

Varenicline (Chantix): A New Treatment Option for Smoking Cessation

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INTRODUCTION

Currently, an estimated 44.5 million adults in the U.S. smoke cigarettes.¹ One in five people who smoke have at least one serious smoking-related illness.¹ Tobacco smoking is the second leading cause of death in the U.S. and the single most preventable cause of disease, with an estimated 438,000 deaths annually.^{2,3}

Smoking is responsible for a large number of illnesses, including ischemic heart disease and pulmonary diseases, such as lung cancer and chronic obstructive pulmonary disease (COPD) (Figure 1). Smoking cessation should always be a major health care goal, because it is associated with clear health benefits and subsequent reductions in overall health care costs.

Tobacco dependence is a chronic condition for which repeated interventions are most frequently required. Nicotine withdrawal symptoms (Table 1) play a major role in the inability of many people to quit smoking. Most smokers relapse within the first few days of attempting to quit.

Some existing treatment options can produce long-term or even permanent abstinence. Counseling, social support, and pharmacological approaches are effective treatment modalities, particularly when they are used in combination. However, the average smoker makes almost 10 attempts to stop smoking, with

or without treatment, before successfully quitting.⁴

Current guidelines for the treatment of patients with tobacco dependence emphasize the need to identify patients who are willing to quit, patients who are unwilling to quit, and patients who have recently quit.⁵ For patients who are ready to quit, health care professionals should use the “5 A’s”; for patients who are not motivated to quit, they should use the “5 R’s” at every clinician visit (Table 2). Figure 2 illustrates the algorithm discussed in these guidelines for identifying and assessing patients’ tobacco use.

Until recently, the only six available pharmacotherapeutic agents approved by the Food and Drug Administration (FDA) for smoking cessation included sustained-release bupropion HCl (Zyban, GlaxoSmithKline) and nicotine replace-

ment therapies (e.g., the nicotine patch, gum, inhalers, nasal sprays, and lozenges). Use of any one of these agents is recommended by the guidelines as a first-line pharmaceutical therapy for smoking cessation.

For nearly a decade, no other smoking-cessation treatment options had been approved by the FDA. On May 11, 2006, varenicline (Chantix, Pfizer), the first in a new class of medications approved for smoking cessation, was approved.

CHEMISTRY AND PHARMACOLOGY⁶

Varenicline is a partial agonist of the $\alpha_4\beta_2$ ($\alpha_4\beta_2$) neuronal nicotinic acetylcholine receptors in the brain. These receptors are believed to mediate the dependence-producing properties of nicotine.^{6,7}

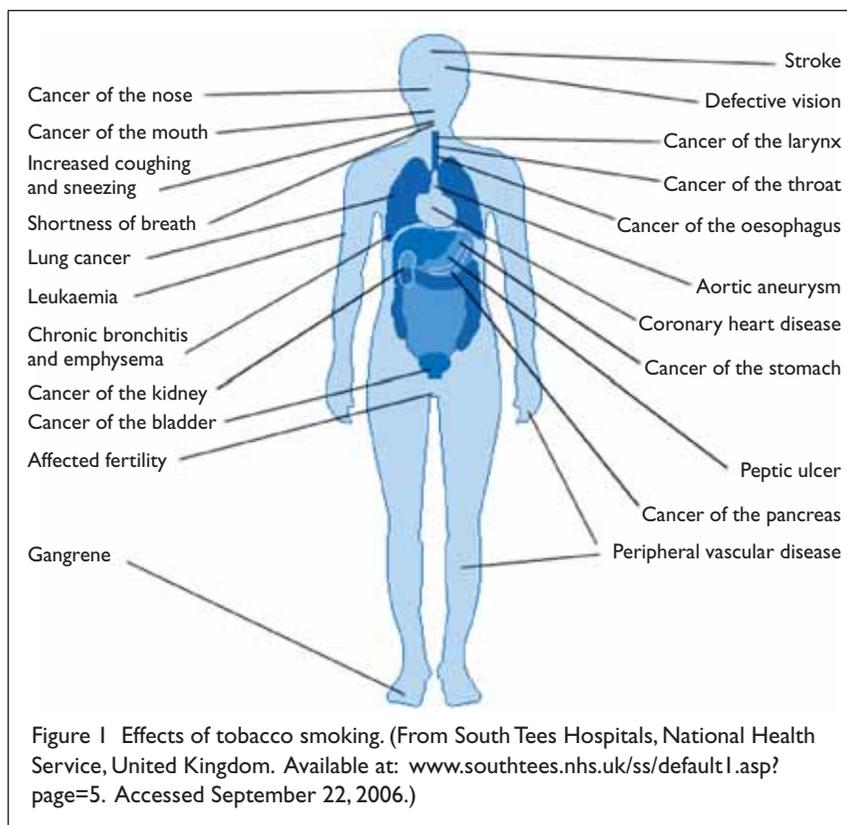


Figure 1 Effects of tobacco smoking. (From South Tees Hospitals, National Health Service, United Kingdom. Available at: www.southtees.nhs.uk/ss/default1.asp?page=5. Accessed September 22, 2006.)

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Table 1 Nicotine Withdrawal Symptoms*

- Anxiety
- Irritability
- Restlessness
- Insomnia
- Headache
- Frustration, impatience
- Difficulty concentrating
- Tobacco cravings†
- Depression
- Decreased blood pressure and heart rate
- Drowsiness
- Increased appetite and weight gain
- Increased skin temperature
- Gastrointestinal disturbances

*The onset of symptoms usually occurs within 24 to 48 hours and may last for several weeks or longer.

†Tobacco cravings may last for years.

Varenicline works by binding to these receptors and stimulating their receptor-mediated activities at a significantly lower level than nicotine, thereby reducing nicotine withdrawal symptoms and cigarette cravings.⁶ This drug simultaneously prevents nicotine binding to these receptors, which block the stimulation of the central nervous mesolimbic dopamine system (the “reward” center in the brain) and the reinforcing effects of continued nicotine use.⁶ Therefore, if a patient does smoke a cigarette while taking this medication, varenicline has the potential to reduce the feelings of satisfaction associated with smoking.

Available as a tartrate salt, varenicline has the following chemical formula: $C_{13}H_{13}N_3 \cdot C_4H_6O_6$. It is a white to slightly off-white to slightly yellow powder. It is highly water-soluble and has a molecular weight of 361.35 daltons. Figure 3 illustrates the agent’s chemical structure.

Varenicline is a highly selective agent and binds more potently to $\alpha_4\beta_2$ receptors than to other common nicotinic receptors (more than 500-fold $\alpha_3\beta_4$, more than 3,500-fold α_7 , and more than 20,000-fold $\alpha_1\beta\gamma\delta$) or to non-nicotinic receptors and transporters (more than 2,000-fold). It also binds with moderate affinity to the 5-hydroxytryptamine (serotonin) ($5-HT_3$) receptor.

Table 2 Guide for Patient Assessment

The “5 A’s”:

- Ask about tobacco use. (How often does patient smoke? How much?)
- Advise tobacco users to quit.
- Assess readiness to make an attempt to quit smoking.
- Assist with the quit attempt (i.e., set a quitting date, anticipate challenges to quitting, and recommend effective pharmacotherapies).
- Arrange follow-up care.

The “5 R’s”:

- *Relevance* of quitting smoking (i.e., discuss the health benefits, financial considerations, and disease risks)
- *Risks* (ask the patient to identify negative consequences of tobacco use)
- *Rewards* (ask the patient to identify potential benefits of smoking cessation)
- *Roadblocks* (identify barriers or impediments to quitting)
- *Repetition* of motivational intervention

PHARMACOKINETICS⁶

After oral administration, maximum plasma concentrations typically occur within three to four hours. Steady-state levels were reached within four days after multiple doses of varenicline were consumed. Varenicline exhibits linear pharmacokinetics after single or repeated doses above the recommended dosing range. A mass balance study demonstrated virtually complete absorption of varenicline following oral administration and high systemic availability. Neither time of day nor type of food affected oral bioavailability.

The drug’s elimination half-life is approximately 24 hours. Plasma protein binding of varenicline is low (less than 20%). Varenicline undergoes minimal metabolism; 92% is excreted unchanged in

the urine and is eliminated primarily through glomerular filtration, as well as by active tubular secretion (possibly via the organic cation transporter OCT2).

In pharmacokinetic studies and population analyses, varenicline has not demonstrated any clinically significant differences with regard to age, race, sex, smoking status, or the use of concomitant medications.

Renal Impairment. In patients with mild renal impairment, the pharmacokinetic parameters of varenicline were unchanged. Mild renal impairment was estimated to be a creatinine clearance (CrCl) of above 50 ml/minute and of less than 80 ml/minute. In patients with moderate renal impairment (CrCl of 30 ml/minute or higher and less than 50

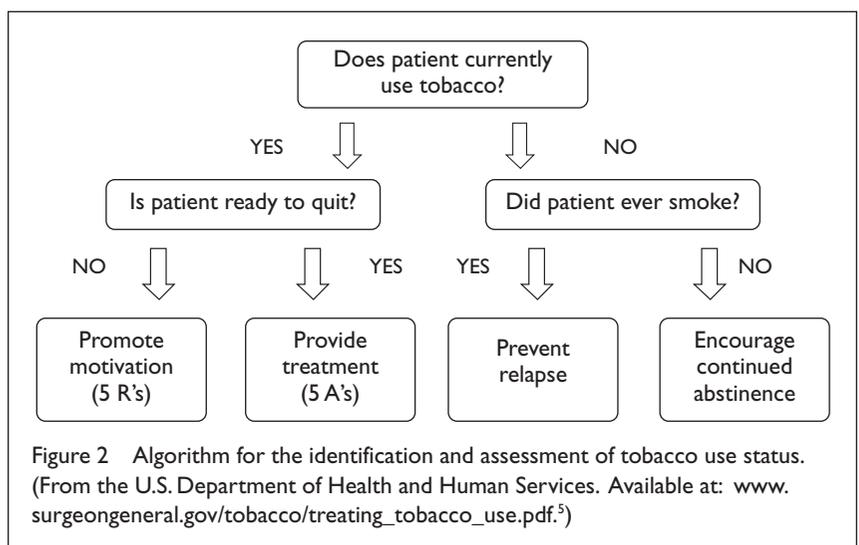


Figure 2 Algorithm for the identification and assessment of tobacco use status. (From the U.S. Department of Health and Human Services. Available at: www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf.)

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ml/minute), serum concentrations of varenicline increased 1.5-fold, compared with subjects without renal impairment (a CrCl above 80 ml/minute). Subjects with severe renal impairment showed a 2.3-fold increase in varenicline exposure. Severe renal impairment was a CrCl of below 30 ml/minute.

Subjects with end-stage renal disease who underwent three-hour hemodialysis sessions three times weekly experienced a 2.7-fold increase in varenicline levels following the administration of 0.5 mg once daily for 12 days. These levels were comparable to those of healthy subjects receiving about 1 mg twice daily.

Varenicline is efficiently removed by hemodialysis; therefore, caution is warranted for renally impaired patients.

Hepatic Impairment. Because varenicline is not metabolized by the liver to a significant extent, its pharmacokinetic profile should not be affected in patients with hepatic insufficiency.

CLINICAL TRIALS^{6,8-10}

The FDA's approval of varenicline was based on six clinical trials. In all of the trials, abstinence from smoking was determined by patients' self-report and then verified by measurement of exhaled carbon monoxide at weekly visits.

Most of the enrolled subjects were Caucasian (79% to 96%), and the number

of men and women was almost equal. The average age of the subjects was 43 years. On average, the participants were smoking about one pack of cigarettes per day for approximately 25 years.

All participants were provided with an educational booklet on smoking cessation, and they received up to 10 minutes of counseling at every weekly treatment visit. They were instructed to set a target date for quitting that would take effect one week after the initiation of treatment.

Continuous Abstinence during Treatment

Gonzales et al.⁸

Gonzales et al. conducted a double-blind, placebo-controlled, multicenter trial that compared the efficacy and safety of varenicline with bupropion (Zyban) or placebo. Participants were "generally healthy" adult volunteers (18 to 75 years of age) who smoked 10 cigarettes per day or more, with less than three months of smoking abstinence in the previous year. Potential participants with any major disease (e.g., diabetes or uncontrolled hypertension) were excluded from the study. Participants were recruited from advertisements and were required to be motivated to quit smoking.

The patients were randomly assigned to receive one of three regimens:

- varenicline, titrated to 1 mg twice daily (n = 352)
- bupropion, titrated to 150 mg twice daily (n = 329)
- placebo (n = 344)

All subjects were advised to set a date to quit smoking beginning on the eighth day of treatment. They were treated for a total of 12 weeks, followed by 40 weeks of non-drug follow-up. In the treatment phase, they were given brief weekly counseling during clinic visits. In the non-drug follow-up phase, patients were monitored via monthly telephone contact or a clinic visit.

The primary endpoint was the four-week period of continuous abstinence from smoking during weeks nine to 12, the last four weeks of treatment. Continuous abstinence was confirmed via an exhaled carbon monoxide measurement of 10 parts per million (ppm) or less. Not even "one puff" was allowed.

Secondary endpoints included contin-

uous abstinence during weeks nine to 24 and during weeks nine to 52. The researchers evaluated cravings, withdrawal, and the reinforcing effects of smoking during the drug-treatment phase. Various tools were used, including the Minnesota Nicotine Withdrawal Scale (MNWS), the Brief Questionnaire of Smoking Urges (QSU-Brief), and the Modified Cigarette Evaluation Questionnaire (mCEQ).

Results showed that 44% of patients in the varenicline arm were abstinent, compared with 17.7% of those in the placebo arm ($P < .001$) and 29.5% of those receiving bupropion SR ($P < .001$) during weeks nine to 12. For weeks nine to 24, varenicline offered a superior rate of continuous abstinence (29.5%), compared with that for placebo (10.5%) ($P < .001$) and bupropion SR (20.7%) ($P = .007$).

At weeks nine to 52, varenicline also produced significant improvement (21.9%), compared with placebo (8.4%) ($P < .001$), and provided superior, although nonsignificant, results (21.9%) compared with bupropion SR (16.1%) ($P = .057$).

Varenicline was more efficacious than placebo at all time points, and it was more efficacious than bupropion SR at the end of 12 weeks of treatment and at 24 weeks.

Scores on the MNWS indicated that both varenicline and bupropion SR significantly reduced the urge to smoke and had a negative effect when compared with placebo ($P < .001$).

On the sQSU-Brief, subjects had lower total craving scores ($P < .001$ with varenicline; $P = .001$ with bupropion SR).

The mCEQ revealed that varenicline, compared with placebo, significantly reduced smoking satisfaction ($P < .001$), psychological reward ($P < .001$), relief from cravings ($P < .001$), and enjoyment of respiratory sensations ($P < .001$). Compared with placebo, bupropion SR reduced only psychological reward to a significant extent ($P = .004$).

Rates of discontinuation of the study drug were similar among all groups: 60.5% of varenicline patients, 56% of bupropion SR patients, and 54% of patients in the placebo arm completed the 52-week study. Loss of participants to follow-up was the most common reason for discontinuing the study during the treatment phase and during the non-drug follow-up phase.

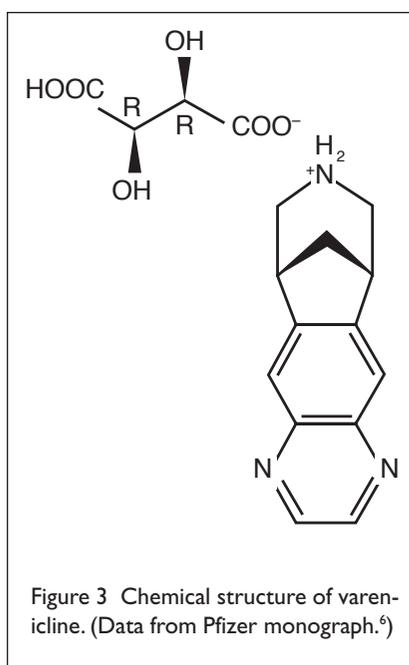


Table 3 Most Common Treatment-Emergent Adverse Events in Fixed-Dose, Placebo-Controlled Studies of Varenicline*

	Varenicline 1 mg Twice Daily (n = 821)	Placebo (n = 805)
Nausea	30%	10%
Insomnia	18%	13%
Headache	15%	13%
Abnormal dreams	13%	5%
Constipation	8%	3%
Abdominal pain	7%	5%
Fatigue/malaise/asthenia	7%	6%
Flatulence	6%	3%
Dyspepsia	5%	3%
Vomiting	5%	2%
Sleep disorder	5%	3%
Dysgeusia	5%	4%
Upper respiratory tract disorder	5%	4%

* Occurring at a rate of 5% or more in the group of patients receiving varenicline 1 mg twice daily and at least 0.5% more than in those receiving placebo.
Data from varenicline (Chantix), package insert. Pfizer, May 2006.⁶

Varenicline was generally well tolerated. The most common adverse effect was nausea (in 28.1%). Insomnia was the most common adverse effect reported with bupropion SR (in 21.9%).

Jorenby et al.⁹

Jorenby et al. conducted a similar study using the same design and methods as those in the Gonzales trial.⁸ The researchers enrolled 1,027 volunteers. The primary endpoint was the four-week period of continuous abstinence from smoking during weeks nine to 12. Secondary endpoints included continuous abstinence during weeks nine to 24 and weeks nine to 52.

Varenicline was reported to be superior to both placebo and bupropion SR at all time points. Abstinence rates were significantly higher at weeks nine to 12 for varenicline: 43.9% versus 17.6% for placebo ($P < .001$) and 29.8% for bupropion SR ($P < .001$), with participants maintaining abstinence during the last four weeks of treatment.

At weeks nine to 24, 29.7% of the varenicline-treated patients maintained abstinence, compared with 13.2% of the placebo group ($P < .001$) and 20.2% of the bupropion group ($P = .003$).

During weeks nine to 52, 23% of the varenicline patients maintained abstinence, compared with 10.3% of those

receiving placebo ($P < .001$) and 14.6% in the bupropion group ($P = .004$).

Study-withdrawal rates were similar among all groups. The most common adverse effect reported with varenicline, in 29.4% of patients, was nausea, classified as mild in most cases. Insomnia was the most common adverse effect reported by subjects taking bupropion SR (21.2%).

Maintenance of Abstinence with Extended Treatment

Tonstad et al.¹⁰

Tonstad et al. conducted a study to evaluate whether an additional 12 weeks of varenicline therapy would yield greater continuous abstinence rates compared with placebo. The participants were initially given varenicline 1 mg twice daily for a total period of 12 weeks. They also received brief counseling in the clinic during weeks one to eight, at week 10, and at week 12. At the end of week 12, patients were assessed for abstinence in the previous seven days; 64.1% had not smoked, used tobacco, or used nicotine replacement therapy. The researchers then randomly assigned 62.8% (n = 1,210) of these participants to receive either varenicline 1 mg twice daily or placebo for 12 more weeks (weeks 13 to 24).

The primary endpoint assessed continuous abstinence rates from smoking during weeks 13 to 24, as confirmed with a

carbon monoxide test. The secondary endpoint measured continuous abstinence during weeks 13 to 24.

During weeks 13 to 24, the rate of continuous abstinence was significantly higher with varenicline patients (70.5%) than placebo patients (49.6%) ($P < .001$). At weeks 13 to 52, continuous abstinence rates with varenicline, compared with placebo, were still significantly higher (43.6% vs. 36.9%; $P = .02$). The median time to first lapse of abstinence was 198 days with varenicline and 87 days with placebo ($P < .001$).

ADVERSE DRUG EVENTS^{6,8,9}

Varenicline was generally well tolerated in clinical trials. The most common side effects were nausea, insomnia, abnormal dreams, and headache (Table 3). In the Jorenby study,⁹ 10.5% of patients receiving varenicline stopped taking the medication as a result of adverse events, compared with 12.6% of the bupropion SR subjects and 7.3% of the placebo subjects.

In the Gonzales study,⁸ 28.1% of the patients experienced mild-to-moderate nausea, although only 2.6% of patients discontinued the study drug for that reason. Patients who experience intolerable nausea should be advised to take varenicline with meals, and they may decrease the dose of varenicline.

PREGNANCY AND LACTATION⁶

Varenicline is classified as a pregnancy category C agent. Animal studies have demonstrated that varenicline can be transferred to nursing pups; however, it is not known whether the drug is excreted in human breast milk.

DRUG INTERACTIONS⁶

Based on *in vitro* studies and the pharmacokinetic profile of varenicline, no clinically meaningful drug interactions have been identified. Drug-interaction studies with certain agents such as digoxin, warfarin, bupropion, cimetidine, transdermal nicotine, and metformin did not result in clinically significant drug interactions (see Pharmacokinetics on page 21).

DOSAGE AND ADMINISTRATION⁶

Patients should begin taking varenicline one week before their “quit smoking” date. Varenicline should be tapered

as follows: 0.5 mg once daily for the first to third days, 0.5 mg twice daily for the fourth to seventh days, and 1 mg twice daily thereafter. If the patient cannot tolerate the adverse effects, the dose may be decreased. Varenicline should be taken after eating and with a full glass of water.

Patients should take varenicline for 12 weeks. Patients who have successfully quit smoking after 12 weeks with varenicline can continue taking it for an additional 12 weeks to enhance the likelihood of preventing a relapse. Patients who do not successfully quit smoking after 12 weeks of therapy should be encouraged to restart varenicline treatment after factors contributing to the relapse have been identified and addressed.

SPECIAL POPULATIONS⁶

Renally Impaired Patients. On the basis of present pharmacokinetic studies, dosage requirements are not necessary for patients with mild-to-moderate renal impairment. Patients with severe renal impairment (CrCl below 30 ml/minute) should begin varenicline at a dose of 0.5 mg once daily; this dose may be titrated to a maximum dose of 0.5 mg twice daily.

The maximum dose for patients with end-stage renal disease undergoing hemodialysis is 0.5 mg once daily if it is well tolerated.

Elderly patients should be monitored closely for declining renal function and subsequent dosage adjustments. Because varenicline is substantially excreted by the kidney, patients with impaired renal function are at higher risk of developing toxic reactions to this agent. Caution is warranted in the elderly population because of the possibility of an increased sensitivity to the product.

Hepatically Impaired Patients. No dosage adjustments are necessary for those patients with hepatic impairment.

Young Patients. Varenicline has not been studied in patients younger than 18 years of age; thus, it is not recommended for use in this patient population.

OVERDOSAGE⁶

To date, there has been no experience with patients on dialysis following a drug overdose; however, varenicline is dialy-

zable in patients with end-stage renal disease (see Pharmacokinetics, page 21). Standard supportive measures should be implemented as required if an overdose occurs.

CONTRAINDICATIONS⁶

Currently, there are no contraindications to the use of varenicline; however, this product is not recommended for use in patients under 18 years of age.

PATIENT COUNSELING⁶

Guidelines for patients beginning varenicline treatment are as follows:

- Health care professionals should instruct patients to set a date for smoking cessation and to start varenicline therapy one week before that date.
- Patients are advised to take varenicline after eating and with a full glass of water.
- Patients should be shown how to titrate the varenicline dose.
- Patients should be encouraged to continue to try to quit smoking even if they experience early relapses.
- Patients should be informed that nausea and vomiting are common side effects that are usually transient. If these symptoms persist, patients should contact their health care providers so that a dose adjustment may be considered.
- Clinicians should provide support with educational materials and necessary counseling.
- Patients should be informed that they may require some dosage adjustments of other drugs after they quit smoking (e.g., theophylline).
- Patients who plan to become pregnant or to breast-feed should be advised of the risks and benefits of smoking cessation with varenicline.

THE GETQUIT SUPPORT PLAN¹¹

The GETQUIT Support Plan is a behavioral support program designed to enhance a patient's chances of success in smoking cessation. For Chantix patients, this program is available at no additional cost. The plan, which incorporates the principles of cognitive therapy, was designed by smoking-cessation experts to educate patients on how to manage cravings and behavioral triggers.

This program, customized to each

patient's needs, contains daily reminders, either through e-mail or phone calls, to encourage abstinence. A personalized Web page helps patients track their daily progress. The program provides encouragement, advice, activities, and information about the quitting process. The daily contact reminders become less frequent after the initial 12 weeks. The program is available to patients for up to one year.

COST¹²

Varenicline is supplied as a Starting Month Pak, which contains the recommended structured dose titration schedule (see Dosage and Administration), and a Continuing Month Pak, which contains 56 tablets in a strength of 1 mg. Bottles of 56 tablets are also available in 0.5-mg and 1-mg strengths.

As of December 2006, the average wholesale prices, based on a one-month supply, were as follows:

- all Chantix packages and strengths, \$112 per month
- bupropion SR (Watson Labs), 150-mg tablets, \$116.10
- bupropion HCl (Zyban, Glaxo-SmithKline), 60 tablets, \$181.30

For easy dose titration, patients initiating varenicline therapy should begin with the Starting Month Pack. They can then use either the Continuing Month Packs or the monthly bottle supply.

CONCLUSION

Varenicline is the first agent in its class that was developed to maintain abstinence in tobacco-dependent patients. It works by binding to the $\alpha_4\beta_2$ receptors in the brain and stimulating their receptor-mediated activities at a significantly lower level than nicotine, resulting in fewer nicotine-withdrawal symptoms and cigarette cravings. Varenicline also simultaneously prevents nicotine binding to these receptors; as a result, it blocks the stimulation of the central nervous mesolimbic dopamine system and the reinforcing effects of continued nicotine use.

In clinical trials, varenicline had superior efficacy to that of bupropion SR, and it was well tolerated. It is hoped that varenicline will provide a better option than standard treatment regimens for patients willing to quit smoking through

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DRUG FORECAST

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its unique mechanism of action and its favorable side-effect profile. As with all smoking-cessation agents, varenicline is more likely to be effective for patients who are motivated to quit smoking, and it should be used as part of a comprehensive treatment program that includes psychosocial support.

The proven detrimental health effects of smoking tobacco significantly increase morbidity and mortality in our population. Varenicline should be considered a viable option for patients who are willing to quit smoking.

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