928 to receive open-label varenicline for 12 weeks. They then randomly assigned those who had been abstinent during the 12th week to receive either varenicline or placebo for 12 weeks of double-blind treatment. Regardless of smoking status, everyone then continued in a nontreatment phase for an additional 28 weeks, for a total of 52 weeks. The dose of varenicline was 1.0 mg twice daily, double the dose in the other 2 varenicline trials. The primary endpoint was reported abstinence from any nicotine product during the double-blind treatment phase, as confirmed by negative results on an exhaled carbon monoxide test. Participants had regular contact in person or by telephone during the posttreatment phase up to 52 weeks.

A total of 1236 of the 1928 patients (64.1%) were abstinent during the 12th week of the open-label treatment phase and eligible for randomization. At the end of the 12-week, double-blind treatment period, the rate of abstinence since the beginning of the period was 70.5% in the varenicline group and 49.6% in the placebo group ( $P < 0.001$ ). By 52 weeks, the end of the posttreatment period, the corresponding continuous abstinence rates were

43.6% and 36.9%, respectively ( $P = 0.02$ ). Weight gain in continuously abstinent participants from before the open-label treatment to the end of the double-blind period were 3.62 kg and 4.03 kg, respectively.

These reports raise several questions. First, why is varenicline important for physicians? It is good news in 2 ways—it provides another option to help smokers quit, and the expected intense direct-to-consumer marketing campaign by the manufacturer (Pfizer) should send additional smokers the message to quit smoking. Second, is varenicline a magic bullet for smokers? Of course not. The trial shows that most smokers who try varenicline will not be able to quit. In addition, the success rates achieved in the trials are probably higher than those that would ordinarily be achieved. The trials involved in-person and telephone counseling that is much more intensive than what could be done in the community. The authors excluded patients with mental health or substance abuse problems—groups that make up a large fraction of the smoking population. Third, does the study on relapse prevention show unique advantages for varenicline? Tonstad and coworkers (6) claim that their trial achieved abstinence according to a uniquely rigorous measure: no smoking since initial cessation. By contrast, 2 other trials of relapse prevention showed either an effect of bupropion on 52-week point prevalence—not smoking at the time of the interview, but not necessarily continuous abstinence (7), or no effect (8). Fourth, will varenicline improve maintenance of abstinence beyond 52 weeks, especially since it had a relatively small margin of superiority over placebo (43.6% vs 36.9% abstinent at 52 weeks)? Further questions remain. Will nicotine replacement therapy be effective when used with varenicline? Will postmarketing surveillance show rare but serious complications that did not arise in the trials? Will health insurance plans cover the drug? As we await the answers to these questions, a prudent course would be to view varenicline as a valuable addition to the small number of drugs available to help smokers quit. It might prove to be particularly appropriate for those in whom other therapies have failed.

Most important, the ability to prescribe varenicline, the first drug designed to interact with a key brain receptor involved in nicotine addiction, should galvanize all physicians and health systems to step up efforts to treat our most

important health problem. Even a small increase in sustained quit rates will yield health benefits that far exceed any other clinical intervention.

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