Oral Varenicline for Smoking Cessation

Seena L Zierler-Brown and Jeffrey A Kyle

The former US Surgeon General C Everett Koop noted that cigarette use is the single most preventable cause of death in our society (1 of every 5 deaths) and the most important public health issue of our time.\(^1\) In 2004, an estimated 22.5% of adults (46 million Americans) were cigarette smokers, with the highest prevalence among Native Americans and Alaska natives (40.8%), followed by whites (23.6%).\(^1,2\) In 2000, an estimated 4.83 million premature deaths occurred worldwide due to tobacco use.\(^2-4\) Public health advocates continue to work toward identifying effective ways to prevent the onset of tobacco use and help people to quit using tobacco due to nicotine dependence. Although smokers may succeed in quitting on their own, this usually requires several attempts to achieve abstinence from tobacco.\(^5\)

Progress in understanding the pharmacologic nature of tobacco addiction, along with the modest success rates achieved by the nicotine replacement therapies, has provided the major impetus for the development of novel agents to enhance success rates and synergy between therapies. Varenicline, approved by the Food and Drug Administration (FDA) on May 11, 2006, is a novel agent that has the potential to increase the efficiency of the quit–relapse cycle and aid smokers to achieve lasting smoking cessation much sooner.

The use of pharmacotherapy by smokers, in conjunction with behavioral modification, can produce long-term abstinence at up to double the rate achieved by smokers without pharmacotherapy. Pharmacotherapies approved by the FDA for treatment of smoking dependence include nicotine replacement therapies (eg, gum, lozenges, nasal spray, inhaler,
transdermal), antidepressants (eg, bupropion), and anxiolytic
drugs (eg, clonidine, nortriptyline, mecamylamine), although
anxiolytics have been used as second-line agents.5-10

This article reviews evidence from controlled trials of
varenclines effect on smoking cessation attempts. Clinici-
cians should also incorporate motivational interventions
during a quit attempt, utilizing the 5 A’s, as described in
the Treating Tobacco Use and Dependence guide from the
Agency for Healthcare Research and Quality (Table 1).6

Data Sources

A MEDLINE search (2001–December 2006) was con-
ducted for clinical trials published in English and limited to
human subjects, using the key words varencline and nicot-
tine replacement therapy. Clinical trials evaluating the
safety and efficacy of varencline were selected. Data on
varencline recently published by the manufacturer were
also included. Studies evaluating drug interactions or ad-
verse effects of varencline were evaluated, as well as clinical
trials investigating drug-to-drug comparison of previously
approved therapy and self-adjusted dose escalation.

Pharmacology

Varencline is a partial agonist selective for the α4β2
nicotinic acetylcholine receptor subtype.9,11-19 This tartrate
salt is highly soluble in water, with a molecular weight of
361.35 Daltons.16

With tobacco use, a bolus of nicotine activates the dopa-
mine reward pathway leading to pleasurable and de-
pendence activities through arousal, appetite suppression, cog-
nitive enhancement, and reduction in anxiety and tension.14,16,19,20 The transient activation of the reward pathway
is succeeded by a gradual decline in nicotine levels, lead-
ing to withdrawal. Nicotine replacement therapy delivers
nicotine to the body at various rates, depending on the for-
mulation, and lacks the addictive constituents found in to-
bacco, thereby minimizing the potential for addiction. De-
pendence-producing effects of nicotine are associated with
agonist activity on the neuronal nicotinic acetylcholine re-
ceptor located in the central and peripheral nervous sys-
tems. It has been hypothesized that partial activation will
diminish withdrawal symptoms by enhancing mesolimbic
dopamine levels, which become decreased when a smok-
ing cessation attempt causes an absence of nicotine.14,16,19,20

Pharmacokinetics

Each varencline tablet contains the following inactive
ingredients: microcrystalline cellulose, anhydrous dibasic
calcium phosphate, croscarmellose sodium, colloidal silica-
don dioxide, magnesium state, and Opadry coloring.16 Maximal plasma concentrations are reached within 3–4
hours and, after multiple doses, steady-state concentration
occurs within 4 days. Varencline has a half-life of 24
hours.16,21 Oral bioavailability is not affected by food or time
of administration.16,17 Twice daily administration (after the
first 3 days) is associated with higher quit rates compared
with those of bupropion therapy. Varencline exhibits linear
pharmacokinetics and low plasma protein binding (≤20%),
regardless of a patients age and renal function.15,16,21

Varenclines method of excretion and its metabolites
were analyzed by Obach et al.22 Animals (18 mice, 6 rats,
4 cynomolgus monkeys) and healthy human volunteers (3
smokers, 3 nonsmokers) received oral carbon-14-labeled
varencline. The humans received 1 mg of varencline, and
both blood and urine samples were collected. The findings
showed that 92% of varencline was excreted unchanged in
the urine.

Pharmacokinetic parameters of varencline in regard to
glomerular filtration are shown in Table 2.16 Pharmacoki-
netic studies in the elderly demonstrated activity similar to
that observed in young adults.15 Safety and efficacy have
not been established in the pediatric population (<18 y of
age).16 Dosage adjustments are not required in patients
with hepatic insufficiency.16,17 Drug–drug interactions have
been evaluated, with no clinically significant findings
shown with varenicine or co-inhibitors of the human or-
ganic cation transporter, which mediates renal secretion of
varencline. Substrates such as warfarin, digoxin, cimeti-
dine, metformin, bupropion, and transdermal nicotine do
not alter pharmacokinetic parameters when coadministered
with varencline. In vitro studies do not demonstrate a cy-

<table>
<thead>
<tr>
<th>Table 1. The 5 A’s of Motivational Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention</strong></td>
</tr>
<tr>
<td>Ask about tobacco use</td>
</tr>
<tr>
<td>Advise to quit</td>
</tr>
<tr>
<td>Assess willingness to make a quit attempt</td>
</tr>
<tr>
<td>Assist in quit attempt</td>
</tr>
<tr>
<td>Arrange follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Dosage Adjustment for Renal Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal Impairment</strong></td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>C cr ( &gt;50 \text{ to } \leq 80 \text{ mL/min} )</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>C cr ( \geq 80 \text{ mL/min} )</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>C cr ( &lt;30 \text{ mL/min} )</td>
</tr>
<tr>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>C cr</td>
</tr>
</tbody>
</table>
tochrome P450 enzyme effect. Varenicline safety with coadministration of nicotine replacement products has not been established.

No significant differences in dosing have been established in regard to age, race, gender, tobacco use, or concurrent use of other drugs. Preliminary evidence has shown varenicline to be safe in patients with stable cardiac disease; however, evidence is lacking on its use in acutely unstable patients. It should not be used in patients with a recent myocardial infarction (<2 wk).

Clinical Trials

Clinical trials (Table 3) evaluating efficacy have been conducted in more than 3500 chronic smokers. Varenicline was compared with sustained-release (SR) bupropion SR and placebo in 2 trials (N = 2052). Data synthesized reflected the incidence of abstinence, adverse event rate, and tolerability. Varenicline 1 mg twice daily for 12 weeks was superior to bupropion SR and placebo. An additional 12 weeks of therapy with varenicline increased long-term abstinence outcomes compared with placebo.

A short-term, placebo-controlled pharmacokinetic study of 22 patients evaluated concurrent administration of varenicline 1 mg twice daily with transdermal nicotine 21 mg/day over 12 days. Increased incidence of adverse events was evident with combination therapy (nausea, headache, vomiting, dizziness, dyspepsia, fatigue). Thirty-six percent (n = 8) of the patients discontinued combination therapy due to adverse events versus 6% (n = 1) of patients who received nicotine replacement therapy and placebo. There was no effect on varenicline’s pharmacokinetics.

Adverse Effects

Since varenicline has a ceiling effect of agonist activity, it confers a lower risk of nicotine-related adverse effects compared with current forms of pharmacotherapy, with the exception of bupropion. Nausea incidence was mild: 2.3–2.6%, 1.4% in an open-label trial, and 0.2% during a double-blind maintenance phase of a trial. Overall nausea was dose-dependent and was reported in 30% of all patients treated with varenicline 1 mg twice daily and, to a lesser extent (16%), in those who received 0.5 mg twice daily. Treatment discontinuation due to nausea occurred in 3% of subjects beyond 12 weeks of therapy.

The nicotinic subtype that is related to reinforcing effects of nicotine is the α₄β₂ subtype. It is believed that a compound that binds with a high degree of specificity or greater affinity will confer higher safety and efficacy. Additional recurring adverse events associated with varenicline consisted of insomnia (18%; early awakening), headache (15%), and abnormal dreams (13%). Minor adverse events consisted of constipation, flatulence, headache, and vomiting.

Precautions and Contraindications

Nausea was the most common adverse event associated with varenicline use. A dose reduction should be considered in patients with intolerable nausea.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Sample (N)</th>
<th>Treatment</th>
<th>CAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jorenby (2006)⁵⁵</td>
<td>double-blind, comparative; 12 wk treatment, 52 wk posttreatment</td>
<td>1027</td>
<td>varenicline 2 mg/day</td>
<td>weeks 9–12</td>
</tr>
<tr>
<td>Gonzales (2006)⁵⁶</td>
<td>bupropion SR 150 mg bid placebo</td>
<td>1025</td>
<td>varenicline 44%</td>
<td>weeks 9–24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>bupropion SR 30%</td>
<td>(OR 3.85; 95% CI 1.38 to 2.89; p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo 17%</td>
<td>weeks 9–24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>varenicline 29%</td>
<td>(OR 3.85; 95% CI 2.42 to 5.60; p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>bupropion SR 21%</td>
<td>weeks 9–24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo 11%</td>
<td>(OR 3.09; 95% CI 0.99 to 2.17; p = 0.057)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>varenicline 22%</td>
<td>weeks 13–24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>bupropion 16%</td>
<td>(OR 2.48; 95% CI 1.95 to 3.16; p &lt; 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo 8%</td>
<td>weeks 13–52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>varenicline 70%</td>
<td>(OR 1.34; 95% CI 1.06 to 1.69; p = 0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo 50.0%</td>
<td></td>
</tr>
<tr>
<td>Tonstad (2006)⁵⁷</td>
<td>long-term abstinence, open-label, additional 12 wk, wk 13–52: posttreatment, double-blind phase</td>
<td>1927</td>
<td>varenicline 1 mg bid placebo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>placebo</td>
<td></td>
</tr>
</tbody>
</table>

CAR = continuous abstinence rate; SR = sustained-release.
The Annals of Pharmacotherapy

Varenicline has been established as a pregnancy category C drug. No studies have been conducted to investigate whether varenicline is excreted in human milk; thus, it is recommended to be avoided in lactating women. Teratogenicity is unknown.

Drug Interactions

No clinically significant drug interactions with varenicline have been discovered to date. That said, the abstinence from tobacco and resulting withdrawal of nicotine’s influence on drug metabolism may result in alterations in the pharmacokinetics and pharmacodynamics of medications such as theophylline, tacrine, warfarin, and oral contraceptives. Dosage adjustments may be warranted for these medications.

Dosage and Administration

Varenicline is supplied orally in 2 strengths: 0.5 mg (a white tablet containing 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline base) and 1.0 mg (a blue tablet containing 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline base).

Varenicline treatment should be initiated one week prior to a quit attempt or stop date. The titration schedule consists of a one week lead-in phase followed by a dose of 1 mg twice daily after eating and a full glass of water to reduce associated nausea. The gradual increase in titration is recommended to limit the occurrence of nausea.

A 12 week course of treatment is recommended, with an additional 12 weeks included to ensure long-term abstinence. Successive attempts are recommended for those who relapse or fail therapy. The titration schedule is as follows: days 1–3, 0.5 mg daily; days 4–7, 0.5 mg twice daily; and, starting on day 8, 1.0 mg twice daily. A maximum dosage of 0.5 mg daily is recommended for patients undergoing hemodialysis for end-stage renal disease.

Varenicline is packaged in an initial package of one blister pack (0.5 mg, with 11 tablets in each pack) and 3 blister packs (1 mg, with 14 tablets in each pack). Refills are provided as 4 blister packs (1 mg with 14 tablets in each pack). Alternatively, bottles of 56 tablets are available for both strengths. Tablets should be stored at room temperature (25 °C), with an acceptable range of 15–30 °C.

Cost

The initial month’s blister pack is estimated to cost $100, while refills of the blister packs are to range between $90 and $100. Total cost associated with a 12 week course of therapy is estimated to be $300. Patients are encouraged, at no additional cost, to enroll in a behavioral modification program known as the GETQUIT support plan. This program was developed by Pfizer, with input from smoking cessation experts, and focuses on using the principles of behavior modification to help educate patients about managing cravings and behavioral triggers. The program includes a “Habit Changer” to identify and address the patient’s personal triggers to smoke and daily diaries that help track the patient’s progress.

Summary

Varenicline has the potential to be highly effective since it targets the area of the brain most affected by nicotine and withdrawal symptoms. To improve smoking cessation, slow-release nicotine delivery can be combined with rapid or intermediate-release nicotine delivery. The combination of a nicotine patch, which may prevent the appearance of severe withdrawal, and an inhaler or gum, which may provide relief from urges or triggers, can result in an excellent treatment option over either therapy alone.

The literature reviewed here suggests that varenicline shows efficacy comparable to that of bupropion SR and superior to that of placebo. This agent is only approved for individuals above the age of 18 and should not be used in pregnant or lactating women. Varenicline may be prescribed for patients who have a contraindication to bupropion (eg, already on selective serotonin-reuptake inhibitors, seizure disorder, eating disorder). Safety and efficacy of varenicline in combination with other smoking cessation therapies has not been well studied. Preliminary kinetic data involving combination therapy with the transdermal patch illustrate an increased incidence of adverse events. Varenicline has FDA approval as monotherapy, with further studies needed evaluating combination therapy in the future.

References

Varenclina para la cesación del tabaquismo

OBJETIVO: Repasar la farmacología, la farmacocinética, la eficacia, y la seguridad de varenclina y proveer una revisión de los datos clínicos relevantes.


Selección de fuentes y método de extracción de información: Todas las pruebas clínicas disponibles de varenclina en humanos fueron seleccionadas para revisión. Las referencias de los artículos identificados fueron utilizadas para obtener citas adicionales.

SÍNTESIS: Varenclina selectivamente tiene como objetivo a los receptores nicotínicos α4β2 en el cerebro que son responsables por el deseo y la abstinencia asociados con el uso y la dependencia de nicotina. Las concentraciones máximas en plasma se alcanzan dentro de 3 a 4 horas y, después de dosis múltiples, se alcanza una concentración en estado estable dentro de 4 días. Varenclina tiene una vida media de 24 horas y su biodisponibilidad oral no se afecta por los alimentos o por el tiempo de administración. Este fármaco presenta una farmacocinética lineal y un bajo enlace a las proteínas del plasma (≤20 %) independiente de la edad y del estado renal; puede ser administrado una vez al día. No se requiere un ajuste en las dosis de pacientes con insuficiencia hepática pero en insuficiencia renal severa puede que los ajustes sean necesarios. Las interacciones entre fármacos han sido evaluadas sin obtener hallazgos clínicamente significativos al compararse con el transportador del catión orgánico humano, que media la secreción renal de varenclina. Substratos como la warfarina, la digoxina, la metformina, el bupropion, y la nicotina transdérmica no alterarán los parámetros farmacocinéticos cuando se co-administren con varenclina. Los estudios in vitro no demuestran una inclinación por la enzima P450. La seguridad de varenclina con la co-administración del reemplazo de nicotina no ha sido bien establecida.

CONCLUSIONES: Varenclina es un agente oral efectivo para dejar de fumar.

Brenda R Morand

RÉSUMÉ

OBJECTIF: Revoir la pharmacologie, la cinétique, l’efficacité, et l’innocuité de la varénicline et évaluer les données cliniques.


SÉLECTION DES ÉTUDES ET EXTRACTION DES DONNÉES: Tous les essais cliniques réalisés chez les humains ont été sélectionnés. Les références ont été revues pour identifier des références additionnelles.

SYNTHÈSE DES DONNÉES: La varénicline est sélective pour les récepteurs à la nicotine α4β2 situés dans le cerveau et responsable pour les symptômes de dépendance et de sevrage. Les concentrations plasmatiques maximales sont atteintes 3–4 heures suivant l’administration et après plusieurs doses, l’état d’équilibre est atteint après environ 4 jours. Le temps de demi-vie est de 24 heures. La biodisponibilité n’est pas affectée par la nourriture ou par le moment de l’administration. La cinétique est linéaire et la liaison aux protéines plasmatique est faible (≤20%) indépendamment de l’âge et de la fonction rénale. Elle peut être administrée une fois par jour. Les ajustements de la dose ne sont pas requis chez les patients présentant une insuffisance hépatique, mais peut être nécessaire chez ceux présentant une insuffisance rénale sévère. Les interactions médicamenteuses ont été évaluées sans aucun effet clinique significatif rapporté lorsque comparé avec le transporteur rénal cationique qui contrôle la sécrétion dans le rein. Les substrats tels que la warfarine, la digoxine, la metformine, le bupropion, et la nicotine par voie transdermique ne modifient pas les paramètres pharmacocinétiques lorsqu’ils sont administrés avec la varénicline. Les études in-vitro ne suggèrent pas d’effet au niveau du cytochrome P450. L’innocuité de la varénicline lorsqu’administrée avec la nicotine n’a pas été bien établie.

CONCLUSION: La varénicline est un médicament administré par voie orale efficace pour aider à cesser le tabac.