Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Varenicline for Smoking Cessation

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Context and policy issues:

The prevalence of smoking in Canada continues to drop, according to the 2005 Canadian Tobacco Use Monitoring Survey.[1] In the mid-1960s, about half Canadian adults smoked cigarettes; by 2003, this proportion was 23%; and by 2005, it was 16.5%. Young adult (20 – 34 years) and middle-aged (35 – 44 years) subjects have the highest smoking rate (19.9% and 21%, respectively) of all age groups. Smoking is one of the risk factors of cancer, respiratory and cardiovascular diseases.

The addiction to tobacco is difficult to overcome. However, the chances of success increase with each year of abstinence. According to the National Population Health Survey[1] from 1994/1995 to 2002/2003, approximately 20% of adult daily smokers who had quit in the past two years resumed smoking. The risk of relapse however dropped to 1% after five years or more of abstinence.

Various methods and drugs are available aid in smoking cessation, but their rates of success vary. Varenicline is a new type of medication being used for smoking cessation. It was approved by the FDA in the US in May 2006 and by the European Medicines Evaluation Agency (EMEA) in September 2006. Its trade name in the US is Chantix® and Champrix ® in Europe

Varenicline is a nicotinic acetylcholine receptor partial agonist. It binds to the nicotinic receptor and has a similar effect to that of nicotine in stimulating the release of dopamine, although the effect is weaker, slower and longer lasting. The binding of varenicline to the receptor reduces the binding site availability for nicotine. Thus, varenicline reduces craving when smokers abstain and are deprived of nicotine, and it also results in a weaker response when people take the drug while smoking.

This report provides a summary review of the clinical effectiveness including efficacy and safety of using varenicline for smoking cessation. The sources of evidence were focused on health technology assessment and systematic reviews, guidelines and randomized controlled trials.

Research questions:
What is the clinical effectiveness of using varenicline as a smoking cessation treatment?

Methods:
A literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 2, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI's HTAIS, EuroScan, international HTA agencies, and a focused Internet search. Results include English language publications from 2002 to date.

Summary of findings:
From the limited search, we identified one health technology assessment (in progress), three systematic reviews, three guidelines, and eight randomized controlled trials (RCT) providing evidence on varenicline.

a) Health technology assessments and systematic reviews/meta-analyses

The health technology assessment on varenicline in smoking cessation conducted by NICE[1] is in progress. Its objective is to appraise the clinical and cost effectiveness of varenicline for smoking cessation and to provide guidance to the NHS in England and Wales. The expected date of the issue is July 2007.

In all three systematic reviews,[2-4] varenicline was found superior to placebo in term of continuous abstinence rate at 12 weeks of treatment and up to 1 year of follow-up (Table 1). Varenicline was found comparable or slightly better than bupropione in smoking cessation. The most common adverse event associated with varenicline treatment was nausea, which was dose-dependent. Other adverse events included insomnia, headache, abnormal dreams, constipation, flatulence, and vomiting. Titration of the dosage was suggested to reduce the adverse events.

Table1: Summary table of systematic reviews

Author, year	Objective	Included trials (author, year)	Results		Comments
			Efficacy	Safety	
Zierler-Brown, 2007[2]	To review the pharmacology, pharmacokinetics, efficacy, and safety of varenicline and provide a review of relevant clinical data	Jorenby, 2006[5] Tonstad, 2006[6] Gonsalez, 2006[7]	Varenicline was comparable to bupropion SR and superior to placebo as reflected by the continuous abstinence rate. Jorenby[5], Gonzales[7] At 12 wk treatment, abstinence rate for 44%; for bupropion SR,	Half life: 24 h Dosage adjustments are not required in patients with hepatic insufficiency, but caution should be given to patients with renal insufficiency. Adverse events: nausea (dose-dependent),	Safety and efficacy of varenicline in combination with other smoking cessation treatments has not been well studied.

Author, year	Objective	Included trials (author, year)	Results		Comments
			Efficacy	Safety	
			30%; for placebo, 17% Tonstad[6] At 12 wk posttreatment, abstinence rate for veranicline, 70%; for placebo, 50% A 40 wk posttreatment, abstinence rate for veranicline, 44%; for placebo, 39%	insomnia, headache, abnormal dreams, constipation, flatulence, and vomiting. The drug is only approved for individual above the age of 18 and not for pregnant or lactating women	
Wu, 2006[3]	To assess the relative efficacy of pharmacological interventions (Nicotine Replacement Therapy (NRT), bupropion and varenicline) in smoking cessation	Four trials of varenicline versus placebo, of these three also had varenicline versus bupropion Gonzales, 2006[7] Jorenby, 2006[5] Nides, 2006[8] Oncken, 2006[9]	Cessation effects of varenicline versus placebo: •Short term (OR 3.75, 95% CI, 2.65-5.30) •At 1 year (OR 2.96, 95% CI, 2.12-4.12) Varenicline versus bupropion •At 1 year (OR 1.58, 95% CI, 1.22-2.05) Using indirect comparisons, varenicline was superior to NRT (OR 1.66, 95% CI, 1.17-2.36)	Adverse events (significant): nausea, flatulence, constipation Severe events (not significant): atrial fibrillation, pneumonia, possible stroke, chest pain and high blood pressure	Recommend future studies that examine the effects of combination therapy or therapy targeted to the particular type of symptoms experienced during cessation.
Cahill, 2007[4]	To assess the efficacy and tolerability of nicotine receptor partial agonists, including varenicline and cytosine, for smoking cessation	Gonzales, 2006[7] Jorenby, 2006[5] Nides, 2006[8] Oncken, 2006[9] Tonstad, 2006[6]	Varenicline was superior to placebo Continuous abstinence: •At 12 wk (OR 4.07, 95% CI, 3.28, 5.05) •At 24 wk (OR 3.53, 95% CI, 2.74-4.54) •At 1 year (OR 3.22, 95% CI 2.43-4.27)	Adverse events: nausea (dose dependent), headache	Additional and independent RCTs of varenicline are needed to confirm those early finding s from those industry trials

b) Guidelines

Of the three identified guidelines,[10-12] two[10,11] have recommendations for the use varenicline for smoking cessation based on collective evidence from RCTs (Table 2). These include counseling, dose titration to minimize adverse effects, and follow-up to ensure the success rate of abstinence.

Table 2: Summary table of guidelines

Guideline, year	Source of evidence	Recommendations
ASH Guideline (UK), 2006[10]	Gonzales, 2006[7] Jorenby, 2006[5] Champix SPC, European Medicines Agency (EMEA) http://www.emea.europa.eu/humandocs/Humans/EPAR/champix/champix.htm	1. Prescriptions to patients with psychiatric illnesses should be done with close surveillance and follow-up. 2. Varenicline should be prescribed to patients who receive weekly support from counseling. 3. Patients should be encouraged to report adverse effects. 4. If the patient is not confident at the end of 12 week treatment, an additional course of 12 weeks may be considered. The clinician should make a judgment as to whether the patient will benefit from continue support, bearing in mind that the relapse rates back to smoking are high. 5. Varenicline should be taken with a glass of water to help reduce nausea, and taking the second pill at dinner time rather than bedtime may help reduce insomnia and disturbed dreams.
UMSH smoking Cessation Guideline (US), 2006[11]	Not mentioned	3-A,s and Refer model: **A**sk, **A**dvice, **A**ssess and **R**efer **ASK** all patients about smoking status and assess smoker's readiness to quit **ADVISE** all smokers to seriously consider making a quit attempt using a clear and personalized message **ASSESS** all smokers' willingness to make a quit attempt **REFER** patients interested in quitting withing 30 days to a Tobacco Treatment Specialist or other appropriate tobacco cessation program **Treatment options:** • **ASSIST** those ready to make a quit attempt: – Set a quit date – Give advice on quitting and provide supplement materials – Prescribe appropriate pharmacologic therapy: Nicotine replacement therapies, bupropion, and varenicline • **ARRANGE** follow-up either by phone call or office visit **Pharmacologic therapy with varenicline:** • Starting dose should be 0.5 mg per day for three days, then increasing to twice per day for the next four days, followed by 1 mg twice a day, beginning on the quit day. • According to published studies, total duration of treatment ranged from 12-24 weeks. • Varenicline should not be used in conjunction with NRT products
American College of Physicians Guideline, 2007[12]	Not mentioned	The guideline considers drug treatment modalities for smoking cessation, including nicotine replacement, bupropion, and varenicline. It summarizes key findings from RCTs and systematic reviews for different drug treatment modalities. It also highlights the limitations and adverse effects of treatments. No specific recommendations regarding to varenicline for smoking cessation were found.

c) Randomized controlled trials

Of the RCTs, three are phase 3 clinical trials, one phase 2 clinical trial and two phase 1 clinical trials, conducted by the same research group. All RCTs were sponsored or conducted by Pfizer and their quality was scored high (3 or above) from the quality assessment using the criteria put forth by Jadad et al. (Table 3).

The phase 3 study of Jorenby et al[5] of the Varenicline Study Group determined the efficacy and safety of varenicline for smoking cessation compared with placebo and bupropion. It was sponsored by Pfizer Inc., and had generally healthy participants, who had no indicated chronic diseases or drug abuse. The treatment duration was 12 weeks, with weekly counseling, and followed by 40 weeks no drug follow-up. During both short-term treatment and long-term follow-up, varenicline was superior to both bupropion and placebo reflected by continuous abstinence from smoking. Varenicline and bupropion had higher discontinued rates due to adverse events than placebo. The most common adverse events with varenicline was nausea (29.4%) compared with bupropion (7.4%) and placebo (9.7%). Other adverse events occurred at a rate of 5% or higher in participants receiving varenicline compared with those receiving placebo were constipation, flatulence, dry mouth, dyspepsia, vomiting, insomnia, abnormal dreams, sleep disorder, and anxiety.

The study of Gonzales et al[7] was an identical phase 3 clinical trial as that of Jorenby et al,[5] but at different centers. The results including primary outcomes and adverse effects of both trials were similar.

The study of Tonstad et al[6] was conducted by the Varenicline Phase 3 Study Group.[5,7] The objective was to determine whether smokers who quit after 12 weeks of treatment with varenicline (open-label) maintain greater abstinence rates than placebo during additional 12 weeks of treatment (double-blind) and 40 weeks of non-drug follow-up. The results showed varenicline treatment had a significant greater abstinence rate in weeks 13 to 24 compared with placebo. This advantage was maintained through 40 weeks of non-drug follow-up. Nausea (33.5%) was the most common adverse events during open-label varenicline phase. No difference in adverse events was observed during double-blind period.

The study of Oncken et al[9] was conducted by the Varenicline Study Group, evaluating the efficacy, safety and tolerability of four varenicline dose regimens. Two with progressive dosing over the first week (titrated) and two with a fixed dosing schedule (non-titrated). The continuous abstinence rates were greater in 0.5-mg and 1.0-mg group versus placebo. Reports of nausea, which was a common adverse event associated with varenicline treatment, were lower for titrated versus non-titrated dosing. Numbers of withdrawals due to nausea were also lower in titrated dosing.

The study of Williams et al[13] was conducted by Pfizer Global Research & Development Group assessing the safety of long-term (52 weeks of treatment) varenicline administration for smoking cessation. It was found that varenicline at 1 mg twice daily can be safely administered for up to 1 year. Common varenicline-associated adverse events were nausea, abnormal dreams and insomnia. Other adverse events that were higher in the varenicline group included dyspepsia, constipation, flatulence, vomiting, dysgeusia and dizziness. Weight increase, hypertension and increased appetite rates were slightly higher in varenicline group compared to placebo. No statistical analysis was reported in this study.

In addition, a phase 2 clinical trial by Nides et all[8] was conducted by the Varenicline Study Group and a phase 1 clinical trial conducted by the Pfizer Global Research and Development Group[14] were also identified but are not included in this summary. The objective of the phase 1 clinical trial was to determine the clinical pharmacology of varenicline administered to smokers, while that of the phase 2 clinical trial was to evaluate the efficacy, tolerability and safety of three varenicline doses for smoking cessation.

Table 3: Summary table of RCTs

Author, year	Population	Interventions	Comparators	Outcomes (include adverse events and limitations)	Jadad Score
Jorenby, 2006[5]	Adult smokers, 18 to 75 years, smoked 10 cigarettes or more during previous year, had no period of smoking abstinence longer than 3 months in the past year. Included subjects were free of chronic diseases, had no history of alcohol or drug abuse	1 mg varenicline twice daily (n=344) 12 week treatment Weekly counseling No drug follow-up with 40 weeks	150 mg bupropion twice daily (n=342) Placebo (n=341)	1. Continuous abstinence • Varenicline versus placebo – Weeks 9-12: OR, 3.85; 95% CI, 2.69-5.50 – Weeks 9-24: OR, 2.83; 95% CI, 1.91-4.14 – Weeks 9-52: OR, 2.66; 95% CI, 1.72-4.11 • Varenicline versus bupropion – Weeks 9-12: OR, 1.90; 95% CI, 1.38-2.62 – Weeks 9-24: OR, 1.69; 95% CI, 1.19-2.42 – Weeks 9-52: OR, 1.77; 95% CI, 1.19-2.63 2. Discontinued due to adverse events • Varenicline: 10.5% • Bupropion: 12.6% • Placebo: 7.3% 3. Adverse events with varenicline: nausea, constipation, flatulence, dry mouth, dyspepsia, vomiting, insomnia, abnormal dreams, sleep disorder, anxiety 4. Completion rates • Varenicline: 70% • Bupropion: 65% • Placebo: 60%	4
Gonzales, 2006[7]	Identical designed trial as that of Jorenby, 2006[5] at different centers	1 mg varenicline twice daily (n=352) 12 week treatment Weekly counseling No drug follow-up with 40 weeks	150 mg bupropion twice daily (n=329) Placebo (n=344)	1. Continuous abstinence • Varenicline versus placebo – Weeks 9-12: OR, 3.85; 95% CI, 2.70-5.50 – Weeks 9-52: OR, 3.09; 95% CI, 1.95-4.91 • Varenicline versus bupropion – Weeks 9-12: OR, 1.93; 95% CI, 1.40-2.68 – Weeks 9-52: OR, 1.46; 95% CI, 0.92-2.17 2. Discontinued due to adverse events • Varenicline: 8.6% • Bupropion: 15.2% • Placebo: 9.0% 3. Adverse events with varenicline: nausea, constipation, flatulence, dry mouth, insomnia, abnormal dreams, irritability, sleep disorder, headache 4. Completion rates • Varenicline: 61% • Bupropion: 56% • Placebo: 54%	4
Tonstad, 2006[6]	Participants who had successfully been through	Additional 12 week treatment	Placebo (n=607)	1. Continuous abstinence • Varenicline versus placebo – Weeks 13-24: OR, 2.48; 95% CI, 1.95-3.16	4

Author, year	Population	Interventions	Comparators	Outcomes (include adverse events and limitations)	Jadad Score
	12-weeks open-label treatment with varenicline were randomly assigned to a 12-week, double blind treatment phase	1 mg varenicline twice daily (n=603) No drug follow-up with 40 weeks		– Weeks 13-52: OR, 1.34; 95% CI, 1.06-1.69 2. Adverse events: no difference in adverse events was observed during double-blind period.	
Oncken, 2006[9]	Healthy cigarettes smokers, aged 18 to 65 years	Varenicline: 1. 0.5 mg twice daily for 12 weeks (n=124) 2. 0.5 mg once daily for 7 days, then 0.5 mg twice daily for 11 weeks (n=129) 3. 1 mg twice daily for 12 weeks (n=124) 4. 0.5 mg once daily for 3 days, then 0.5 mg twice daily for 4 days, then 1 mg twice daily for 11 weeks (n=129)	Placebo (2 tablets twice daily for 12 weeks) (n=121)	1. Continuous abstinence • Weeks 9-12 • 0.5-mg group (44.0%) • 1.0-mg group (49.4%) • Placebo (11.6%, p<0.001 vs both doses) • Weeks 9-52 • 0.5-mg group (18.5%) • 1.0-mg group (22.4%) • Placebo (3.9%, p<0.001 vs both doses) 2. Adverse events: nausea incidence was lower for the titrated versus non-titrated dosing and infrequently led to medication discontinuation. Titration appeared to reduce the overall incidence of nausea, but not other adverse events	3
Williams, 2007[13]	Healthy cigarettes smokers, aged 18 to 75 years	1 mg varenicline twice daily (n=251) 52 weeks of treatment	Placebo (n=126)	1. Continuous abstinence at week 52 • Varenicline: 36.7% • Placebo: 7.9% 2. Varenicline-associated adverse events • Nausea (40.2%) • Abnormal dreams (22.7%) • Insomnia (19.1%) 3. Adverse events leading to discontinuation • Nausea (7.6%) • Abnormal dreams (2.4%) • Insomnia (3.2%) 4. Completion rates • Varenicline: 53.8% • Placebo: 46.8% 5. Laboratory values, vital signs, and ECG: comparable between groups 6. Changes in body weight • Varenicline: 2.09 kg • Placebo: 0.67 kg	3

Conclusions and implications for decision or policy making:

Varenicline is a drug specifically developed for smoking cessation. It was recently approved in the US and Europe for a treatment course of 12 weeks, and for extended use for another 12 weeks in smokers achieving abstinence from the first treatment. The results from the current RCTs however lack the external validity, since the sample populations in those studies were healthy smokers, which may not be representative of individuals looking for treatment. The most common adverse effects associated with varenicline treatment are nausea and psychiatric disorders (i.e., abnormal dreams, insomnia). Discontinuation of varenicline was associated with an increase in irritability, urge to smoke, depression or insomnia in up to 3% of patients. Counseling support appears to be crucial for the efficacy of varenicline in smoking cessation. Administration of varenicline to patients with psychiatric illness, to children or adolescent below 18, and to pregnant women has not yet been tested. Drug-drug interactions and the benefit of the use of varenicline in conjunction with other smoking cessation therapy are also not clear. The evidence on the efficacy, safety and tolerability needs to be reconfirmed by trials independent of pharmaceutical industry. Investigation of the long-term effects of varenicline should also be considered.

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