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REVIEW ARTICLE

Varenicline: A Helping Hand for Smokers to Quit Smoking

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Introduction

Tobacco smoking is one of the leading causes of preventable diseases and deaths worldwide and accounts for 8.8% of global deaths every year [1]. Various disease conditions have also been linked with cigarette smoking, including cardiovascular disease, chronic obstructive pulmonary disease, many cancers (lung, mouth, oesophageal, bladder, pancreatic, gastric, cervical, and others) and pregnancy-related complications [2]. Smoking cessation confers major health benefits for men and women of all ages.

The basis of effective pharmacotherapy for nicotine addiction is to mimic or replace the effects of nicotine. Different classes of drugs for tobacco dependence include nicotinic receptor agonists and dopaminergic-noradrenergic reuptake inhibitors such as bupropion [3].

Compounds that act as nicotinic alpha-4-beta-2 acetylcholine receptors ($\alpha 4\beta 2$ nAChR) partial agonists and simultaneously block the action of nicotine [4],[5] offer a particularly promising new approach to helping smokers quit. Varenicline is a new oral smoking-cessation medication, which has this property and was approved for use on 10 May 2006. Varenicline (6,7,8,9-tetrahydro-6,10-methano-6H-pyrazino[2,3-h][3]benzazaprine) is a partial agonist of the nicotinic alpha-4-beta-2 acetylcholine receptors (nAChRs).

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Chemistry

Mechanism of Action

Varenicline is a partial agonist that binds to $\alpha 4\beta 2$ nAChR with a greater affinity than nicotine. These specific nAChRs are postulated to be responsible for increased dopamine release when activated by nicotine, leading to dependence on the nucleus accumbens and prefrontal cortex of brain. During smoking cessation, due to nicotine abstinence, dopamine levels become low, which is associated with the cravings that often lead patients to relapse. Varenicline blocks nicotine from binding and stimulates receptor-mediated activity and thus release of dopamine, but to a lesser degree than nicotine.

These nicotinic receptor partial agonists' action provides a low-to-moderate level of dopamine stimulation to reduce craving and withdrawal symptoms, and the lower level of dopamine release may be less dependence forming than the intermittent spikes in dopamine release by inhaled nicotine [4].

Pharmacokinetics

Varenicline is rapidly absorbed across the gastric mucosa, reaching a peak plasma concentration in about 4 hours. With daily dosing, plasma concentrations reach a steady state after 4 days. Varenicline has a half-life of 17–24 hours; it is minimally metabolised and is excreted virtually unchanged by the kidneys (92%). The two minor metabolites are varenicline N-cabamoyl glucuronide and 2-hydroxyvarenicline, which account for 3% and 4%, respectively. Pharmacokinetic profiles in both smokers and non-smokers do not differ [6].

Clinical Studies

The effect of varenicline was demonstrated in various studies. A phase 2 multi-centred, randomised, double-blind, placebo-controlled study was conducted to evaluate the efficacy and safety of three varenicline doses compared with sustained-release (SR) bupropion for a period of 7 weeks. Subjects were randomised to receive 0.3 mg of varenicline daily ($n = 127$) and 1.0 mg of varenicline daily ($n = 128$), 1.0 mg of varenicline twice daily ($n = 127$) for 6 weeks plus placebo for 1 week, 150 mg of SR bupropion twice daily for 6 weeks plus placebo for 1 week, or placebo. The continuous quit rates (CQR) were significantly higher for the 1.0 mg of varenicline-daily group (37.3%) and 1.0 mg of varenicline-twice-daily group (48.0%), compared with both placebo (17.1%) and bupropion (33.3%). Varenicline 1.0 mg was also reported to significantly reduce both craving and smoking satisfaction versus placebo. During this trial, discontinuation rates for varenicline were 11.2–14.3% compared with 15.9% for bupropion and 9.8% for placebo [7].

Other published studies include two randomised, double-blind, placebo-controlled trials, which were identically designed and compared the continuous smoking-cessation rates of varenicline 1 mg twice daily, with bupropion SR 150 mg twice daily and with placebo. At 12 weeks, in both the studies, continuous smoking-cessation rates were about 18% with placebo, 30% with bupropion SR, and 44% with varenicline, which was statistically significant across the groups. Continuous smoking-cessation rates after 9 months in both the studies were observed to be 8% and 10% with placebo, 15% and 16% with bupropion SR, and 22% and 23% with varenicline [8],[9].

Another trial evaluated whether an additional 12 weeks of treatment with varenicline was beneficial for those who had stopped smoking during the first 12 weeks of treatment. A total of 1928 subjects initially received open-label varenicline 1 mg twice daily. At 12 weeks, those who responded and had not smoked for at least 7 days (63%) were randomised to continue varenicline or switch to placebo. Continuous smoking-cessation rates were significantly better with varenicline than with placebo at the end of the second 12 weeks of treatment (71% vs. 50%) and remained better from weeks 13–52 (44% vs. 37%) [10].

Adverse Effects

Varenicline has been demonstrated to be safe and well tolerated in clinical studies. Most frequent adverse effect of varenicline in clinical trials was dose-dependent nausea, which was mild to moderate in severity and became less severe with continued use of the drug. Other observed adverse effects include insomnia, headache, abnormal dreams, changes in taste, irritability, dyspepsia, flatulence, constipation, respiratory tract infection, and asthenia [11].

Drug Interactions

Varenicline has negligible effects on the cytochrome P450 system. The H₂ antagonist cimetidine, which decreases the renal clearance of varenicline, increased its serum concentration by 29%.

Precautions

Specific contraindications have not been determined for varenicline therapy. Severe renal impairments may increase the varenicline exposure. Hence, for patients with severe renal impairment, the recommended starting dose is 0.5 mg orally once daily to a maximum daily dose of 0.5 mg twice daily. Smoking cessation may alter the pharmacokinetics or pharmacodynamics of some drugs including theophylline, warfarin, and insulin. In case of intolerable nausea with the drug, dose reduction should be considered [12].

Indication and Dose

Varenicline is indicated as an aid to smoking-cessation treatment. Varenicline therapy should begin 1 week prior to the date set by patients to stop smoking: initially a 1-week titration with 0.5 mg orally once daily on days 1 through 3, then 0.5 mg twice daily on days 4 through 7, and then 1 mg twice daily for 12 weeks (including 1-week titration). In patients who have successfully stopped smoking after 12 weeks, a second 12-week course is recommended to increase possibility of long-term abstinence [11].

Conclusion

Varenicline is a novel smoking-cessation aid approved by the US FDA in 2006, which has a unique mechanism of action compared with the available first-line agents. Studies have demonstrated that varenicline is more effective than bupropion and placebo in CQR and continued abstinence rates up to

1 year. Varenicline has the potential advantage of having fewer nicotine-related side effects. But there are no sufficient data to compare its effects with nicotine replacement therapy.

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