

Areas in **blue** are additional information in the DIR that is not found in a common reference source.

Areas in **grey** are those that provide information in a concise, easy-to-find format.

VARENICLINE

TRADE NAME(S): Champix

CLASSIFICATION: Smoking cessation aid; nicotine receptor partial agonist

ACTION:

Stimulates the receptors that mediate nicotine addiction. Partial agonist at alpha-4-beta-2 nicotinic acetylcholine receptors (nAChR). Nicotine addiction is possibly due to stimulation of alpha-4-beta-2 nAChR in the ventral tegmental (mesolimbic) area of the brain, leading to increased release of dopamine in the nucleus accumbens, as well as receptor desensitization. Upregulation also occurs. When nicotine administration is stopped, the resultant lower level of dopamine in this area of the brain leads to withdrawal symptoms and nicotine cravings.

- Varenicline stimulates alpha-4-beta-2 nAChR more weakly than nicotine, resulting in 30-60% of the maximal nicotine effect on dopamine levels. It can therefore substitute for nicotine while a person is quitting and reduce withdrawal symptoms and cravings. Varenicline is also an antagonist at alpha-4-beta-2 nAChR and partially blocks the effect of any nicotine administered (30-55%). Thus any lapse while trying to stop smoking will not produce the full nicotine effect, avoiding nicotine toxicity while reducing the reward connection between nicotine smoking and smoking behaviour and dopamine release. Theoretically smoking will be less enjoyable. A less potent high affinity partial agonist at alpha-3-beta-four nAChR and a full agonist at alpha-7 nAChR; clinical implications unknown but unlikely to contribute to effects on smoking cessation. Full agonist at 5-HT3 receptors.

- Structural analog to cytisine, an alkaloid found in the weed Cytisus labarnum (false tobacco) that also stimulates nAChR.

PHARMACOKINETICS:

Half-life: 17-31 hours

Absorption: Almost completely absorbed orally. Bioavailability is not altered by administration with food. Peak levels occur after about 4 hours.

Distribution: Low plasma protein binding (less than 20%).

Metabolism: Not metabolized by P450 enzymes. The N-carbamoyl glucuronide and a 2-hydroxy metabolite each account for 3-4% of a drug dose.

Elimination: 92% eliminated in the urine as unchanged drug. Undergoes passive filtration plus active renal secretion by the human organic cation transporter hOCT2. Removed by hemodialysis.

Special populations:

- **Elderly:** In patients over age 65 with normal renal function for their age, no clinically relevant changes were seen in half-life, C_{max} or AUC.

- **Hepatic impairment:** No data.

- **Renal impairment:** Mild impairment: No change. Moderate renal impairment (Cl_{Cr} 30-50 mL/min): 1.5-fold increase in AUC. Severe renal impairment (Cl_{Cr} below 30mL/min): 2.1-fold increase in AUC. End-stage renal disease undergoing hemodialysis 3 days per week given 0.5mg once daily: AUC increased 2.7-fold. Removed by hemodialysis.

- **Sex difference:** No difference found.

- **Race:** No difference found.

- **Adolescents:** Increased C_{max} 30% and shorter half-life of 11 hours in adolescents age 12-17 years.

USES AND EFFICACY:

Uses: Treatment of **nicotine dependence** (smoking cessation aid); used in combination with counseling.

- The odds of abstaining from smoking for one year after attempting to quit increase 2- to 3-fold.

- Reduces the urge to smoke, reduces some of the nicotine withdrawal symptoms, and reduces the satisfaction derived from smoking.

Clinical course:

- Abstinence rates are better than with a placebo by the second week of therapy, and maximal around the 4th week.

Major clinical trials

Versus bupropion (2006): A randomized, double-blind trial compared the efficacy of varenicline titrated to 1mg twice daily, bupropion SR titrated to 150mg twice daily, or placebo given for 12 weeks. Subjects had smoked approximately 21 cigarettes/day for about 25 years. Exclusions from the study included subjects with major depression, panic disorder, drug abuse or dependence, psychosis, bipolar disorder, recent serious disease, uncontrolled hypertension, or COPD. Counseling was provided weekly for the first 12 weeks, then at week 13, 24, 36, 44 and 52, with additional telephone contact at other times. The continuous abstinence rates from weeks 9-12 were 43.9% with varenicline, 29.8% with bupropion and

17.6% with placebo, all statistically significantly different. After 1 year, continuous abstinence rates were 23% with varenicline, 14.6% with bupropion, and 10.3% with placebo (odds of quitting 2.66 for varenicline vs. placebo, all statistically significantly different). Both varenicline and bupropion reduced the urge to smoke, the negative affect due to nicotine withdrawal, and the satisfaction derived from smoking. Other nicotine withdrawal symptoms (restlessness, increased appetite) were not improved with either drug. Weight gain in participants who abstained from smoking during weeks 9-12 occurred in all groups: placebo 3.15 kg, varenicline 2.89 kg, and bupropion 1.88 kg. Adverse events that occurred more frequently with varenicline than with placebo were nausea, vomiting, constipation, flatulence, dry mouth, dyspepsia, abnormal dreams, and sleep disorders. **Study limitations:** Study completion rates were only 60-70%. Higher completion rates in the varenicline group may have led to overestimation of the drug's treatment effect, since noncompleters were considered smokers. In another study with high completion rates in all groups, the odds ratio of quitting after 1 year was lower for varenicline vs. placebo (1.81). Subjects with major illness were excluded. Weekly counseling may have contributed to benefit, thus overestimating the drug effect.

Twenty-four week therapy (2006): A randomized, double-blind, placebo-controlled trial in 1210 patients who had successfully abstained from smoking for 7 days after the usual 12-week treatment with varenicline examined the benefit of continuing varenicline for a further 12 weeks. Continuous abstinence rates after one year were 43.6% with varenicline vs. 36.9% with placebo (odds ratio 1.34, 95% CI 1.06-1.69, NNT 14). Study limitations: Excluding nonresponders at 12 weeks may have resulted in an overestimation of the effect of varenicline. While statistically significant, the absolute difference in 12-month abstinence rates was only 7%.

Comparisons

Vs. bupropion:

- Abstinence rates are significantly superior for varenicline compared with bupropion after 12 and 24 weeks of therapy. One year after quitting smoking, varenicline is slightly superior, with 21-23% of patients given 12 weeks of varenicline and 15-16% of patients given bupropion having completely abstained from smoking. Varenicline is significantly better at reducing the craving for cigarettes but less effective at reducing early weight gain. Insomnia is more common with bupropion.

Vs. nicotine replacement therapy:

- An open-label study compared 12 weeks of varenicline with 10 weeks of transdermal nicotine. The complete abstinence rate was higher for varenicline at 12 weeks (55.9% vs. 43.2%). However, at the end of 24 weeks and at 1 year, abstinence rates did not differ. Both treatment groups gained about 2kg in weight.

Advantages:

- Effective in patients who have already tried to quit smoking.
- Easily administered.
- Well tolerated.
- Simple renal excretion; lacks pharmacokinetic interactions related to P450.
- Compared with nicotine replacement therapy, nicotine toxicity and nicotine dependence should be less likely.
- Not known to lower the seizure threshold.

Disadvantages:

- Studies excluded patients with psychiatric problems or serious disease, thus the efficacy and safety in these populations are unknown.
- It does not prevent the weight gain of 1-3 kg commonly associated with smoking cessation.
- Frequent nausea.
- Rare but serious cases of altered mood, suicidal thoughts and suicide.

Place in therapy:

- Modestly effective as an aid in smoking cessation. The odds ratio of complete abstinence for the first year is 1.8-3.09 versus placebo.
- 50-80% of patients will still smoke one year after trying to quit with varenicline.
- More effective than bupropion as an aid to smoking cessation with less insomnia, but less likely to prevent early weight gain. Bupropion may be more useful in depressed patients. At least as effective as nicotine replacement therapy.
- Reduces some nicotine withdrawal symptoms (depressed mood, irritability, frustration, anger, anxiety, difficulty concentrating, craving) but not increased appetite or insomnia.
- Useful in patients who cannot take bupropion due to contraindications such as seizures, or who are intolerant of or have failed attempts with bupropion or nicotine replacement therapy. Not useful in patients who need to stop smoking immediately, e.g. hospitalized patients.
- Unknowns: the potential to produce addiction since withdrawal symptoms can occur indicating physical dependence; safety in patients with psychiatric disorders, who are more likely to smoke; rebound effect

on discontinuation; effect on relapse rates; safety of combining with bupropion; longterm safety and efficacy; efficacy in other types of drug dependence. Studies are underway.

Investigational/Unapproved Uses:

- **Alcohol dependence:** Theoretically, alcohol dependence may involve activation of the brain reward system through stimulation of nicotinic acetylcholine receptors. Studies in rats have shown that varenicline reduces ethanol seeking and consumption in a selective manner, and does not result in a rebound increase in consumption when discontinued. Studies in humans are required.

CONTRAINDICATIONS AND PRECAUTIONS:

Contraindications:

- **Hypersensitivity**
- **Children under the age of 18 years** (no data; see also Pharmacokinetics).
- **End stage renal disease** (eliminated by the kidneys).

Precautions:

- Psychiatric illness (may exacerbate; monitor carefully). Some experts would not use this drug in patients with depression unless prescribed by an expert and with a clear risk:benefit ratio (risk of suicidality). Schizophrenia may be exacerbated partly because since smoking induces CYP 1A2, smoking cessation itself alters the P450 metabolism of antipsychotic drugs metabolized by this enzyme (e.g. olanzapine).
- Epilepsy, gastrointestinal disease, chemotherapy: caution (no data).
- Renal impairment (dose adjustment required in severe renal impairment).
- Report unexpected or serious reactions to Health Canada.

PREGNANCY AND LACTATION:

- Decreased fertility in rats given very high doses 36 times the maximum recommended human dose. No data in humans; consider risk:benefit. Canadian authorities recommend avoidance. Smoking during pregnancy has risks for the fetus (premature rupture of membranes, placenta previa, placental abruption, preterm delivery).
- Lactation: no data. Consider risk:benefit.

SIDE EFFECTS:

Cardiovascular: Hypertension (11% versus 6%).

CNS: Insomnia (up to 37% versus placebo up to 32%, may be severe); headache (15-19% versus placebo 13%, may be severe); dizziness (frequent); anxiety, depression, emotional disorders, irritability (frequent); sleepiness (9% versus placebo 2%); sleep disorders including abnormal dreams (up to 15% versus placebo 8%), nightmares (1-2% versus 0%); mood swings, panic reactions, aggression (infrequent); suicidal thoughts, suicide, euphoria, hallucinations, homicidal ideation, paranoia (rare).

- Exacerbation of schizophrenia (case report)

- Exacerbation of manic-depression (case report)

- Convulsions (case reports)

Gastrointestinal: Nausea (up to 52% versus placebo 19%, may be severe depending on dose, may persist for months, reduced by administration with food and slow dose titration).

- Flatulence (6-9% vs. placebo 3%)

- Constipation (11% vs. placebo 5%).

- Vomiting (5% versus placebo 2%)

- Abdominal pain (17% versus placebo 3%)

- Dry mouth (5% versus placebo 3%)

- Dyspepsia (15% versus placebo 7%)

- Taste perversion (15% versus placebo 7%)

Genitourinary: Menstrual disorders (frequent)

Hepatic: Abnormal liver tests (frequent).

Musculoskeletal: Arthralgia, myalgia (frequent).

Other: Increased appetite (8% versus placebo 6%); weight gain of 1-3 kg, similar to the weight gain usually seen in patients who successfully stop smoking.

- Rash, Stevens-Johnson Syndrome

- Nose bleeds, respiratory disorders (frequent)

- Withdrawal syndrome (irritability, depression, insomnia; 3% of patients)

- Generalized weakness (case reports)

- Hypoglycemia (case report in a patient with Type 1 diabetes), increased blood glucose (case reports)

- Accidents, falls (case reports)

- Vision disturbances, movement disorders, sudden loss of consciousness (case reports)

INTERACTIONS:

- Varenicline does not induce or inhibit P450 enzymes.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Drugs metabolized by CYP1A2*	Increased drug levels	Removal of smoking- related increase in CYP1A2	Caution, adjust dose of other drug
Inhibitors of hOCT2**	Increased varenicline levels	Decreased renal elimination	Avoid in patients with severe renal impairment
Nicotine replacement therapy	Increased nausea, vomiting, headache, dizziness, dyspepsia, fatigue	Additive	Avoid

*Drugs metabolized by CYP1A2 include: Insulin, olanzapine, theophylline, warfarin (not a pharmacokinetic drug-drug interaction with warfarin).

** Inhibitors of hOCT2 include: Cimetidine, levofloxacin, ranitidine, trimethoprim.

Interactions lacking

A lack of pharmacokinetic interaction has been documented with

- Bupropion
- Digoxin
- Metformin

DOSAGE:

Guidelines

- Start with a low dose and slowly increase in order to reduce nausea.
- If adverse reactions occur, temporarily reduce the dose.
- Patients have been treated safely for up to 52 weeks.

Adults:

- Oral: Days 1-3: 0.5mg once daily. Days 4-7: 0.5mg twice daily. Days 8-end: 1mg twice daily. If side effects occur, reduce the dose. The patient should stop smoking after 1-2 weeks of therapy. Continue drug therapy for a total of 12 weeks. Therapy may be continued for another 12 weeks if successful. Taper the dose slowly to reduce the risk of relapse and withdrawal syndrome.

Elderly:

- No dosage adjustment required, unless renal function is impaired (see DOSAGE: Renal Impairment).

Hepatic impairment:

- No dosage adjustment required.

Renal impairment:

- Reduce dose in severe renal impairment (ClCr below 30 mL/min): Days 1-3: 0.5mg once daily. Days 4-end: 0.5mg twice daily. Contraindicated in end stage renal disease. **In the United States: End stage renal disease undergoing hemodialysis: Maximum 0.5mg once daily if tolerated.**

NURSING IMPLICATIONS:

This drug may be administered with or without food. It is commonly given after a meal to reduce stomach irritation.

Encourage the patient to undergo counseling as well as drug therapy. If the patient has a relapse, encourage continued attempts to quit.

Monitor patient for changes in mood, agitation, and suicidal thoughts, during therapy and soon after stopping. If these occur, notify the physician immediately.

PATIENT INSTRUCTIONS:

Varenicline (**var-EN-i-kleen**) is used to help people quit smoking. It makes it easier to quit by reducing the urge to smoke and lessening the withdrawal symptoms that occur when you quit.

Before starting this medication, be sure that your physician is aware if you have any kidney disease, since a lower dose may be recommended; any psychiatric illness; depression; **epilepsy; gastrointestinal disease; sleep disorders**; if you are pregnant or breast-feeding; all drugs that you are taking, including chemotherapy.

Take this drug exactly as prescribed. It is important to start with a low dose. The usual dose is 0.5mg once a day for three days, then 0.5mg twice a day for four days, then 1mg twice a day. Take one dose in the morning and one dose in the evening. The duration of therapy is usually 12 weeks. At that time consult your physician, who may recommend an additional period of therapy.

It may be taken with food or on an empty stomach. It is commonly taken after a meal to reduce stomach irritation. **Swallow the tablets whole, do not crush or chew them.**

Before starting, decide on a day on which you will quit smoking, and write it down. Start taking this drug 8-14 days before your "quit date". You can keep smoking until your "quit date". If you do not quit on that date, continue this drug and try again.

Since this drug may cause drowsiness and dizziness, avoid driving and operating dangerous machinery until you know how it affects you.

Report immediately to your physician if you notice any of the following side effects: depression, suicidal thoughts, altered mood.

Adverse interactions with other drugs are possible. It may be necessary to adjust the dosage of some medications when you stop smoking. Do not take nicotine replacement therapy while taking this drug, since it will not have additional benefit and may increase adverse effects.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, away from heat, light and moisture, and out of the reach of children.

PRESENTATION:

Tablets: 0.5, 1 mg. Package of eleven 0.5 mg tablets plus fourteen 1 mg tablets.