Rimonabant for treating tobacco dependence

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Abstract: Tobacco use continues to cause 5 million preventable deaths worldwide each year. Despite effective treatments being available, these are underutilized and cessation rates remain low. As tobacco use has complex physiological effects, there are multiple opportunities for novel pharmacological agents to play a role in a comprehensive treatment plan. The endocannabinoid system has been linked to the nicotine reward pathways in animal models. Rimonabant, a selective cannabinoid receptor (type 1) blocker, has been shown in some early clinical trials to have some positive effects in increasing abstinence rates of smokers attempting to stop. In addition, smokers who stop smoking with the assistance of rimonabant may gain less weight than those using placebo. However, the results from these few trials have not been entirely consistent and so its role as an aid to smoking cessation remains to be determined.

Keywords: rimonabant, tobacco, smoking, cessation, medications, pharmacotherapy

Epidemiology of smoking

Tobacco use remains one of the leading causes of preventable death in the world. Despite tobacco's highly addictive nature, the majority of current smokers are interested in quitting (USDHHS 2004). Even with this seeming demand for assistance with stopping tobacco use, it is unclear how well tobacco cessation treatments are being utilized. Over the past 20 years, various cessation medications have become available to improve success for those smokers making a quit attempt. Currently, the United States Food and Drug Administration (FDA) has approved 7 medications as first-line treatments for smoking cessation (Table 1). Despite these effective products, overall abstinence rates even with a comprehensive approach generally fall well below 40% 1 year after the target quit-date. As novel cessation medications enter the market, clinicians have a wider range of tools to assist smokers with their efforts, and the ability to tailor a medication treatment plan to the individual needs of the patient.

Current pharmacotherapies for tobacco dependence treatment

Pharmacotherapy for tobacco dependence is an important component of a comprehensive treatment plan that includes behavioral interventions and psychosocial support. The primary effects of nicotine are mediated by nicotinic acetylcholine receptors, many subtypes of which are widely distributed throughout the central nervous system. A high concentration of α_4 subunits is found in the ventral tegmental area of the brain, where a dense supply of dopamine neurons is linked to the brain's main "reward center," the nucleus accumbens. An increase in extra-synaptic dopamine in the extracellular space appears to be associated with the reinforcing and addictive properties not only of nicotine but also of other psychostimulant drugs of abuse (eg, amphetamine, cocaine) (Kelley 2002).

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Table 1 Currently approved cessation medications

Nicotine replacement medications
Patch
Gum
Lozenge
Inhaler
Nasal spray

Non-nicotine medications
Bupropion
Varenicline

The goal of using cessation medications is to reduce cravings for tobacco and symptoms of nicotine withdrawal that are especially severe during the first few weeks after discontinuing tobacco use. Over the past 20 years, many forms of cessation medications have been developed to assist smokers in quitting (Henningfield 2005; Fagerstrom 2006). The most commonly utilized cessation medications are nicotine replacement medications. These agents deliver nicotine to the brain via various routes (Table 1) in order to replace the nicotine previously supplied by tobacco. "Medicinal nicotine" is delivered in its safest form, as opposed to its most dangerous form accompanied by over 4000 toxins in tobacco smoke, and binds to nicotinic receptors in the brain, reducing cravings and withdrawal. All of these medications have been shown to be effective at increasing abstinence rates in clinical trials and roughly double long-term quit rates (Hughes 1999; Fiore 2000; Silagy 2004).

Other non-nicotine medications, such as antidepressants, have been approved for use in smoking cessation and have slightly different mechanisms of action (Hughes 2004). Bupropion Sustained-Release (Zyban®, GlaxoSmithKline) was approved for smoking cessation in 1997. This medication inhibits reuptake of dopamine and norepinephrine in the central nervous system, resulting in similar effects on these neurotransmitters as caused by nicotine. In addition, bupropion antagonizes nicotinic receptors which may reduce the reinforcing properties of nicotine (Warner 2005). Varenicline (Chantix®, Pfizer) was approved in 2006 for smoking cessation, and is a selective alpha-4-beta-2 nicotinic acetylcholine receptor partial agonist. By this mechanism, varenicline binds to the nicotinic receptors in the ventral tegmental area, generating a dopamine response in the nucleus accumbens that is lower in magnitude than that caused by nicotine. This low-level dopamine response is less likely to result in dependence, yet is effective in reducing

withdrawal symptoms in the absence of nicotine. In addition, this compound acts as an antagonist at the alpha-4-beta-2 nicotinic receptor, thus reducing nicotine's ability to bind to the receptor and cause high-level dopamine release. Thus, varenicline should help in reducing cravings and withdrawal as well as reduce relapse by reducing the rewarding effects of tobacco. In two recent clinical trials, varenicline has been shown to improve abstinence rates over both bupropion and placebo (Gonzales 2006; Jorenby 2006) and in another trial, longer term use (24 weeks) was shown to reduce relapse (Tonstad 2006).

A new mechanism of action for cessation medications

A new class of medications has been developed affecting the endocannabinoid system in the central nervous system. CB1 endocannabinoid receptors are found in many cell surfaces throughout the body including brain, liver, muscle, adipose tissue, myocardium, and others. The primary clinical effect of these medications is to influence metabolism and energy intake. Previous studies have demonstrated that this system is activated by marijuana, leading to increased appetite (Gelfand 2006). It has been hypothesized that blockade of these receptors may be useful in weight loss, and preliminary data suggest that medications that block endocannabinoid receptors may have multiple beneficial clinical effects (Table 2).

Data obtained over the past 5 years have also linked the endocannabinoid system to mechanisms of nicotine dependence (Cohen 2005). Rimonabant is a selective CB1 receptor antagonist, and recent evidence suggests that in addition to other clinical effects, rimonabant may also be effective at improving abstinence among smokers. In the central nervous system, CB1 receptors are found on GABA-related neurons that can modulate dopamine release. Activation of these CB1-mediated GABA neurons results in a decrease of dopamine release. Thus, antagonism of the CB-1 receptor, such as by rimonabant, should increase dopamine

Table 2 Clinical effects of rimonabant

Decrease appetite

Weight loss

Increase HDL cholesterol (independent of weight loss effects)

Decrease triglycerides (independent of weight loss effects)

Smoking cessation

Improved glycemic control from favorable insulin action via higher adinopectin

release, thought to be a major factor in the nicotine-reward pathway.

Evidence for use of rimonabant for smoking cessation

Animal evidence

There is evidence that the endocannabinoid system may influence in nicotine's reward effects in the brain. Studies of the effects of rimonabant using animal models began in 2001, and data have been obtained regarding the potential utility in nicotine dependence. Cohen et al (2005) studied nicotine-seeking behavior in rats. Rats who were given rimonabant displayed decreased nicotine-conditioned behavior as demonstrated by decreasing the self-administration of nicotine and dopamine turnover in the nucleus accumbens after nicotine stimulation. Balerio et al (2006) reported that pretreatment with rimonabant in mice decreased the anxiety-reducing effects of nicotine in mice who had been previously exposed to nicotine. This study supports the link between the endocanabanoid system and nicotine's anxiety-like behaviors.

Clinical trial evidence

Following these animal data, clinical trials in humans began in 2002. The trials evaluating the primary clinical effects of rimonabant (weight loss and metabolic benefit) were presented under the acronym RIO (Rimonabant in Obesity), and consisted of 4 randomized studies in over 6,000 subjects (RIO-Lipids, RIO-Europe, RIO-North America, RIO-Diabetes). These trials demonstrated the clinical benefits of weight loss, increased HDL cholesterol, decreased triglycerides, and improved glucose metabolism in patients with type 2 diabetes (Despres 2005). The most common side-effects in clinical trials utilizing rimonabant are summarized in Table 3.

Another series of studies were designed to demonstrate the benefit of rimonabant for smoking cessation. These were the STRATUS (Studies with Rimonabant and Tobacco Use) trials and they enrolled concurrently with the RIO trials. These included two large multicenter phase III trials (STRATUS-United States and STRATUS-Europe), and one maintenance study (STRATUS-Worldwide). Results of these studies have not yet been published in full, and therefore, the details already in the public domain are summarized here.

STRATUS-US trial

The STRATUS-US trial was a randomized, three-arm (2 treatment), controlled study and enrolled 784 subjects who

Table 3 Side-effects of rimonabant

Nasopharyngitis	10–26%
Upper respiratory tract infection	8–19%
Headache	7–15%
Nausea	7–13%
Dizziness	8–10%
Back pain	7–10%
Influenza	6–10%
Anxiety	3–9%
Diarrhea	6–7%
Arthralgias	5–7%
Insomnia	4–6%
Sinusitis	3–5%

Derived from data of metabolic (Despres 2005) and smoking cessation (Niaura 2005) trials.

smoked 10 or more cigarettes per day for at least 2 months and were motivated to stop smoking (Dale, unpublished data; Anthenelli 2005). Subjects were given 10 weeks of active treatment (rimonabant) or placebo with a 42-week follow-up. Subjects were randomly assigned to one of three treatment conditions (rimonabant 5 mg, rimonabant 20 mg, or placebo). The primary outcome was abstinence during weeks 7 through 10 of the follow-up. This study showed that rimonabant 20 mg roughly doubled abstinence rates compared with placebo. The 5 mg dose had no significant effect on abstinence. In addition, the average weight gain in the rimonabant 20 mg group was less than 1 kg while those in the placebo group gained just under 4 kg.

STRATUS-EU trial

The STRATUS-EU trial was a randomized, three-arm (2 treatment), controlled study with an identical protocol to the STRATUS-US trial and enrolled 789 subjects who smoked 10 or more cigarettes per day for at least 2 months and were motivated to stop smoking (Niaura, unpublished data). Subjects were given 10 weeks of active treatment (rimonabant) or placebo with a 42-week follow-up. Subjects were randomly assigned to one of three treatment conditions (rimonabant 5 mg; rimonabant 20 mg; or placebo). The primary outcome was abstinence during weeks 7 through 10 of the follow-up. Abstinence rates during weeks 7 through 10 were not statistically higher in the rimonabant arms compared with placebo.

STRATUS worldwide

STRATUS Worldwide was a maintenance-of-abstinence trial examining 1 year of treatment outcomes (Niaura, unpublished data). Subjects who were abstinent at 10 weeks

during the first phase of the study were re-randomized to receive placebo, 5 mg rimonabant, or 20 mg rimonabant for an additional 42 weeks. Those who had been on rimonabant 20 mg and were abstinent at 10 weeks were randomized to continue on 20 mg/day, use 5 mg/day, or use placebo. Those who had been abstinent on 5 mg/day were randomized to continue on 5 mg/day or use placebo. Demographic and tobacco related variables were similar among groups. Continued abstinence was determined at 52 weeks. Higher abstinence rates were demonstrated in those subjects continuing on active rimonabant at either dose (20/20 mg and 20/5 mg) compared with the 20 mg/placebo arm. The abstinence rates were similar in the 20/20 mg and 20/5 mg doses. Those who received the 20 mg continuation dose also had reduction in weight gain and higher HDL cholesterol at 52 weeks. Overall adverse event rates were slightly higher in the active arms vs. placebo, with the most frequent side-effects reported being nausea, diarrhea, and vomiting.

Conclusions

These early studies of rimonabant have demonstrated end-of-treatment efficacy and possibly a benefit of continuation of therapy up to 52 weeks of treatment. In the STRATUS-US trial, the effect size was similar to other pharmacotherapies in roughly doubling abstinence rates, but head-to-head comparisons with other proven medicines have not been studied. Utilizing the endocannabinoid system offers an additional option for treating tobacco dependence. The possibility that rimonabant may be more efficacious in certain subgroups of smokers is currently not known, nor is it clear if this agent has additional benefit in combination with other cessation medications, as has been demonstrated in other instances (Blondal 1999; Jorenby 1999; Bohadana 2000; Steinberg 2006). It does have some potential additional benefits compared with the currently available pharmacotherapies including significant decreases in weight gain at the 20 mg dose. The United States FDA provided a decision in February 2006 that rimonabant was "not approvable" for a smoking cessation indication. Despite this decision, once approved for other indications, this product may be prescribed as an "off-label" indication to help smokers stop or to reduce weight gain during smoking cessation. Although further evidence-based data will be needed to fully understand the benefits and risks of this new medication, rimonabant provides a new mechanism of action for the treatment of tobacco dependence and for overall reduction of cardiovascular risk.

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