Kathmandu University Medical Journal (2009), Vol. 7, No. 2, Issue 26, 162-164

Review Article

Varenicline: For smoking cessation

Rao J[1], Shankar PK[2]

[1]Department of Pharmacology, Melaka Manipal Medical College, Manipal, India, [2]Associate 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 worldwide[1]. Approximately 50% of long-term cigarette smokers die prematurely from the adverse effects of smoking, including cancer, cardiovascular disease, lung disease, or other illness[2]. 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 success[3]. Drug therapy has been increasingly relied upon to assist in smoking cessation. The most common of these has been nicotine replacement therapy[4] and anti-depressant therapy specifically the agent bupropion[3]. 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 cessation[5]. Varenicline, is available as a tartrate salt, with the following chemical name: 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3- h] [3]benzazepine, (2*R*,3*R*)-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 nAChR[5]. 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 smoking[6,7].

Pharmacokinetics: Varenicline is completely absorbed after oral administration, with high (>90%) systemic availability based on recovery of unchanged drug in urine[7]. Following administration of multiple oral doses of varenicline, steady-state conditions is reached within four days[8]. 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 hours[7]. 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, OCT2[9].

Correspondence
Dr. Pinakini K Shankar
Associate professor, Department of Pharmacology
American University of Antigua
College of Medicine, Antigua
E-mail: pinakinikshankar@yahoo.co.in

In phase 2 studies, varenicline has been shown to be effective and well tolerated in smokers aged up to 65 years[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[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 (≥10 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[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[13]. 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[7]. One additional trial found that extended use of varenicline effectively reduced relapse to smoking[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; *comparison 02.01*) with a significantly higher one year abstinence rates than bupropion, which was in turn significantly better than placebo[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:

Days 1 – 3: 0.5 mg once daily
Days 4 – 7: 0.5 mg twice daily
Day 8 – End of treatment: 1 mg twice daily

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[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[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[6,7]. Varenicline also achieved significant reductions compared to placebo in urge to smoke, negative affect, smoking satisfaction, psychological reward, and enjoyment of respiratory tract sensations[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 is 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

1. Fiore MC, Croyle RT, Curry SJ, Cutler CM, Davis RM, Gordon C, et al. Preventing 3 million deaths and helping 5 million smokers quit: a national action plan for tobacco cessation. American Journal of Public Health. 2004; 94(2):205–10.
2. Henningfield JE, Fant RV, Buchhalter AR, Stitzer ML. CA Pharmacotherapy for nicotine dependence. Cancer J Clin. 2005; 55(5):281-99.
3. Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: A systematic review and meta-analysis. BMC Public Health. 2006;11(6):300-6.
4. Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2004:CD000146.
5. Mihalak KB, Carroll FI, Luetje CW. Varenicline is a partial agonist at alpha4beta2 and a full agonist at alpha7 neuronal nicotinic receptors. Mol Pharmacol. 2006; 70(3):801-5.
6. Tonstad S. Varenicline for smoking cessation. Expert Rev Neurother. 2007; 7(2):121-7.
7. Keating GM, Siddiqui MA. Varenicline: a review of its use as an aid to smoking cessation therapy. CNS Drugs. 2006; 20(11):945-60.
8. Burstein HA, Fullerton T, Clark JD, and Faessel HM. Pharmacokinetics, Safety, and Tolerability After Single and Multiple Oral Doses of Varenicline in Elderly Smokers. J of Clinic Pharmacol. 2006; 46:1234-40.
9. Orbach RS, Reed-Hagen AE, Krueger SS, et al. Metabolism and disposition of varenicline, a selective α4β2 acetylcholine receptor partial agonist, in vivo and in vitro. Drug Metab Dispos. 2006; 34:121-30.
10. Faessel HM, Gibbs MA, Clark DJ, Rohrbacher K, Stolar M, Burstein AH. Multiple-dose pharmacokinetics of the selective nicotinic receptor partial agonist, varenicline, in healthy smokers. J Clin Pharmacol. 2006 Dec;46(12):1439-48.
11. Oncken C, Gonzales D, Nides M, Rennard S, Watsky E, Billing CB, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. Arch Intern Med. 2006;166:1571-7.
12. Gonzales D, Rennard SI, Nides M, Oncken C, Azoulay S, Billing CB, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:47-51.
13. Jorenby DE, Hays JT, Rigotti NA, Azoulay S, Watsky EJ, Williams KE, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:56-63.
14. Tonstad S, Tonnesen P, Hajek P, Williams KE, Billing CB, Reeves KR. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006; 296:64-71.
15. Nides MCO, Gonzales D, Rennard SI, Watsky EJ, Anziano R, et al. Smoking cessation with varenicline, a selective alpha4beta2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion controlled trial with 1-year follow-up. Arch Intern Med 2006; 166:1561-8.