

New anti-smoking treatments: anything to get fired-up about?

Janet Webb, BSc(Pharm), MSc

Last December a systematic review summarizing recent evidence of effectiveness of smoking cessation strategies, compiled for the National Institutes of Health, was published in the *Annals of Internal Medicine*.^[1] The authors concluded that pharmacotherapy, either with or without counselling, can significantly increase the likelihood of smoking cessation. Their findings confirmed that the use of nicotine replacement therapy (NRT) significantly increases the chances of quitting, and that evidence remains sufficient for bupropion to retain first-line status for smoking cessation. Despite apparently encouraging results, where NRT may double quit rates, it is estimated that at least 70% of people using this treatment will relapse within a year.^[2] With such statistics, alternative approaches are still needed. This article will briefly describe a few new and novel agents targetting successful smoking cessation.

Varenicline

Varenicline was recently approved for smoking cessation in the United States (brand name Chantix®) and in the UK (marketed as Champix®). Varenicline is a partial agonist at central alpha4-beta2 nicotinic receptors, which modulate dopamine release in response to nicotine.^[3] The partial activation at nicotinic receptors helps lessen withdrawal symptoms. At the same time, by occupying this receptor, varenicline attenuates dopamine release which is responsible for the pleasurable effects of smoking.

Two clinical trials of 12 weeks duration compared varenicline 1 mg twice daily with bupropion SR 150 mg twice daily, or placebo in combination with clinical counselling in 1027 ^[4] and 1025 ^[5] patients. The percentage of patients who maintained a continuous quit rate during the last 4 weeks of the 12-week treatment period were 44% for varenicline, compared with 30% for bupropion ($p < 0.001$), and 18% with placebo ($p < 0.001$) in both trials.^[4,5] Adverse effects, which were significantly increased with varenicline, included nausea in nearly 30% of subjects, and abnormal dreams, plus an increased incidence of insomnia and headache.^[4,5] In another trial, 1210 subjects who had successfully quit smoking during 12 weeks of varenicline were randomized to further treatment or placebo for an additional 12 weeks.^[6] Subjects were followed for an additional 28 weeks post-treatment (i.e., 52 weeks since beginning treatment). Between weeks 13-24, 71% of varenicline subjects remained abstinent compared with 50% receiving placebo ($p < 0.001$), and at week 52, 44% of the varenicline group, and 37% of the placebo group were still not smoking ($p < 0.02$). An accompanying editorial mentioned several limitations including the high adverse event incidence, dropout rates, possible introduction of bias in an intention-to-treat analysis which would favour the study drug, inclusion criteria which may not reflect the population at large, and study settings in which patients are likely to receive optimal instruction and monitoring.^[7] Despite these shortcomings, the editorialists conclude that varenicline is likely to aid with successful smoking cessation.^[7] There are no published trials comparing varenicline to nicotine replacement.

Dianicline, which is similar to varenicline, is currently undergoing phase III testing for smoking cessation.[8]

Rimonabant

The endocannabinoid system is thought to be involved in controlling food intake, and also to play a role in dependence and habituation, with receptors in both the brain and adipose tissue.[9] Rimonabant (Acomplia) is the first selective cannabinoid CB1 receptor antagonist.[10] It has received much attention for obesity, especially in patients with diabetes or dyslipidemia, and is approved as adjunctive therapy for this indication in the UK. There was initial hope that it would prove useful in smoking cessation, with the added benefit of preventing weight gain. Three trials have been undertaken, known as the STRATUS (Studies with Rimonabant and Tobacco Use) trials, and although preliminary results were presented in 2004 and the trials were to be terminated at the end of 2004, the results have not been formally published.[10,11] Study design involved administration of rimonabant 5 mg/day, 20 mg/day or placebo along with weekly counselling for a 10-week treatment period with 42 weeks of follow-up.[10] Preliminary results (from the STRATUS-US trial involving 787 patients) presented at the 2004 American College of Cardiology annual meeting demonstrated quit rates of 20%, 36%, and 20%, in the 5 mg, 20 mg, and placebo groups, respectively.[10] This was accompanied by a loss of 0.3 kg in the 20 mg group, and a gain of 1.1 kg in those receiving placebo (not reported for 5 mg). The results from STRATUS-Europe, however, were considered neutral.[11] In early 2006 the United States Food and Drug Administration considered rimonabant “approvable” for weight loss, but not for smoking cessation.[11] The European Medicines Agency granted an approval for weight loss, similarly did not approve rimonabant as an aid to smoking cessation.[12] Whether or not a smoking cessation indication will be further pursued by the developers is unknown.[11]

Nicotine vaccine

Because nicotine readily crosses the blood-brain barrier, strategies are being developed to prevent nicotine delivery into the central nervous system so it cannot act on receptor sites. The goal of vaccine treatment is to induce antibody formation, by administration of a nicotine-protein complex. The nicotine-specific antibodies would then bind to nicotine, and the resultant complex would be too large to cross the blood-brain barrier.[13]

Several companies based in Europe and North America are pursuing this approach, and vaccines are at various stages of development.[14] Trial results assessing safety and immunogenicity of a nicotine-conjugate vaccine, NicVAX, and its effect on smoking behaviour have been published.[15] The study involved 63 adult smokers who were given one of three doses of the vaccine or placebo, in a series of four injections over 26 weeks, with 38 weeks of monitoring. The vaccine appeared safe and well-tolerated. Immunogenic response was dose-related, and those receiving the highest dose (200 micrograms) had antibody levels deemed consistent with vaccine efficacy. This group also had the highest rate of 30-day biochemically-confirmed abstinence from smoking (6/16 subjects vs 2/23 receiving placebo), although the study was not designed to

measure efficacy. There were no reports of compensatory increases in smoking, or withdrawal reactions. The National Institute on Drug Abuse in the United States is currently recruiting patients for an efficacy study.[16]

Other agents which are being investigated, but with insufficient evidence to draw conclusions, include:

- Cytisine which is found in *Cytisus laburnum*, and is the molecule from which varenicline was derived.[17]
- Lazabemide, a reversible inhibitor of monoamine oxidase type B originally developed for parkinsonism.[18]
- Mecamylamine, a nicotine antagonist.[19]

Summary

Current approaches to aid in smoking cessation have been disappointing. Increasing the ability to successfully quit smoking without relapse is an active area of research has led to the development of innovative pharmacotherapeutic approaches. As further investigation is undertaken and research results are published, hope for meaningful advances remains.

References:

1. Ranney L, Melvin C, Lux L, McClain E, Lohr KN. Systematic review: smoking cessation intervention strategies for adults and adults in special populations. *Ann Intern Med.* 2006;145:845-56.
2. McRobbie H, Lee M, Juniper Z. Non-nicotine pharmacotherapies for smoking cessation. *Resp Med.* 2005;99:1203-12.
3. Nides M, Oncken C, Gonzales D, et al. Smoking cessation with varenicline, a selective $\alpha 4\beta 2$ nicotinic receptor partial agonist. *Arch Intern Med.* 2006;166:1561-8.
4. Gonzales D, Rennard SI, Mides M et al. Varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296:47-55.
5. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA.* 2006;296:56-63.
6. Tonstad S, Tønnesen P, Hajek P et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. *JAMA.* 2006;296:64-71.
7. Klesges RC, Johnson KC, Somes G. Varenicline for smoking cessation: definite promise, but no panacea. *JAMA.* 2006;296:94-95.
8. Clinical trial: Efficacy and safety of varenicline treatment as an aid to smoking cessation in cigarette smokers (Ameridian). [U.S. National Institutes of Health

- Clinical Trials Web site]. Available at: <http://www.clinicaltrials.gov>. Accessed January 16, 2007.
9. Hey K, Ussher MH, Lancaster T. Cannabinoid type 1 receptor antagonists (rimonabant) for smoking cessation [protocol]. Cochrane Database of Systematic Reviews. 2006; Volume 4.
 10. Boyd ST, Fremming BA. Rimonabant – a selective CB1 antagonist. *Ann Pharmacother*. 2005;39:684-90.
 11. Wood S. FDA gives nod to antiobesity effects of rimonabant but balks at smoking-cessation indication. [theheart Web site]. February 20, 2006. Available at: <http://www.theheart.org>. Accessed February 23, 2006.
 12. Adcock H. Clinical developments in 2006. *Pharm J*. 2007;278:21-4.
 13. Hall W. The prospects for immunotherapy in smoking cessation. *Lancet*. 2002;360:1089-91.
 14. Le Houezec J. Why a nicotine vaccine? *Clin Pharmacol Ther*. 2005;78:453-5.
 15. Hatsukami DK, Rennard S, Jorenby D et al. Safety and immunogenicity of a nicotine conjugate vaccine in current smokers. *Clin Pharmacol Ther*. 2005;78:456-67.
 16. Clinical trial: Efficacy of NicVAX in smokers who want to quit smoking. [U.S. National Institutes of Health Clinical Trials Web site]. Available at: <http://www.clinicaltrials.gov>. Accessed January 16, 2007.
 17. Etter J-F. Cytisine for smoking cessation: a literature review and meta-analysis. *Arch Intern Med*. 2006;166:1553-9.
 18. Berlin I, Aubin H-J, Pedarriosse A-M, et al. Lazabemide, a selective, reversible monoamine oxidase B inhibitor, as an aid to smoking cessation. *Addiction*. 2002;97:1347-54
 19. Lancaster T, Stead LF. Mecamylamine (a nicotine antagonist) for smoking cessation [reviews]. Cochrane Database of Systematic Reviews. 2006; Volume 4.