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Newest Agent for Smoking Cessation: Varenicline (Champix®)

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Introduction

In 2005, an estimated 5.9 million Canadians, or 22% of the population over the age of 12, were smokers.¹ This is somewhat lower than the world's adult population which is estimated at 33%.² Tobacco is the leading cause of preventable disease, disability, and mortality accounting for more than 47,500 deaths per year in Canada.³ The Canadian Centre on Substance Abuse (CCSA) estimates that the direct and indirect costs of smoking in 2002 totaled 17 billion dollars nationally.⁴ Tobacco use is associated with causing multiple cancers, heart disease, stroke, chronic obstructive pulmonary disease, and complications of pregnancy.⁵

First line options for smoking cessation available have been extended release bupropion and nicotine replacement therapy (NRT) with gum, lozenges or patch.

Varenicline, the newest agent to be marketed for smoking cessation, is derived from cytisine, an alkaloid found in the golden rain tree (*Cystus laburnum* L.) The leaves of the tree were used in World War II to decrease nicotine craving.⁶ Varenicline is a partial agonist of the alpha-4, beta-2 acetylcholine receptor type.⁷

Pharmacology of Nicotine Addiction

When nicotine is inhaled through the lungs, it is estimated to reach the brain within 11 seconds.⁸ The degree of pleasure experienced during smoking has been correlated with dopamine release.⁹ It is

these effects on dopamine and the quick onset of action that explain its addictive qualities. Nicotine stimulates acetylcholine receptors that are connected to dopamine containing neurons. This stimulation causes an overflow of dopamine and increased firing of dopaminergic neurons in the reward center of the brain.¹⁰ There are several acetylcholine receptor subtypes, but it is the alpha-4 beta-2 subtype that is thought to be the principal mediator of nicotine addiction.^{11,12} Acetylcholine is degraded quickly but nicotine remains active for a prolonged period of time. Prolonged nicotine stimulation causes acetylcholine receptors to desensitize, which means it causes up-regulation of receptors. It is this desensitization that is thought to be the underlying cause of physical dependence, tolerance, and withdrawal symptoms, which all add to the propensity for nicotine addiction.¹²

Pharmacology of Varenicline

Varenicline selectively binds to the alpha-4 beta-2 receptor with high affinity. It is the first partial agonist of this receptor in its class. It also binds at the serotonin receptor with moderate affinity, which is thought to explain the nausea associated with the agent.⁷

Varenicline, as a partial agonist at the acetylcholine alpha-4 beta-2 receptor, stimulates the release of sufficient dopamine to reduce craving and withdrawal. It also simultaneously acts as a partial antagonist by blocking the binding and reinforcing effects of nicotine. In vitro studies have found that varenicline elicits 68% of the response attained by the binding of nicotine to alpha-4 beta-2 receptors. In vivo studies

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reported the dopamine response to varenicline to be 32-60% of that achieved by nicotine. Varenicline prevents access to the alpha-4 beta-2 receptor by nicotine because it competes with nicotine for the receptor site. Thus, repeated exposure to nicotine stimulation is reduced.¹¹

Pharmacokinetics

Varenicline is completely absorbed orally and the amount absorbed is not affected by food. It reaches steady state within 4 days, has a half-life of approximately 24 hours and exhibits linear kinetics. Protein binding is low at less than 20% and it is not metabolized with 92% excreted unchanged in the urine.

Although moderate to severe renal failure increases the area under the concentration time curve (AUC), it is not thought to be of clinical significance.⁷

Clinical Efficacy

Two multi-centered randomized, placebo-controlled, double-blinded studies involving 1025 and 1027 subjects compared varenicline with sustained release bupropion and placebo. All patients received counseling and all smoked at least 10 cigarettes a day on entry into the studies.^{13, 14} Details of the individual studies have been listed in **Table 1** (see Page 3). The primary end point for both studies was carbon monoxide-confirmed 4-week continuous quit rates (CQRs) during weeks 9 through 12. Continuous abstinence was also measured for both studies during weeks 9 to 52 after all medication had been discontinued.^{13, 14}

In both studies, from weeks 9 through 12, varenicline was significantly more effective in CQRs than both bupropion (44% vs. 29.5%, $p < 0.001$ ¹³, and 43.9% vs. 29.8%, $p < 0.001$ ¹⁴) and placebo (44.0% vs. 17.7%, $p < 0.001$ ¹³, and 43.9% vs. 17.6%, $p < 0.001$ ¹⁴).

However, during the follow-up of weeks 9 to 52 (weeks 13 to 52 were free of medication), the percentage of patients still abstinent from smoking dropped. Varenicline was still significantly more effective in terms of continuous abstinence than bupropion in the study by Jorenby et al, (23% vs. 14.6%, $p = .004$)¹⁴ but not in the Gonzalez's trial (21.9% vs. 16.1%, $p = 0.057$).¹³ Varenicline was significantly more effective than placebo at 52 weeks in both studies.^{13, 14}

Results on the Modified Cigarette Evaluation Questionnaire (mCEQ) indicated that, compared with placebo, varenicline significantly reduced smoking satisfaction, psychological reward, enjoyment of respiratory tract sensations and craving relief after smoking, with moderate effect sizes. Bupropion SR also significantly reduced psychological reward compared with placebo but the effect size was half

that of varenicline.¹³

The third study began with a 12 week-open label study ($n=1927$) followed by another 12 weeks of a double-blind placebo controlled study.¹⁵ In this study patients received 24 weeks of varenicline treatment compared to 12 weeks in the previous studies. During the last week of the open label study 64.1% became abstinent from all nicotine intake, a much higher rate than in the previous two studies. However, abstinence was not confirmed by carbon monoxide testing which likely accounts for the better reported results. The second part of the study followed patients from weeks 13 to 52 and included 98% ($n=1210$) of those considered to be abstinent after the first 12 weeks (which represents 63% of the original cohort of patients) In this case carbon monoxide testing was used for confirmation. At the end of the study 43.6% of the patients on varenicline were still abstinent compared to 36.9% in the placebo group, statistically not significant. The percentage of patients who were abstinent at 52 weeks in this study likely appears higher than the two previous studies^{13, 14} (22.5% varenicline and 15.4% placebo) because it was calculated using only the abstinent patients ($n=1210$) enrolled in the second part of the study and not the initial cohort ($n=1927$).

Safety and Tolerability

Study discontinuation rates due to adverse effects were 8.6% and 10.5% with varenicline, 15.2% and 12.6% for bupropion SR and 9.0% and 7.3% for placebo.^{12, 13} Nausea, which diminished over time, was the most common adverse effect with varenicline (28.1%).

Taking varenicline with food and starting treatment with lower doses decreases nausea. Other common adverse effects with varenicline include insomnia and abnormal dreams. Insomnia was the most common adverse effect with bupropion SR (21.9%), followed by headache and dry mouth.¹³

More recently, the FDA has received reports of drowsiness, suicidal thoughts and aggressive and erratic behavior among patients taking varenicline. Many, but not all, of the cases reflected new onset of depressed mood and some had concomitant alcohol use. The FDA recommends that "patients should get in touch with their doctor if they experience behavior or mood changes."

Drug Interactions

There were no significant drug interactions reported during investigational trials with cimetidine, bupropion, digoxin, transdermal nicotine, metformin and warfarin.⁷ Combining varenicline with other medication that cause nausea and with nicotine replacement

therapies may increase nausea.

Administration and availability

Varenicline (trade name Champix®) was released in April 2007 in Canada by Pfizer and approved for smoking cessation. It is dispensed in a starter pack with 0.5 mg a day for 3 days, 0.5 mg twice a day for 4 days and then 1 mg twice a day as maintenance for 12 weeks in total. A second 12 week treatment phase, for those who stopped smoking, has been used in clinical trials but there is no evidence at this time that a second trial leads to higher abstinence rates by the end of 52 weeks.

Cost Comparison: Riverview Hospital

Medication	Cost
Bupropion SR 150 mg bid	\$22 / 28 days
Champix 1 mg bid	\$95 / 28 days
Nicotine patch 14 & 21 mg	\$71 / 28 days
Nicotine lozenges 4 mg	\$51 for 105
Nicotine gum 4 mg	\$38 for 105
Inhaler	\$23.63/kit

Summary

Varenicline is the second drug after bupropion to be approved for smoking cessation that is not a nicotine replacement agent. Two studies^{13,14} found the continuous abstinence rate for weeks 9 to 24 to

Table 1. Summary of Varenicline Studies

Study	Interventions	Primary Endpoint	Secondary Endpoint
Gonzales 2006 ¹³ N= 1025 R,DB, PC, MCT Duration: 12 weeks treatment phase Follow up 52 weeks (optional)	VAR 0.5 mg od x 3 days, then 0.5 mg bid x 4 days, then 1 mg bid to week 12 vs. Bupropion 150 mg od x 3 days, then 150 mg bid x 12 weeks vs. Placebo	<u>Continuous quit rate (CQR) validated by continuous CO monitoring from 9-12 weeks</u> 44% VAR vs.17.7% placebo (OR 3.85 95% CI 2.7-5.5) 44% VAR vs. 29.5% BSR (OR 2.0 95% CI 1.38-2.89)	<u>CQR from 9-24 weeks</u> 29.5% VAR vs. 10.5% placebo (OR 3.68 95% CI 2.42-5.60) 29.5% VAR vs. 20.7% BSR (OR 1.63 95% CI 1.14-2.33) <u>CQR from 9-52 weeks</u> 21.9% VAR vs. 8.4% placebo (OR 3.09 95% CI 1.95-4.91) 21.9% VAR vs. 16.1% BSR (OR 1.46 95% CI 0.99-2.17)
Jorenby 2006 ¹⁴ N= 1027 R,DB,PC,MCT Duration: 12 weeks treatment phase Follow up 52 weeks (optional)	VAR 1 mg bid x 12 weeks (dose titration over 1 st week) vs. BSR 150 mg bid (dose titration over 1 st week) vs. Placebo	<u>CQR validated by continuous CO monitoring from 9-12 weeks</u> 43.9% VAR vs. 17.6% placebo (OR 3.85 95% CI 2.69-5.50) 43.9% VAR vs. 29.8% BSR (OR 1.9 95% CI 1.38-2.62)	<u>CQR from 9-52 weeks</u> 23% VAR vs. 10.3% placebo (OR 2.66 95% CI 1.72-4.11) 23% VAR vs. 14.6% BSR (OR 1.77 (95% CI 1.19-2.63)
Tonstad 2006 ¹⁵ N= 1928 open label phase Those that had successfully quit for the last 7 days at the end of 12 wks were randomized for active treatment phase (N= 1210)	Open label phase: VAR 0.5 mg od x 3 days, then 0.5 mg bid x 4 days, then 1 mg bid x 11 weeks Double blind phase: VAR 1 mg bid x 12 weeks	<u>CQR validated by continuous CO monitoring from 13-24 weeks</u> 70.5% VAR vs. 49.6% placebo OR 2.48 (95% CI 1.95-3.16).	<u>CQR from 13-52 weeks</u> 43.6% VAR vs. 36.9% placebo OR 1.34 (95% CI 1.06-1.69)

Table completed by Rumi Pattar, Pharm.D. Candidate

CO= Carbon monoxide CQR = continuous quit rate

BSR= Bupropion SR, VAR= varenicline, NRT= nicotine replacement therapy

R, DB, PC, MCT = randomized, double blind, placebo controlled multicentre trial

be significantly better for varenicline than bupropion SR, however, only one¹⁴ of the two studies found that this difference was maintained at 52 weeks. It is well tolerated, not associated with drug interactions, but more expensive than bupropion SR. Varenicline is an effective alternative to NRT, when bupropion is contraindicated, or for those who have failed a trial with bupropion or cannot tolerate bupropion.

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