



Newer Options for Smoking Cessation: Focus on Varenicline

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BACKGROUND

In the United States, approximately 20.8% (45.3 million) of adults smoke cigarettes which claims 438,000 lives each year. A reported 70% of adult smokers want to quit smoking completely and an estimated 44.2% (19.2 million) adult smokers quit smoking for at least one day in 2006.¹ Due to targeted policy prevention and cessation efforts in El Paso, the number of adult smokers in El Paso, Texas has decreased from 21.5% in 1996 to 14.7% in 2006.²

Varenicline (Chantix®) is a smoking cessation product that was released in May 2006. This article will provide information on varenicline, its safety concerns and how it compares to other smoking cessation products. Varenicline has received more news press in the past year due to questions and concerns about its use in the psychiatric population. Attributing to varenicline's popularity are recent patient reports of strange behavior such as violence, vivid dreams and depression.

MECHANISM OF ACTION

Varenicline's unique mechanism acts as a partial agonist selective for the $\alpha 4 \beta 2$ nicotinic acetylcholine receptor. This receptor is responsible for nicotine dependence. Varenicline acts on the receptor similar to nicotine to lessen nicotine cravings while preventing nicotine binding to the receptor. Nicotine causes the release of the pleasure neurotransmitter dopamine which is thought to be the neuronal mechanism responsible for reinforcement and reward experienced from smoking.^{3,4,5} Patients taking varenicline do not experience the reward they get from smoking. Varenicline stimulates receptor-mediated activity, but at a lower level than nicotine. Because of its mechanism, varenicline is not indicated for use with nicotine replacement therapy.

PRE-MARKETING & POST-MARKETING

Neuropsychiatric adverse drug reactions recently became the main safety concern with the use of varenicline. After months of marketing varenicline, Pfizer received bad publicity for reported neuropsychiatric adverse drug reactions seen during post-marketing surveillance. As a result, the FDA requested that Pfizer increase and update the warnings and precautions of the product package insert to include mood and behavior change adverse drug reactions.^{6,7} Clinicians must assess patient's psychiatric state before starting therapy. Patients should be advised and assessed on an on-going basis for agitation, depressed mood, changes in behavior, unusual or strange dreams, and suicidal ideation or suicidal behavior.^{3,6,7} The FDA also worked with Pfizer on developing a

medication guide for patients taking varenicline.⁶

A reason why the old package insert warnings and precautions may not have included neuropsychiatric adverse drug reactions before marketing is because during pre-marketing patients with underlying psychiatric illness such as bipolar, schizophrenia, and depression were not included in the studies. Therefore, safety and efficacy were not established in the psychiatric population.³ Another reason why these adverse drug reactions may have been overlooked is withdrawal symptoms can mimic drug side effects.

Despite these new post-marketing reports, there is yet to be an established connection between varenicline and the neuropsychiatric symptoms experienced after taking varenicline. A proposed cause of the neuropsychiatric symptoms with varenicline is nicotine withdrawal. Withdrawal symptoms include depression, frustration, irritability, anxiety, difficulty concentrating, and tobacco cravings. Patients with depression, schizophrenia, and alcoholism have a higher rate of smoking than the general population and have more difficulty quitting smoking. Therefore, these patients are more likely to suffer from withdrawal symptoms.⁸

ADVERSE DRUG REACTIONS

Besides the highly publicized adverse drug reactions, the most common adverse drug reactions experienced after starting varenicline 1 mg twice daily therapy include: nausea (30%), insomnia (18%), headaches (15%), abnormal dreams (13%), constipation (8%), flatulence (6%), and vomiting (5%).^{3,4,5}

DOSING

Varenicline is an appropriate smoking cessation alternative to nicotine replacement therapy (NRT) or the next step for patients who fail NRT. It is currently the only agent in the newest class of smoking cessation medications. Varenicline is initially indicated as a 12 week treatment, however, therapy may be continued for another 12 weeks.³ For those who are actively quitting, the extended use of varenicline for an additional 12 weeks will increase the chances of long-term cessation. Therapy begins with 0.5 mg once daily on days 1 to 3, then 0.5 mg twice daily on days 4-7, and 1 mg twice daily on day 8 to the end of treatment. For patient with mild and moderate renal impairment, no dosing adjustment is necessary. The recommended starting dose for severe renal impairment is 0.5 mg once daily and then titrated as needed to a maximum

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dose of 0.5 mg twice daily. Patients with end-stage renal disease undergoing hemodialysis may be administered a maximum of 0.5 mg once daily if tolerated well.³

VARENICLINE (CHANTIX®) VERSUS BUPROPION SR (ZYBAN®)

Bupropion SR is the only other FDA-approved prescription smoking cessation medication not containing nicotine. The exact mechanism of action of bupropion SR is not well established; however, it is thought to work by blocking the reuptake of dopamine, serotonin, and norepinephrine.⁴ The efficacy of bupropion SR in smoking cessation is probably not due to its anti-depressive effects because it has been shown to work equally well in patients regardless if they had a past history of depression.⁸

There are several head-to-head studies comparing varenicline and bupropion SR. Data analyzed from two randomized, double-blind, placebo control trials comparing varenicline, bupropion SR, and placebo demonstrated that varenicline significantly reduces the craving and reward after smoking compared to bupropion SR and placebo. The results of the study also showed that bupropion SR significantly reduces craving compared to placebo. Varenicline was not any different than bupropion SR in reducing restlessness, insomnia, and appetite.⁹ One study showed continuous abstinence rate for weeks 9 to 24 weeks was superior for varenicline (29.5%) compared to placebo (10.5%) and bupropion SR (20.7%). However, continuous abstinence for weeks 9 to 52 was significantly greater for varenicline (21.9%) compared to placebo (8.4%), but no longer significant compared to bupropion SR (16.1%).¹⁰

NICOTINE REPLACEMENT THERAPY

Nicotine replacement therapy (NRT) is an alternative to non-containing nicotine products. NRTs are safe and effective first line therapy for smoking cessation. Over-the-counter NRT products include the patch, lozenge, and gum. The nasal spray and inhaler are only available as a prescription. Products within the nicotine replacement class of medication produces a similar cessation rate, decrease in withdrawal symptoms, and urge to smoke.⁴ The estimated cessation rate is between 19% to 26%.¹¹ Because there are several forms of nicotine replacement, therapy can be tailored to the patient based on preference.⁴ Nicotine replacement therapy should be initiated as monotherapy. These products may be used in combination and when used in combination may improve cessation rates.¹¹

CONCLUSION

In light of the heightened precautions and warnings of varenicline, health care professionals should continue to encourage and remain persistent in helping their patients quit. Clinicians must also keep in mind that all the available smoking cessation products may not be appropriate for all patients. Patient medical history and personal preference should guide clinicians in providing options to their patients for smoking cessation. Using a combination of behavioral changes and drug therapy is the most effective method to smoking cessation. At this time, clinicians should and can consider varenicline for the treatment of smoking cessation. However, clinicians must consider and follow FDA recommendations of advising patients of the potential rare adverse drug reactions associated with varenicline before beginning therapy especially in

patients with underlying psychiatric conditions.

PATIENT SMOKING CESSATION SUPPORT PROGRAM

For local and internet behavior cessation support, patients may be referred to:

Smoking Quit Line
(915) 534-QUIT

www.quitnet.com/ www.smokefree.gov

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Table 1: Appropriate 1st Line Treatments for Smoking Cessation^{11,12}

Medication Name	Prescription Required	Dosage Side Effects*	Common	Duration
Nicotine Gum Nicorette® (2mg, 4 mg)	No	Smoke <25 cigarettes/day: <i>2mg every 1-2 hours x 6 weeks</i> Smoke ≥25 cigarettes/day: <i>4mg every 1-2 hours x 6 weeks</i> Maximum: 24 pieces/day	Mouth sores hiccups, dyspepsia, and jaw ache	Up to 12 weeks
Nicotine Lozenge Commit™ (2mg, 4 mg)	No	Smoke 1 st cigarette after 30 min of awakening: <i>low dependence, initiate 2 mg lozenge</i> Smoke 1 st cigarette within 30 min. of awakening: <i>high dependence, initiate 4 mg lozenge</i> Weeks 1-6: <i>1 lozenge every 1-2 hours</i> Weeks 7-9: <i>1 lozenge every 2-4 hours</i> Weeks 10-12: <i>1 lozenge every 4-8 hours</i> Maximum: 20 lozenges/day	Nausea, hiccups, heartburn, headache (<10%), and cough (<10%)	Up to 12 weeks
Nicotine Patch NicodermCQ® (7, 14, 21 mg/24 hr) Nicotrol® (5, 10, 15mg/16 hr)	No	NicodermCQ®: <i>21 mg/day x 4-6 weeks, then 14 mg/day x 2 weeks, then 7 mg/day x 2 weeks</i> Nicotrol®: <i>15 mg/day x 6 weeks, then 10 mg/day x 2 weeks, then 5 mg/day x 2 weeks</i>	skin reactions (50%), insomnia, and vivid dreams	Up to 10 weeks
Nicotine Nasal Spray Nicotrol® NS (0.5 mg/metered spray)	Yes	Initial dosing: <i>1-2 doses per hour, increasing as needed for symptom relief</i> Maximum: 40 doses/day (5 doses/hour)	Nasal irritation (94%) in first 2 days, nasal congestion, and changes in smell	Up to 6 months
Nicotine Inhaler Nicotrol® Inhaler (4 mg/metered spray)	Yes	Recommended: <i>6-16 cartridges/day</i> Final 3 months: <i>Taper dosage</i>	Mouth and throat irritation (40%), cough (32%), and rhinitis (23%)	Up to 6 months
Varenicline Chantix® (0.5, 1 mg)	Yes	<i>0.5 mg once daily x 3 days, then 0.5 mg twice daily x 4 days, then increase to 1 mg twice daily x 3 months</i>	Nausea (30%), insomnia (18%), headache (15%), vivid, and strange dreams	Up to 6 months
Bupropion SR Zyban® (150 mg)	Yes	<i>Start with 150 mg every morning x 3 days, then increase to 150 mg twice daily</i> Maximum: 300 mg daily	Insomnia (35%-40%) and dry mouth (10%)	Up to 6 months

*Refer to FDA package inserts for a comprehensive list

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