The American Journal of Medicine (2008) Vol 121 (4A), S20–S31

ELSEVIER

THE AMERICAN JOURNAL *of* MEDICINE®

Update on Pharmacologic Options for Smoking Cessation Treatment

Mitchell Nides, PhD

Los Angeles Clinical Trials, Los Angeles, California, USA

ABSTRACT

Although the proportion of the adult population in the United States that smokes has decreased steadily, the rate of successful quit attempts is still low. Smokers develop nicotine dependence that resembles other addictions, and may require multiple attempts and long-term treatment to sustain abstinence. Currently available first-line agents for smoking cessation therapy include nicotine replacement therapy, which is available in several formulations, including transdermal patch, gum, nasal spray, inhaler, and lozenge; bupropion, an atypical antidepressant; and varenicline, a partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor that was recently developed and approved specifically for smoking cessation therapy. Second-line agents are nortriptyline, a tricyclic antidepressant agent, and clonidine, an antihypertensive drug. With the exception of varenicline, which has been shown to offer significant improvement in abstinence rates over bupropion, all of the available treatments appear similarly effective. However, the adverse event profiles of nortriptyline and clonidine make them more appropriate for second-line therapy, when first-line treatments have failed or are not tolerated. Rimonabant, a cannabinoid-1 receptor antagonist that was being developed for smoking cessation, received a nonapprovable letter from the FDA in 2006 and there is no further information as to whether development for this indication is continuing for this agent. Nicotine vaccines are under investigation and offer promise, especially for relapse prevention. Ultimately, selection of pharmacologic agent should be based on the patient's comorbidities and preferences, as well as on the agent's adverse event profile.

KEYWORDS: Antidepressants; Clonidine; Nicotine replacement; Smoking cessation; Varenicline

The US Surgeon General has characterized smoking cessation as "the single most important step that smokers can take to enhance the length and quality of their lives."[1] Over 70% of smokers say they want to quit[2] and approximately 40% make a quit attempt each year.[3] Unfortunately, the overwhelming majority of quit attempts are unaided, resulting in abstinence rates at 6 months of approximately 3% to 5%.[4] Why are so few unaided quit attempts successful? Smokers trying to quit have to simultaneously cope with the psychological, behavioral, and physical aspects of tobacco dependence. Psychologically, many smokers become dependent on nicotine as a mood stabilizer, and negative affect is a common reason given for relapse.[5,6] Behaviorally, through repeated pairing with tobacco use, everyday events such as seeing others smoke, drinking coffee or alcohol, driving the car, or taking a break become powerful triggers to smoke. Physically, due to nicotine's short half-life (<2 hours), strong cravings can develop within several hours of the last cigarette.[7] This is primarily due to reduced release of dopamine in the nucleus accumbens, one of the areas in the brain associated with reward. Other withdrawal symptoms may soon develop, including difficulty concentrating, irritability, frustration, anxiety, depressed mood, and increased appetite.[8] The withdrawal symptoms tend to peak within the first 7 days, but can last for weeks or months.[9] Studies have shown that the majority of smokers relapse within the first week of quitting.[4]

Statement of conflict of interest: Please see Author Disclosures section at the end of this document.

Requests for reprints should be addressed to Mitchell Nides, PhD, Los Angeles Clinical Trial Picture Quitting, the Entertainment Industry's Quit Smoking Program, 4116 West Magnolia Boulevard, Suite 100, Burbank, California 91505.

E-mail address: mnides@laclinicaltrials.com.

0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2008.01.016

Table 1 Odds ratios of abstinence with first- and second-line smoking cessation therapy[21,31,60]

Treatment	Odds Ratio (95% CI)*
First-line therapies	
NRT: All forms, pooled (meta-analysis of 123 studies with ≥6 mo follow-up)	1.77 (1.66–1.88)
Gum	1.66 (1.52–1.81)
Patch	1.81 (1.63–2.02)
Inhaler	2.14 (1.44–3.18)
Lozenge	2.05 (1.62–2.59)
Nasal spray	2.35 (1.63–3.38)
Bupropion (meta-analysis of 19 trials with ≥6 mo follow-up)	2.06 (1.77–2.40)
Varenicline†	Gonzales et al (2006)[45] (phase 3 trial of 1,027 smokers) 12 wk: 3.85 (2.70–5.50) 52 wk: 3.09 (1.95–4.91) Jorenby et al (2006)[46] (phase 3 trial of 1,025 smokers) 12 wk: 3.85 (2.69–5.50) 52 wk: 2.66 (1.72–4.11)
Second-line therapies	
Nortriptyline (meta-analysis of 6 trials with ≥6 mo follow-up)	2.14 (1.49–3.06)
Clonidine (meta-analysis of 6 trials with ≥12 wk follow-up)	1.89 (1.30–2.74)

CI = confidence interval; NRT = nicotine replacement therapy.
*Odds ratios are derived from *Cochrane Review* articles unless otherwise noted.
†Due to the relatively recent availability of clinical trial data for varenicline, there is currently no *Cochrane Review* or other meta-analysis of this agent.

Although unsuccessful attempts to stop smoking can be disheartening, patients who receive optimal pharmacologic treatment together with nonpharmacologic cessation counseling have greatly improved odds of attaining long-term abstinence. This article reviews the mechanisms of action, efficacy, safety, and place in the therapeutic armamentarium of pharmacologic treatments currently available or in development for smoking cessation.

CURRENTLY AVAILABLE PHARMACOTHERAPY FOR SMOKING CESSATION

First-line Therapies

First-line therapeutic agents are approved by the US Food and Drug Administration (FDA) for smoking cessation therapy and are proved to reliably increase smoking abstinence rates without causing excessive adverse events. A summary of their efficacy in clinical trials, expressed as odds ratios (ORs) of abstinence compared with control, is given in **Table 1**. **Table 2** provides information for product selection and administration.

Nicotine Replacement Therapy. The most recent Department of Health and Human Services (DHHS) guidelines for treatment of nicotine dependence recommend nicotine replacement therapy (NRT) for first-line treatment, except in the presence of contraindications.[10] Currently, there are 6 NRT formulations: transdermal patch, nasal spray, gum, lozenge, vapor inhaler, and sublingual tablet (not available in the United States).[11] Recommended dosages for the specific formulations are given in Table 2.

The multiple formulations of NRT offer smokers a choice in the route of administration, which may have a positive influence on adherence to treatment. The transdermal patch system offers a continuous release of nicotine over 16 or 24 hours, whereas the other formulations (gum, lozenge, inhaler, and nasal spray) are short-acting NRT (SANRT), so the dose can be self-titrated. The choice of agent is primarily driven by patient preference, word-of-mouth, advertising, price, route of administration, and perceived adverse effects. Allowing smokers to sample the various delivery systems before initiation of therapy is a way to encourage the use of SANRT, allowing patients to find the formulation that works best for them. As part of a multicomponent smoking cessation program for entertainment industry workers in Los Angeles, smokers tested 1 piece of nicotine gum, 1 nicotine lozenge, and 1 inhaler cartridge for about 5–10 minutes each at the first visit.[12] As a result, >90% of participants chose to use 1 of the products as part of their medication plan. Studies by Schneider and colleagues[13,14] have also shown that half-day testing of SANRT results in strong individual preferences that could potentially translate to improved utilization and quit rates.

Mechanism of Action. The principal mechanism of action of NRT is to partially replace the nicotine formally obtained from tobacco, which aids smoking cessation by reducing the severity of withdrawal symptoms and cravings[15] and also reduces the reinforcing effects of nicotine delivered via tobacco while providing an alternative source of some reinforcing and cognitive effects.[16] Differences in formulations may have an impact on the efficacy for some of these effects. For example, the more rapid delivery of nicotine obtained with the nasal spray appears to provide faster relief of withdrawal symptoms. Furthermore, the inhaler formu-