OREGON DUR BOARD NEWSLETTER©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter

December 2006 Volume 8, Issue 6

Varenicline: What is its role for smoking cessation?

By Ehsan Seyedhossini, Nick Crozier, Pharm.D. candidates and Dean Haxby, Pharm.D. OSU College of Pharmacy

The FDA approved varenicline (Chantix) as an addition to counseling for smoking cessation treatment in May 2006. Varenicline is the first new compound to be approved for smoking cessation since bupropion sustained release (Zyban) was approved in 1997. The goal of this article is to review the data available on varenicline and evaluate its place in therapy.

Background: Medications currently FDA-approved for smoking cessation include bupropion sustained release (SR) and various forms of nicotine replacement therapy (NRT).[1-4] Clonidine and nortriptyline are not FDA approved, but studies suggest effectiveness for smoking cessation.[1-4] Pharmacotherapy is used as an adjunct to comprehensive counseling to increase success. All medications with the FDA-indication are labeled as *aids* to smoking cessation treatment, indicating that much depends on patient willingness to quit and counseling effectiveness.[4] When combined with an adequate counseling regimen, both bupropion SR and NRT are shown to approximately double abstinence rates when compared to placebo plus counseling alone.[5-7]

Counseling techniques are well developed and thorough guidelines are available at the Department of Health and Human Services website.[2] Pharmacotherapy is appropriate for patients committed to making a serious attempt to quit along with counseling. Counseling is divided into practical- and supportive-counseling advice. Practical advice includes teaching patient's skills which to help cope with the urge to smoke and how to recognize and avoid situations that bring about that urge, and strategies to prevent relapse. Supportive advice involves encouragement and the communication of caring and concern. As the frequency and intensity of counseling sessions between patient and practitioner increases, quit rates increase.[3]

Clinical Pharmacology: Varenicline is a non-nicotine agent that is a partial agonist selective for alpha-4-beta-2 nicotinic acetylcholine receptor subtypes. When varenicline binds to the receptor, it produces agonist activity, but at a significantly lower level than nicotine. At the same time, varenicline prevents nicotine from binding to the receptor, preventing additional stimulation of dopaminergic pathways in the central nervous system, the mechanism underlying reinforcement and reward experienced when smoking.[8]

Efficacy: The efficacy of varenicline was compared to bupropion SR and placebo in two identical one-year phase-III randomized controlled trials. All subjects received weekly 10 minute counseling sessions for smoking cessation during the first 12 weeks of drug treatment plus four additional follow-up visits from weeks 24 to 52. All subjects were 18-75 year-old smokers and motivated to quit. Patients were excluded if they had serious or unstable disease within 6 months, seizure risk, diabetes mellitus requiring medications, hepatic or renal impairment, clinically significant cardiovascular disease within 6 months, uncontrolled hypertension, severe COPD or a body mass index <15 or >38 kg/m^2. Thus only relatively healthy individuals were studied.

Overall, varenicline was shown to be superior to placebo and showed a general trend toward superiority over bupropion SR in smoking cessation abstinence over one year (Table 1).[9,10] Jorenby, et al. showed significant improvement in continuous abstinence rates at one year with varenicline treatment (23%), compared to placebo (10.3%) or bupropion (14.6%). Bupropion was not more effective than placebo (p=.08) in this study, thus it performed less well than has been demonstrated in many other studies. Gonzales, et al. found that one-year continuous abstinence rates were significantly higher with varenicline versus placebo. There was, however, no significant difference in quit rate between the varenicline and bupropion treatment groups.

A third study by Tonstad, et al. compared varenicline to placebo for prevention of relapse.[11] In the initial open-label cessation phase, all eligible patients were first administered varenicline for 12-weeks. Patients who had not smoked at any point during the last seven days were deemed successful quitters and were randomized to either continue with varenicline or switch to placebo for the blinded 12-week relapse prevention phase of the study. Participants received 20 counseling visits. Of 1927 enrolled in the study, 1236 (64%) had not used tobacco or NRT during the last week of the open-label phase. Of these, 1210 were randomized to receive varenicline or placebo and were evaluated for weeks 13-52. At 52 weeks, 44% of varenicline and 37% of placebo patients were continuously abstinent. Although 52-week abstinence was higher in the group receiving varenicline (p=0.02), the absolute benefit of 24 weeks of active drug compared to 12 weeks

Table 1. Varenicline Evidence Table

Ref	Patient Population	Drug regimens	Endpoint	Results
Jorenby[9] n=1,027	Inclusion Criteria - Smoked 10 or more cigarettes/day during the previous year - No period of smoking abstinence longer than 3 months during previous year Exclusion Criteria - Previous use of, or contraindications to bupropion - BMI < 15 or >38 - unstable cardiovascular disease within 6 months - diabetes mellitus - hepatic or renal impairment - History of alcohol/drug abuse - NRT, clonidine, or nortriptyline within 1 month	1st Phase- 12 weeks 1. Varenicline titrated over 1 week to 1mg BID 2. Bupropion SR titrated to 150mg BID 3. Placebo 2nd Phase- 40 weeks - Non treatment follow-up phase	Continuous abstinence rates from week 9-52. Confirmed by carbon monoxide test.	52-week Continuous Abstinence Week 9-52 (%) P-value NNT vs. placebo Varenicline 23.0 8 vs. bupropion 12 Bupropion SR 14.6 *0.004* Placebo 10.3 *<0.001*
Gonzales[10] n=1,025				Week 9-52 (%) P-value NNT vs. placebo Varenicline 21.9 7 Bupropion SR 16.1 *NS* Placebo 8.4 *<0.001*

was modest.

Adverse effects: Overall, varenicline was well tolerated in clinical trials however nausea was reported by approximately 30% of patients. Nausea was generally described as mild or moderate and often transient but for some subjects, it was persistent over several months. Other adverse effects associated with varenicline were sleep disturbance, headache, constipation, flatulence, and vomiting. Dropout rates due to adverse effects in the Jorenby study were: Varenicline: 4%, Bupropion: 4.6%, Placebo: 3.8 %.[9] Dropout rates due to adverse effects in Gonzales were: Varenicline: 3.9%, Bupropion: 10.3%, Placebo: 7%.[10] Further experience is needed to fully evaluate the safety of varenicline, especially when used in patients with significant co-morbid conditions.

Dosing: Varenicline treatment should be initiated one week prior to quit date. Varenicline should be titrated up to the maintenance dose of 1 mg twice daily to reduce the severity of nausea as follows: Days 1-3: 0.5 mg once daily; Days 4-7: 0.5 mg BID; Day 8–End of treatment (Total 12 weeks): 1 mg BID[8].

Conclusion: Published data following over 3,000 patients for one year have shown varenicline to be a useful adjunct to frequent counseling sessions in promoting smoking cessation.[9-11] It is more effective than placebo and it may offer an advantage over bupropion SR. Additional studies are needed comparing varenicline to NRT and use with a less intensive counseling regimen that is more reflective of general clinical practice to better define the its role. Additional studies are needed before recommending varenicline therapy longer than 12 weeks. Varenicline is reasonably well tolerated with nausea as the most common side effect, but more experience in diverse populations is needed to better establish its safety.[10] One limitation is the cost of varenicline, which is higher than that of other options (Table 2). The advantages and disadvantages of smoking cessation options are summarized in Table 3. Varenicline should be reserved for motivated patients receiving a counseling program.

Table 2. Cost table of commonly prescribed smoking cessation products

Medication	Dose per day	Cost per day*	Duration of therapy	Cost per treatment course
Nicotine Patch 21mg	Once daily	$2.18	8 weeks	$125
Bupropion SR 150mg	Twice daily	$2.67	8 weeks	$150
Nicotine Gum 4mg	12 pieces	$3.94	9-26 weeks	$250-$720
Varenicline 1mg	Twice daily	$3.59	12 weeks	$300

*Lower of AWP-15%, Oregon MAC or FUL October 2006

Reviewed by: Dr. Richard Leman, Chronic Disease Epidemiologist, Oregon Public Health Division; Suzanne Gauen, RPh, Kaiser Permanente Northwest; Teresa M. Maddalone, PharmD, BCPS, Providence Medical Group

REFERENCES

1. Corelli RL and Suchanek HK, Medications for smoking cessation, West J Med. 2002 March; 176(2): 131–135.
2. U.S. Public Health Service Treating Tobacco Use and Dependence—Clinician's Packet. A How-To Guide For Implementing the Public Health Service Clinical Practice Guideline, March 2003. Available at: http://www.surgeongeneral.gov/tobacco/clinpack.html Accessed October 2006.
3. AHCPR Clinical Practice Guidelines. Available at: http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat2.chapter.7644 Accessed October 2006.
4. Henningfield J, et. al. Pharmacotherapy for Nicotine Dependence. Clinical Journal of Cancer. 2005 (55) 281-299.
5. Fiore MC, et. al. The effectiveness of the nicotine patch for smoking cessation. A meta-analysis. JAMA. 1994; 271(24): 1940-7.
6. Hurt R, et. al. A Comparison of Sustained-Release Bupropion and Placebo for Smoking Cessation. NEJM. 1997; (337)1195-1202.
7. Product information: Zyban (Bupropion SR), GlaxoSmithKline, 1997.
8. Product information: Chantix (varenicline), Pfizer. 2006.
9. Jorenby D, et. al. Efficacy of Varenicline, an alpha-4-beta-2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Placebo or Sustained- Release Bupropion for Smoking Cessation. JAMA. 2006; 296(1): 56-63.
10. Gonzales D, et. al. Varenicline, an alpha-4-beta-2 Nicotinic Acetylcholine Receptor Partial Agonist vs. Sustained-Release Bupropion and Placebo for Smoking Cessation. JAMA. 2006; 296(1): 47-55.
11. Tonstad S, et. al. Effect of Maintenance Therapy with Varenicline on Smoking Cessation. JAMA. 2006; 296(1): 64-71.

Table 3. Advantages and disadvantages to current smoking cessation pharmacotherapy

	Advantages	Disadvantages
Nicotine Transdermal	- Widely studied and used - Once daily administration - Well tolerated - Least expensive option - Available generically and over-the-counter	- Minor skin reactions and other minor side-effects
Bupropion SR (Zyban)	- Oral, non-nicotine product - Well studied - Relatively low cost - Available generically	- Associated with serious side effects such as seizure, psychiatric reactions and anaphylaxis. - Produces a variety of minor side effects such as dry mouth and insomnia.
Nicotine gum/lozenge	- Well studied - Dose can be titrated to patient need. - Available generically and over-the-counter	- Must be administered frequently to maintain levels. - Minor local/GI side effects. - Acidic beverages block absorption.
Varenicline (Chantix)	- Oral, non-nicotine product. - Appears well tolerated - May be more effective than bupropion SR.	- Limited experience to date - Expensive
Nicotine Inhaler/ nasal spray	- Dose can be titrated to patient need.	- Expensive - Must be administered frequently to maintain levels - Local side effects
Clonidine[2,4]	-inexpensive.	- Not as well studied for smoking cessation as NRT and bupropion. - Has a number of side effects: constipation, dizziness, drowsiness, dry mouth, tiredness or weakness, allergic reaction, bradycardia and decreased blood pressure.
Nortriptyline[2,4]	-inexpensive.	- Only tested in small studies. - Most common side effects: tachycardia, blurred vision, urinary retention, dry mouth, constipation, weight gain or loss, and low blood pressure on standing.