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September, 2006

## Drug Update

# New Smoking-Cessation Agent Stops Nicotine Withdrawal Symptoms



Varenicline (Chantix; Pfizer), the first smoking cessation aid to be approved in nearly a decade, provides double-barreled action that may enable many of the 44.5 million smokers in the United States to end their addiction for good. Every year, almost 41% of smokers try to quit, and only about 1 in 10 is successful.

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In addition to quelling nicotine withdrawal symptoms, varenicline blocks some of the pleasurable effects of nicotine that may compel some quitters to start smoking again.

Varenicline is the latest drug to go through the fast-track review process recently instituted by the FDA. It qualified for the rapid process because of its potential for significant health benefits for millions of Americans, in addition to the level of the evidence.

"I have tested everything that is currently available," says Elbert D. Glover, PhD, chair, Department of Public and Community Health, Maryland University in College Park. His involvement with all smoking cessation agents approved by the FDA has led him to conclude that "every time we develop something, incrementally it gets a little better." And, he says, varenicline now holds the honor of being that incrementally better treatment.

It is the reward that gets people hooked on nicotine, Dr Glover says. "You inhale, and the smoke affects the central nervous system [CNS], and then there is a dopamine surge in the nucleus accumbens."

According to Dr Glover, today's smoker is much more recalcitrant and addicted than the smoker in years past. "In 1915, the average smoker smoked about 10 cigarettes a day. Twenty years ago it was closer to 20 cigarettes a day. Today it's about 24 to 26 cigarettes a day."

Dopamine is at the heart of all addictions. The problem is magnified in smoking because the strong addictive component, nicotine, is accompanied by a strong behavioral component. "When you're smoking 30 cigarettes a day, and you're taking 10 drags off each cigarette, that's 300 pharmacologic hits, or about 300 arterial boluses a day." This is how habits are developed, and eventually "habit, or environmental cue, is sufficient to trigger the desire to smoke."

### Attacking the Reward Pathway

Five of the 6 agents previously approved for smoking cessation were

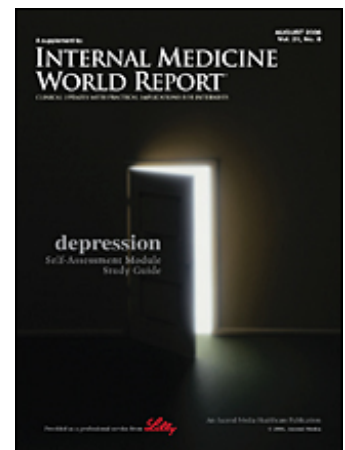


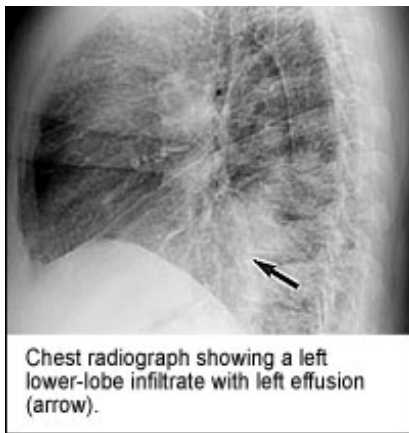
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nicotine replacements in the form of gum, patch, nasal spray, oral inhaler, and lozenge. "Essentially you're getting the very drug that you're addicted to, but you're getting it a little differently," Dr Glover explains. Inhaling is the quickest way to deliver nicotine to the CNS.

With nicotine replacement therapy, nicotine delivery is slower and more leveled out, without the arterial spikes that occur with inhalation and thus without the huge release of dopamine. The other previously approved therapy, sustained-release bupropion (Zyban), works along dopaminergic and nor-adrenergic pathways to remove some of the reward from nicotine.

Varenicline, Dr Glover says, is "taking that a bit further. It was deliberately designed for the  $\alpha 4\beta 2$  receptor as an  $\alpha 4\beta 2$  nicotinic

receptor partial agonist (with dual agonist and antagonist properties). Varenicline binds to and partially stimulates the  $\alpha 4\beta 2$  receptor without creating full nicotinic effect (agonist properties). In the presence of nicotine, however, varenicline blocks the receptor, preventing the nicotine from binding and thereby attenuating nicotine's effect (antagonist properties)."

### Significant Evidence

The safety and efficacy of varenicline were confirmed in 3 large, randomized, controlled trials that included more than 3200 participants. The first 2 trials included 2052 healthy adults (aged 18-75 years) who smoked at least 10 cigarettes daily and had not been able to quit smoking for more than 3 months during the previous year. Participants were randomized to 12 weeks of treatment with varenicline, bupropion, or placebo (*JAMA*. 2006; 296:47-55; 56-63). At various intervals, carbon monoxide-confirmed sustained smoking abstinence was evaluated.

During the last 4 weeks of treatment, varenicline-treated patients were about 4 times more likely to be abstinent than placebo-treated patients and about 2 times more likely to be abstinent than bupropion-treated patients. Varenicline continued to outperform bupropion therapy and placebo even after treatment had ended (Table).

**Table. Continuous smoking abstinence with 12-wk use of varenicline, bupropion, or placebo**

Duration	Smokers abstained, %		
	Varenicline	Bupropion	Placebo
<b>Study 1 (n = 1025)</b>			
Weeks 9-12	44.0	19.5	17.7
Weeks 9-24	29.5	20.7	10.5
Weeks 9-52	21.9	16.1	8.4
<b>Study 2 (n = 1027)</b>			
Weeks 9-12	43.9	29.8	17.6
Weeks 9-24	29.7	20.2	13.2
Weeks 9-52	23.0	14.6	10.3
<b>Patients reporting nausea, %</b>			
<b>Study</b>			
1	28.1	12.5	8.4
2	29.4	7.4	9.7

Sources: *JAMA*. 2006;296:47-55; 56-63.

And even though almost 30% of patients treated with varenicline complained of nausea, those treated with bupropion were more likely to withdraw because of side effects than those receiving varenicline (average, 13.5% vs 9.0%, respectively).

The third study compared 12 weeks of varenicline maintenance therapy with placebo in patients who were able to abstain from smoking for at least 7 days after 12 weeks of varenicline treatment (*JAMA*. 2006;296:64-71).

In that study, patients in the varenicline group were significantly more likely to continue abstaining from smoking at weeks 13 to 24 compared with placebo-treated patients (70.5% vs 49.6%, respectively) as well as at weeks 13 to 52 (43.6% vs 36.9%, respectively).

### Indications

Varenicline is indicated for adults older than 18 years who are motivated to quit smoking. The starting dosage is 0.5 mg/day, which is to be titrated during the first week to the recommended dose of 1 mg twice daily.

For patients who cannot quit smoking after 12 weeks of treatment, an additional 12 weeks of therapy is an option.

### Side Effects

Having conducted more than 50 trials with various compounds, Dr Glover says, "From my perspective, this is about as safe as anything we've ever worked with." He emphasizes that "there are no contraindications and no warnings. About 92% of varenicline is eliminated via the urine."

The 30% incidence of nausea seen in clinical trials with varenicline, Dr Glover says, is "a real concern." He therefore recommends taking this agent after a meal, with water. But, he adds, "If you look closely, 98% of the nausea was in the mild-to-moderate category."

The few cases of severe nausea that occurred were spread equally among the varenicline, bupropion, and placebo groups. "I have yet to hear from any of the physicians I know who have been prescribing it, 'the nausea was so severe, my patient couldn't handle it,'" he says.

"I know a lot of the companies hate when I tell the last drug 'goodbye,'" Dr Glover says, adding that for the past decade, bupropion has been his drug of first choice, but now he thinks that varenicline is "the best thing out there."

He cautions physicians "to adjust your sights and understand it's no magic bullet. It's not going to make all your patients quit smoking overnight."

### Counseling Patients Is Key

All available smoking cessation agents also recommend supplementing with counseling, to help patients change their habitual patterns and learn how to recognize triggers. As Dr Glover states, "The habit and the addiction are intertwined," thus both aspects must be addressed.

"I know that especially for primary care physicians, time is money," he says, emphasizing, "Smoking is a chronic, relapsing type of disease. Just because a patient has quit smoking for 6 months, you're not through with him. You need to periodically check to see how he is doing." If there is a traumatic event or another stressor, the way the patient has traditionally dealt with it was by smoking, and he may find himself smoking again without even realizing it.

"Unfortunately, in many physicians' hands, that's where the model falls apart," Dr Glover laments. "They give the drug and the script, but they don't follow up with the counseling and social support that is so greatly needed."

A website developed by the manufacturer of varenicline ([www.get-quit.com](http://www.get-quit.com)) and designed for patients may also help physicians in counseling their patients. It offers daily feedback and helpful tips for those trying to quit smoking.

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