Varenicline

Novel agent to help smokers quit

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Varenicline tartrate—the first nicotine-free medication FDA-approved for smoking cessation in nearly a decade (*Table 1*)—has helped patients stop smoking and remain smoke-free for up to 1 year in clinical trials. Its selective action on the receptor subtype that makes tobacco enjoyable offers a novel approach to antismoking therapy.

Table 1

Varenicline: Fast facts

Brand name: Chantix
Class: Partial nicotinic acetylcholine receptor agonist
Indication: Tobacco dependence
Approval date: May 10, 2006
Manufacturer: Pfizer
Dosing forms: 0.5- and 1-mg tablets
Recommended dosage: 0.5 mg/d for 3 days, 0.5 mg bid for next 4 days, then 1 mg bid for 11 weeks. Patients who quit successfully should receive an additional 12-week course to reduce relapse risk.

HOW IT WORKS

Unlike other FDA-approved smoking cessation treatments such as nicotine replacement therapy and sustained-release bupropion, varenicline selectively targets the α4β2 nicotinic acetylcholine receptor (nAChR),[1] which helps mediate nicotine's reinforcing effects.[2-4] By targeting this receptor subtype, varenicline ultimately diminishes these effects in the mesocorticolimbic dopamine system—the brain's "reward center."

As a partial α4β2 nAChR agonist, varenicline offers a two-pronged approach to smoking cessation:[1]

- During abstinence, varenicline stimulates low-level dopamine release by binding to α4β2 receptors located on dopamine neurons. This action, which compensates for loss of exogenous nicotine after quitting, can help counteract craving and other signs and symptoms of nicotine withdrawal caused by dopamine depletion.
- If the patient resumes smoking, varenicline makes tobacco less pleasurable by competitively binding at the α4β2 receptor.[1,5]

continued

Table 1

Smoking abstinence* rates among patients during varenicline phase-3 clinical trials

	4 weeks of continued abstinence, weeks 9 through 12	Continued abstinence, weeks 9 through 24	Continued abstinence, weeks 9 through 52
Gonzales et al 2006[9]			
Varenicline, 1 mg bid	44%	29.5%	21.9%
Bupropion SR, 150 mg bid	29.5%	20.7%	16.1%
Placebo	17.7%	10.5%	8.4%
Jorenby et al 2006[10]			
Varenicline, 1 mg bid	43.9%	29.7%	23%
Bupropion SR, 150 mg bid	29.8%	20.2%	14.6%
Placebo	17.6%	13.2%	10.3%

* Confirmed by self-report and exhaled carbon monoxide ≤10 ppm.

PHARMACOKINETICS

Varenicline is rapidly absorbed across the gut mucosa and reaches maximum concentration in approximately 4 hours. After repeated dosing, the drug reaches steady-state concentrations within 4 days, and its elimination half-life is 17 to 24 hours.

Because varenicline's simple benzazepine structure lacks bulky moieties that would promote hepatic biotransformation,[5] 90% of the drug is excreted through the kidneys. To date, no clinically relevant drug-drug interactions have been reported.[6]

EFFICACY

Varenicline showed a dose-dependent effect in phase-2 clinical trials,[7,8] with 1 mg bid providing optimal efficacy and tolerability. Compared with placebo, varenicline was significantly more effective in initiating:

- continuous abstinence for ≥4 weeks during active treatment, confirmed by measuring carbon monoxide (CO) in exhaled breath
- long-term abstinence, evidenced by self-report and exhaled CO ≤10 ppm at 24 and 52 weeks.[7,8]

Odds ratios calculated for patients who stayed smoke-free for ≥4 weeks during 7 to 12 weeks of active treatment suggest that smokers who use varenicline, 1 mg bid, are approximately 4 to 8 times more likely to achieve short-term abstinence during this active treatment period than those who received placebo.[7,8]

In phase-3 trials,[9-11] patients were also followed for up to 1 year and received brief, standardized counseling along with medication or placebo—as recommended in the U.S. Department of Health and Human Services Clinical Practice Guideline, Treating Tobacco Use and Dependence.[12]

12-week treatment trials.[9,10] A total of 2,052 adults in two randomized, double-blind trials received varenicline, sustained-release (SR) bupropion, or placebo for 12 weeks. Based on phase-2 trial results—which showed that varenicline was better tolerated after a 1-week dosage titration period—varenicline was given at:

- 0.5 mg/d for days 1 through 3
- 0.5 mg bid for days 4 through 7
- 1 mg bid through week 12.

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Bupropion SR was given at 150 mg/d for days 1 through 3, then 150 mg bid through week 12.

Patients were then followed for up to 40 weeks after drug discontinuation. Patients had been smoking ≥10 cigarettes/day at baseline and were motivated to stop smoking.

Overall, varenicline was associated with higher short- and long-term abstinence rates compared with bupropion SR or placebo (*Table 2, page 92*), although the comparison with bupropion SR was not statistically significant (P=0.057) for weeks 9 through 52 in one study.[9] As in the phase-2 studies, abstinence was confirmed by measuring CO in exhaled breath.

Compared with placebo, varenicline also reduced cravings and other signs and symptoms of tobacco withdrawal as measured with the Brief Questionnaire of Smoking Urges and Minnesota Nicotine Withdrawal Scale.[9,10]

Relapse prevention study. Tonstad et al[11] investigated whether extended varenicline treatment prolongs smoking abstinence. A total of 1,210 patients who quit smoking after 12 weeks of open-label varenicline treatment continued taking varenicline at 1 mg bid or were switched to placebo during a 3-month, double-blind phase.

Compared with placebo, rates of continuous smoking abstinence were significantly higher among the varenicline group during the double-blind active treatment phase (70.5% vs. 49.6%) and for 6 months after drug discontinuation (43.6% vs. 36.9%).[11] These data suggest that an extended varenicline regimen might promote long-term abstinence.[6,13]

TOLERABILITY

Overall, varenicline was safe and well tolerated in clinical trials.

Nausea was the most commonly reported adverse event in fixed-dose, placebo-controlled studies.[6] Although approximately 3% of patients stopped varenicline prematurely because of upset stomach,[6] most rated their nausea as mild to moderate and reported reduced nausea with continued varenicline use. For patients with intolerable nausea, consider reducing the dosage.

Sleep disturbance, constipation, flatulence, and vomiting were twice as prevalent among the varenicline groups compared with placebo.[6] Overall treatment discontinuation rates were similar with varenicline, 1 mg bid, and placebo (12% vs. 10%) in 12-week phase-2 and phase-3 clinical trials.[6]

To improve tolerability, the FDA recommends splitting varenicline into twice-daily doses.[6,13]

DOSING

Start varenicline at 0.5 mg/d for 3 days, 0.5 mg bid for the next 4 days, then 1 mg bid through week 12. To improve tolerability, advise patients to take varenicline after eating and with a full glass of water.

Setting a target quit date (TQD) is a critical element of smoking cessation treatment. Schedule the TQD for the same day the patient begins 1 mg bid varenicline dosing so that the medication is approaching maximal steady-state concentrations during the quit attempt to help counter withdrawal. Allow patients to continue smoking during the 1-week titration period, but stress the importance of trying to quit on the TQD.

Because varenicline is primarily eliminated

Bottom Line

Varenicline helped patients stop smoking for up to 1 year in clinical trials. It is designed to compensate for nicotine depletion after quitting and to make tobacco less pleasurable if the patient resumes smoking. Use varenicline with behavioral counseling to maximize outcome.

Related resources

- Varenicline Web site. www.chantix.com.
- World Health Organization. Causes of death. In: *Epidemiology and burden of disease*. Geneva: World Health Organization, 2003.
- Fiore MC, Bailey WC, Cohen SJ, et al. Clinical practice guideline. Treating tobacco use and dependence. Rockville, MD: U.S. Department of Health and Human Services, 2000. www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf.

DRUG BRAND NAMES

Bupropion SR • Wellbutrin, Zyban
Varenicline • Chantix

DISCLOSURE

Dr. Anthenelli is a consultant for Alkermes and Cephalon and a speaker and consultant for Pfizer and sanofi-aventis.

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through the kidneys, limit dosages to 0.5 mg bid in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). Monitor renal function in older patients with lesser degrees of renal impairment.[6,13]

Varenicline has not been studied in patients with substance use and other psychiatric disorders—patients who account for most of a psychiatrist's caseload and whose nicotine dependence is difficult to treat. Even so, the medication's lack of discernible drug-drug interactions and selectivity of α4β2 nAChR action make varenicline worth considering for these patients.

Varenicline also has not been tested or approved for use in adolescent or pregnant smokers; research is needed on how the medication works in these patients.

ROLE OF BEHAVIORAL TREATMENT

The Clinical Practice Guideline, Treating Tobacco Use and Dependence[12] suggests combining antismoking pharmacotherapy with counseling to maximize outcome. To that end, varenicline's manufacturer has developed a personalized behavioral support program for patients taking the medication.[14] Adjunctive therapy via the Internet, telephone, or direct mail can complement other extra-treatment supports—such as toll-free quit lines and classes offered through health organizations—and more-formal, intensive behavioral interventions.

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