Varenicline: For smoking cessation

Rao J1, Shankar PK2
1Department of Pharmacology, Melaka Manipal Medical College, Manipal, India, 2Associate Professor, American University of Antigua, College of Medicine, Antigua

Abstract
Varenicline, a partial agonist of α4β2 nicotinic acetylcholine receptor (nAChR), is the most recently approved drug for smoking cessation. Despite the availability of effective treatments for smoking cessation, such as nicotine replacement therapy and Bupropion sustained-release, abstinence rates remain less than optimal. As a nAChR partial agonist, Varenicline attenuates the craving and withdrawal symptoms that occur with abstinence from nicotine and also reduces the rewarding effects of nicotine obtained from smoking in patients who lapse. Clinical trials have demonstrated superior efficacy of this drug over Bupropion-SR for achieving abstinence from smoking, and Varenicline has also been shown to significantly delay smoking relapse. As the latest agent approved for smoking cessation, the mechanism of action, efficacy, and safety of Varenicline has been reviewed in this paper.

Key words: α4β2 nicotinic acetylcholine receptor, Varenicline, smoking cessation, partial agonist.

Smoking is the main preventable cause of morbidity and premature death worldwide1. Approximately 50% of long-term cigarette smokers die prematurely from the adverse effects of smoking, including cancer, cardiovascular disease, lung disease, or other illness2. Given the multitude of health benefits of smoking cessation, considerable effort has been focused on identifying mechanisms to assist smokers in quitting. However, smoking cessation is challenging and behavioral interventions have had only modest success3. Drug therapy has been increasingly relied upon to assist in smoking cessation. The most common of these has been nicotine replacement therapy4 and anti-depressant therapy specifically the agent bupropion3. New trials have demonstrated the effectiveness of a new agent Varenicline, with a novel mechanism of action, in improving cessation rates.

Chemistry
Varenicline is a partial agonist selective for α4 β 2 nicotinic acetylcholine receptor (nAChR) developed by Pfizer under the trade name Chantix™ approved by FDA in 2006 for smoking cessation5. Varenicline, is available as a tartrate salt, with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6H-pyrazino[2,3-h] [3]benzazepine, (2R,3R)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons.

Mechanism of action: Varenicline is a novel selective nAChR partial agonist that binds specifically to the α4β2 nAChR5. Being a partial agonist, varenicline partially activates this receptor with sufficient pharmacologic efficacy so as to minimize craving and withdrawal symptoms in abstinent subjects. It blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking6,7.

Pharmacokinetics: Varenicline is completely absorbed after oral administration, with high (>90%) systemic availability based on recovery of unchanged drug in urine7. Following administration of multiple oral doses of varenicline, steady-state conditions is reached within four days8. Oral bioavailability is unaffected by food or time-of-day dosing. Plasma protein binding of varenicline is low (<20%) and independent of both age and renal function. Maximum plasma concentration of varenicline typically occurs within three to four hours after oral administration. The elimination half-life of varenicline is approximately 24 hours7. Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion possibly via the organic cation transporter, OCT29.
In phase 2 studies, varenicline has been shown to be effective and well tolerated in smokers aged up to 65 years\textsuperscript{10}. With single-dose oral administration of Varenicline, smokers and nonsmokers tolerated up to 3 and 1 mg, respectively; nausea and vomiting were the dose-limiting effects. With multiple-dose oral administration, 2 mg/d was the maximum tolerated dose in smokers. Varenicline exhibits linear kinetics when given as single or repeated doses up to 3 mg/d in smokers\textsuperscript{8, 10}.

Clinical studies

The efficacy of Varenicline in smoking cessation was demonstrated in six phase three clinical trials in which a total of 3659 chronic cigarette smokers (\geq10 cigarettes per day) were treated with Varenicline. In all clinical studies, abstinence from smoking was determined by patient self-report and verified by measurement of exhaled carbon monoxide (CO<10 ppm) at weekly visits.

Five clinical trials which compared Varenicline to placebo for smoking cessation found statistically significant results in favor of the intervention at all the selected endpoints\textsuperscript{11,12,13,14,15}. Twelve weeks treatment with Varenicline was associated with significantly higher continuous abstinence rates at weeks 9-12 than placebo or bupropion sustained-release\textsuperscript{11}. In the longer term treatment studies for 52 weeks, the odds of remaining abstinent were 2.7 to 3.1 times higher with Varenicline treatment than with placebo\textsuperscript{11}. One additional trial found that extended use of varenicline effectively reduced relapse to smoking\textsuperscript{14}.

Three of the varenicline trials compared the Varenicline with Bupropion. The pooled odds ratio for the three trials at 12 months was 1.66 (95%CI 1.28 to 2.16; \textit{comparison} 02.01) with a significantly higher one year abstinence rates than bupropion, which was in turn significantly better than placebo\textsuperscript{11,12,14}. Based on responses to the Brief Questionnaire of Smoking Urges and the Minnesota Nicotine Withdrawal scale “Urge to Smoke” item, Varenicline reduced urge to smoke compared to placebo in all the studies.

Use and recommended dosage

Varenicline is the first non-nicotine-containing medication developed with the sole purpose of treating nicotine addiction. It was approved as a prescription-only aid to smoking cessation in 2006 by the American Food and Drug Administration under the trade name Chantix, and by the European Medicines Evaluation Agency under the trade name Champix. The recommended dose of Varenicline is 1 mg twice daily following a one week titration as follows:

<table>
<thead>
<tr>
<th>Days</th>
<th>Dose</th>
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<tbody>
<tr>
<td>1 – 3</td>
<td>0.5 mg once daily</td>
</tr>
<tr>
<td>4 – 7</td>
<td>0.5 mg twice daily</td>
</tr>
<tr>
<td>8 – End</td>
<td>1 mg twice daily</td>
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Adverse effects

The main adverse effect of varenicline was nausea, headache, vomiting, flatulence, insomnia, abnormal dreams, and dysgeusia which was generally mild to moderate, diminished over time, and was associated with low discontinuation rates\textsuperscript{11, 15}.

Drug-Drug Interactions: Drug interaction studies were performed with Varenicline and Digoxin, Warfarin, transdermal nicotine, Bupropion, Cimetidine and Metformin. No clinically meaningful pharmacokinetic drug interactions have been identified\textsuperscript{5, 6, 7}.

Advantages and disadvantages: The evidence from trials conducted so far suggests that Varenicline increases the probability of successful smoking cessation. Varenicline was reported to reduce craving compared with placebo and demonstrated greater efficacy than Bupropion in craving reduction\textsuperscript{6,7}. Varenicline also achieved significant reductions compared to placebo in urge to smoke, negative affects, smoking satisfaction, psychological reward, and enjoyment of respiratory tract sensations\textsuperscript{12, 14}.

Future: Trials comparing the long-term success of extended treatment with standard 12-week treatment are needed. Direct comparisons with nicotine replacement therapy and further comparisons with Bupropion would establish Varenicline relative effectiveness and safety. Further trials over longer follow up periods are needed to determine whether extended treatment leads to higher long term cessation rates.

In contrast to a nicotine replacement therapy or an antidepressant, Varenicline designed to selectively target the alpha 4-beta 2 nicotinic receptors in the brain and thereby to reduce craving and the related withdrawal symptoms of quitting and block rewards from smoking makes it a promising treatment option for smoking cessation.

Conclusion

Effective treatment of nicotine addiction is essential for reducing the predicted morbidity and mortality associated with tobacco smoking. Varenicline a novel nAChR partial agonist is efficacious for treatment of tobacco dependence. The phase 3 clinical trials with this agent suggest that it is more efficacious than Bupropion, the only other non nicotine medication approved for tobacco dependence. The safety profile of this agent is excellent with the most common adverse
event being mild nausea. Varenicline adds significantly to the armamentarium of treatment options and should be considered for smokers who are motivated to quit smoking.

References


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