

SMOKING Cessation ROUNDS

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Systematic Approaches to Smoking Cessation

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Welcome to the inaugural issue of *Smoking Cessation Rounds*. The importance of smoking cessation cannot be overemphasized. It has been termed the “gold standard” of all preventive strategies, and yet, it has been noted that although there are now effective interventions, there has until recently been a disinclination on the part of many clinicians to involve themselves in this important area of preventive practice. The application of a simple systematic approach to the identification and counseling of all smoking patients can dramatically improve the rates of cessation in virtually any practice setting and do so while enhancing physicians’ efficiency and effectiveness.

Willie Sutton, the notorious bank robber, was reported to have said that he “robbed banks because that was where the money was!” At a time when preventive strategies in medicine are receiving greater and greater emphasis, it is important to remind ourselves that, like money in a bank, smoking cessation is where the greatest preventive payoff can be found. Smoking is the #1 cause of premature death in Canada.¹ No other clinical intervention can produce a reduction in predictable morbidity and premature mortality that can equal successful smoking cessation! It has been estimated that reduced smoking was responsible for >40% of the reduction in cancer deaths among US men between 1991 and 2003.² In addition, no other preventive intervention is more cost-effective than smoking cessation. While successful smoking cessation costs between \$2,000-\$6,000 for each life-year saved, hypertension may cost as much as \$26,000 per life-year saved and hyperlipidemia treatment may require the expenditure of \$196,000 for each life-year saved.³

Most smokers want to quit, and most have indicated the desire to do so in the near future. While changes in the social environment have “de-normalized” smoking, encouraged quit attempts, and supported those who have recently stopped smoking, a significant proportion of the population remains addicted to tobacco. The central role of nicotine addiction in smoking cannot be overemphasized. Smoking is not a “habit” or a “lifestyle choice.” The overwhelming majority of today’s smokers are caught in the grip of a very tenacious addiction. There have been great gains in reducing the incidence of smoking in Canada. In fact, just 19% of Canadian adults smoke today, as compared to >50% a few decades ago. Arguably, those who found smoking cessation relatively easy, have already quit. Conversely, those who are still smoking are more likely to be more significantly addicted. The conclusion is obvious: Efforts should be made by all physicians – irrespective of their practice setting – to ensure a systematic, sustained, and strategic approach to the identification of all smokers. The provision of sympathetic and supportive interventions thereafter will greatly enhance our ability to assist smokers to become smoke-free.

Unfortunately, many physicians report that they feel they are prevented from helping smokers in any systematic way because of the limitations of time, expertise, and a lack of confidence in the effectiveness of their interventions.⁴ This is all the more ironic, since there is evidence that by increasing the effectiveness of smoking cessation interventions, there



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Table 1. The effect of physician advice on cessation

Intervention	Odds ratio
No advice to quit	1.0
Minimal physician advice to quit	1.3
Low-intensity counseling (3-10 mins)	1.6
High-intensity counseling (>10 mins)	2.3

Adapted from: Fiore MC, Bailey WC, Cohen SJ, et al. *Treating Tobacco Use and Dependence*. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. June 2000.gdfgs

could be, by way of an example, a 60% reduction in cancer deaths in the 50 years to come.⁵

Communication is important

In this and forthcoming issues of *Smoking Cessation Rounds*, our intention is to ensure that our readers receive straightforward practical advice that will allow the development and application of simple, but effective, smoking cessation strategies in every practice and professional setting. Most physicians are already familiar with the “Ask, Advise, Assess, Assist, Arrange” schema that guides appropriate smoking cessation practice. Identifying the smokers in a clinical practice is a fundamental challenge, but one that can be met by simply asking at the time of patient registration, “Has any form of tobacco been used in the previous 6 months?” By applying a chart “reminder” reflecting the patient’s smoking status, the physician is cued to provide a personalized, unambiguous, nonjudgmental offer of assistance with smoking cessation. Assessing a patient’s “readiness to quit” by evaluating motivation and self-confidence provides a clearer indication of the likelihood of a quit attempt and, in itself, communicates to the patient that this is an issue that is taken seriously by the physician. Counseling alone has been demonstrated to enhance spontaneous smoking cessation rates⁴ (Table 1). Simple advice regarding the selection of a “quit date,” the development of ways to deal with those circumstances or situations in which smoking ordinarily takes place, and the offer of more specific assistance in the form of self-help materials or referral to community agencies or programs can be very helpful.

While some physicians are interested in helping their smoking patients quit and wish to be involved in that process, others may be less interested in such clinical activity. In the latter case, patients should be referred to those with an expertise or interest in these matters. The availability of provincial “Smokers Help Lines” and a variety of web-based resources allow easy access to organizations and programs with expertise in cessation.

The development of more effective pharmacotherapies (see below) enhances our ability to help our smoking patients (Table 2) and every practitioner should become

Table 2. The effectiveness of smoking cessation pharmacotherapy

Pharmacotherapy	Odds ratio
Placebo	1.0
Nicotine gum	1.60
Nicotine patch	1.63
Bupropion	1.56
Varenicline	2.96

Adapted from: Wu P, Wilson K, Dimoulas P, Mills EJ. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis. *BMC Public Health*. 2006;6:300.

familiar with the principles and practice of pharmacotherapy for smoking cessation.

The fundamentals of pharmacotherapy for smoking cessation

Over the past 25 years, our ability to help smokers has improved considerably. A range of products and, in some cases, delivery systems, is now available. The provision or prescription of smoking cessation therapies is not complicated. An understanding of the relative advantages and potential shortcomings of the 3 currently available therapies is fundamental to smoking cessation practice (Table 3).

Nicotine replacement therapy (NRT)

The recognition that smoking is sustained because of an addiction to nicotine spurred the investigation into a number of approaches where nicotine is administered in low doses, stimulating the brain to eliminate the discomfort and pangs of withdrawal, while permitting the acquisition of a whole new repertoire of nonsmoking behaviours. This led to the development of nicotine replacement therapy (NRT) and proof of its efficacy followed.^{6,7}

A distinct benefit of this approach is that the smoker – no longer dependent on cigarettes – is spared any exposure to the carcinogens and the thousands of other chemical constituents in smoke. In recent years, the other constituents of cigarette smoke have been examined to assess their role in maintaining cigarette smoking.^{8,9} The arterial and venous levels of nicotine produced by the slow absorption of nicotine through the oral or nasal mucosa (via NRT chewing gum or ‘inhaler’), or the skin (via an NRT patch) are a fraction of those produced by cigarette smoking. Smoking a cigarette produces a rapid, dramatic elevation in arterial levels of nicotine as might be expected when the drug is absorbed via the alveoli and enters the arterial circulation almost instantly; however, NRT never produces arterial levels of nicotine that are anywhere close to those achieved by smoking. Consequently, the use of NRT is much safer in every respect than continued smoking. The gradual, sustained release of low levels of nicotine through the skin or mucosal membranes into the venous circulation produces

Table 3. Pharmacotherapy for smoking cessation

Therapy	Titration?	Advantages	Potential disadvantages
Nicotine gum	N/A	<ul style="list-style-type: none"> • Can be used at times of increased concern • Can supplement other NRT products • OTC 	<ul style="list-style-type: none"> • Affected by food and drink • Clings to dental work • Must remember it!
Nicotine patch	Yes (to meet NRT needs)	<ul style="list-style-type: none"> • Ease of use – OTC • Discrete • Steady state • OTC 	<ul style="list-style-type: none"> • Skin irritation • Sleep disturbance • Price in bulk purchase
Nicotine inhaler	Yes (to meet NRT needs)	<ul style="list-style-type: none"> • Ease of use – OTC • Can be used at times of increased concern • More precise control of nicotine needs • Can supplement other NRT products 	<ul style="list-style-type: none"> • Must remember it! • Price in bulk purchase
Bupropion (Zyban®)	Yes (to initiate therapy)	<ul style="list-style-type: none"> • Non-nicotine therapy • Antidepressant effect • 52 weeks of use possible 	<ul style="list-style-type: none"> • Side effects – seizures, etc. • Drug interactions
Varenicline (Champix®)	Yes (to initiate therapy)	<ul style="list-style-type: none"> • Non-nicotine therapy • Enhanced efficacy • No interactions 	<ul style="list-style-type: none"> • Side effects – nausea

OTC = over the counter

levels of nicotine that are maintained at a relatively constant level. It is the fall in plasma levels of nicotine below a certain, often “personalized” threshold that causes the urge to smoke and the emergence of withdrawal symptoms in the absence of nicotine.

Prior to their introduction as prescription medications, NRT products were the focus of clinical trials that specifically did not involve teenagers, pregnant women, or people with cardiovascular (CV) disease. As a consequence, the initial clinical indications for their use specifically precluded these populations. After gaining over-the-counter (OTC) status in Canada, the product instructions did not change and reflect the original limitations. Increasingly, clinicians are considering the use of NRT preparations in virtually all smokers, given that the risks associated with NRT are far less than those associated with the continuation of smoking. In particular, the purported risks of NRT in patients with CV disease have been the focus of much discussion and it is generally acknowledged that there is no evidence of increased CV risk associated with the use of these medications.¹⁰⁻¹² The use of NRT in pregnant women is now frequently considered and, in many communities, is recommended given the important role that smoking cessation can play in dramatically reducing the incidence of low birth-weight babies, while enhancing the health of the mother.^{13,14} Addressing nicotine addiction in adolescents and teenagers has a profound impact on their lifetime health-risks and, as a result, many physicians have recommended NRT in dealing with this important and often difficult-to-treat population.^{15,16} Concerns about the abuse potential of NRT products have been shown to be largely unfounded.^{17,18}

NRT is effective. Perhaps the most significant limitations to its use are lingering misperceptions about its safety and effectiveness in some physicians and in many smokers. Nicotine is not carcinogenic and smokers are already addicted to

nicotine. The view that is expressed occasionally by some health professionals – that they do not want patients to become “dependent” on the patch or gum – reflects a misunderstanding about approaches to treatment that is both profound and disappointing. Some experts believe that the effectiveness of NRT can be enhanced by ensuring appropriate nicotine replacement, an approach that is achieved by carefully titrating nicotine replacement in accordance with cravings or the emergence of withdrawal symptoms.¹⁹

The bottom line: NRT is a well-established approach to pharmacotherapy that can double the likelihood of cessation. Careful titration of NRT to nicotine needs may conceivably enhance its success rate. Patients (and physicians) need to be educated regarding the safety and effectiveness of this proven therapy. Nighttime use (patch) may be associated with vivid dreams or sleep disturbance; however, both can be alleviated by using the patch only during daytime hours. Users of NRT gum should be reminded that their mouths should be rinsed before use because residual food or beverage alter the pH and inhibit nicotine release. Users should have their gum with them at all times! Users of the NRT inhaler which, despite its name, causes nicotine to be absorbed principally via the oral mucosa, report that it facilitates the management of acute cravings and allows them to titrate their nicotine needs more carefully. All forms of NRT may be combined. Smokers smoke to maintain certain nicotine levels and NRT is intended to approximate these levels and eliminate cravings. However, when using NRT, former smokers will never derive levels of nicotine equal to those produced by smoking.

Bupropion (Zyban®)

Several years ago, bupropion became the first non-nicotine medication to be approved for the treatment of nicotine dependence.^{20,21} Originally developed as an antidepressant

(Wellbutrin®), bupropion was noted to facilitate smoking cessation among patients enrolled in a clinical trial examining its antidepressant properties. The realization that smoking cessation was distinctly assisted by bupropion use led to its significant role as an anti-smoking medication. It is believed that bupropion possesses noradrenergic and dopaminergic properties allowing it to reduce the cravings and moderate the discomfort of withdrawal that characteristically accompany any quit attempt.²²⁻²⁴ The use of bupropion for smoking cessation doubles the effectiveness of any quit attempt and, until recently, was demonstrably the most effective of all the smoking cessation pharmacotherapies.²⁵ Bupropion is started and titrated several days prior to a “quit date” to ensure that there are adequate levels of the drug present in the system at the time that smoking ceases. The recommended dosage is 150 mg twice a day.

Clinicians must be familiar with a range of side effects that may accompany bupropion use. It is contraindicated in those predisposed to seizures (dose-related, particularly in those with a history of seizure activity, bulimia or anorexia, or recent head injuries) and in patients using a monoamine oxidase inhibitor (MAOI) or other forms of bupropion. Some patients, however, may report minor side effects, including a dry mouth, a skin rash, or a nonspecific sense of unease/anxiety. Such symptoms are often managed by reducing the dose with minimal impact on the effectiveness of bupropion as an aid to smoking cessation.²⁶ In clinical practice, Canadian investigators have noted levels of effectiveness similar to those in clinical trials, but accompanied by higher rates of discontinuation as a consequence of side effects.²⁷ The experience of a Canadian Armed Forces’ smoking cessation program, for instance, illustrates that bupropion can be highly effective, but may result in side effects in many users.²⁸ Nevertheless, experience in many settings has demonstrated the effectiveness of bupropion in a variety of clinical environments.²⁹ The safety and effectiveness of bupropion in treating cardiovascular patients has been demonstrated in several settings.^{30,31} Overall the substantial benefits of bupropion have been calculated to very significantly outweigh the minimal likelihood of significant side effects.³² Considerable experience has accumulated in the use of this drug and, thus far, bupropion has demonstrated significant benefit in increasing rates of cessation and doubling the likelihood of success during any quit attempt.³³

Interest in a genetic susceptibility to various forms of pharmacotherapy continues to grow; there is evidence that some genotypes predispose to a diminished or enhanced response to bupropion therapy.³⁴⁻³⁷

The bottom line: Bupropion has exceeded the effectiveness of NRT in clinical trials. It affects the uptake of dopamine in the mesolimbic area of the brain and reduces cravings and withdrawal symptoms. It may play a special role in assisting cessation in those with a history of depressive illness, given its antidepressant

properties. Bupropion must be titrated gradually over a few days and can produce an array of side effects; but its effectiveness is not in doubt. It may be given for up to 52 weeks in cases where prolonged therapy is deemed appropriate. Because it is not a nicotine product, it has frequently been used in settings where it was once thought that NRT was inappropriate, eg, in the treatment of CV disease patients.

Varenicline (Champix®)

Recognizing that nicotine addiction is mediated by the effect of nicotine on neurochemistry and neurophysiology, attempts were made to develop agents that might block or modify its central effects. Varenicline is a selective, nicotinic acetylcholine receptor partial agonist that represents a novel pharmaceutical approach to smoking cessation. Designed to bind to the $\alpha 4\beta 2$ nicotinic receptors in the midbrain (the receptors thought to be most important in stimulating and sustaining nicotine addiction), varenicline partially stimulates the receptors (producing some of the effects associated with smoking and forestalling the emergence of withdrawal symptoms) while, at the same time, blocking the receptor and preventing any “benefit” that might occur with exposure to nicotine.

It is important to realize that varenicline is not a nicotine product, is almost completely metabolized and excreted in the urine, does not appear to interact with any of the myriad of other commonly-prescribed medications, and does not influence the activity of the enzyme systems commonly involved in drug metabolism. A reduction in the dose is recommended only in patients with advanced renal disease. The drug is started at a dose of 0.5 mg per day and titrated over the course of several days to a dose of 1 mg twice daily.

Varenicline has been evaluated in comparison to placebo and bupropion and, in terms of both short- and long-term efficacy, exceeded them both.^{38,39} Ordinarily, it is recommended that varenicline be used for an initial period of 12 weeks; however, its use for an additional 12 weeks has revealed evidence of enhanced effectiveness.⁴⁰ It is evident that varenicline is approximately twice as effective as bupropion. Nausea is the most common side effect experienced by those taking varenicline; however, it is seldom severe enough to warrant discontinuation. Approximately 4% of those taking varenicline in clinical trials experienced nausea at a level sufficient enough to prompt discontinuation.⁴¹ Nausea is noted to be reduced when the drug is titrated at the start of therapy.

Varenicline has been available in both Europe (Champix®) and the USA (Chantix®) for several months and it was recently approved for use in Canada where it will be known as Champix®. Because varenicline is not a nicotine product, its use may be contemplated in populations and circumstances where, until recently, the use of NRT or other pharmacotherapy has ordinarily not been considered. Investigations regarding the use of

varenicline in teenagers, pregnant women, and those with cardiac disease are contemplated or are in progress.

The bottom line: Varenicline is a novel anti-smoking medication that specifically blocks nicotinic acetylcholine receptors in the midbrain. It eliminates cravings and prevents any further response to nicotine. It is a non-nicotine product that does not interact with other medications. In clinical trials, it is approximately twice as effective as bupropion and more than 4 times more effective than placebo. The dose of varenicline is titrated over several days at the start of therapy, rising to 1 mg twice a day. Nausea is the principal cause of discontinuation and occurs in approximately 3%-4% of patients. It is anticipated that it will be useful in a variety of populations and settings.

Future considerations

In the near future, it is conceivable that a range of other novel pharmacotherapies for smoking cessation will emerge. At the same time, there will be enhanced interest in providing smoking cessation treatment to vulnerable populations: teenagers, pregnant women, and those with cardiovascular disease. Particular attention will be paid to ensuring that hospitals apply systematic approaches to assist admitted patients in dealing with withdrawal (which frequently goes unrecognized or is misinterpreted) and to enhance cessation opportunities.⁴² Our ability to assist in dealing with the community's most significant preventable health problem – nicotine addiction – will only improve.

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Abstract of Interest

Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial.

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CONTEXT: Varenicline, a partial agonist at the alpha4beta2 nicotinic acetylcholine receptor, has the potential to aid smoking cessation by relieving nicotine withdrawal symptoms and reducing the rewarding properties of nicotine.

OBJECTIVE: To determine the efficacy and safety of varenicline for smoking cessation compared with placebo or sustained-release bupropion (bupropion SR).

DESIGN, SETTING, AND PARTICIPANTS: A randomized, double-blind, placebo-controlled trial conducted between June 2003 and March 2005 at 14 research centers with a 12-week treatment period and follow-up of smoking status to week 52. Of 1413 adult smokers who volunteered for the study, 1027 were enrolled; 65% of randomized participants completed the study.

INTERVENTION: Varenicline titrated to 1 mg twice daily (n = 344) or bupropion SR titrated to 150 mg twice daily (n = 342) or placebo (n = 341) for 12 weeks, plus weekly brief smoking cessation counseling.

MAIN OUTCOME MEASURES: Continuous abstinence from smoking during the last 4 weeks of treatment (weeks 9-12; primary end point) and through the follow-up period (weeks 9-24 and 9-52).

RESULTS: During the last 4 weeks of treatment (weeks 9-12), 43.9% of participants in the varenicline group were continuously abstinent from smoking compared with 17.6% in the placebo group (odds ratio [OR], 3.85; 95% confidence interval [CI], 2.69-5.50; P<.001) and 29.8% in the bupropion SR group (OR, 1.90; 95% CI, 1.38-2.62; P<.001). For weeks 9 through

24, 29.7% of participants in the varenicline group were continuously abstinent compared with 13.2% in the placebo group (OR, 2.83; 95% CI, 1.91-4.19; P<.001) and 20.2% in the bupropion group (OR, 1.69; 95% CI, 1.19-2.42; P=.003). For weeks 9 through 52, 23% of participants in the varenicline group were continuously abstinent compared with 10.3% in the placebo group (OR, 2.66; 95% CI, 1.72-4.11; P<.001) and 14.6% in the bupropion SR group (OR, 1.77; 95% CI, 1.19-2.63; P=.004). Treatment was discontinued due to adverse events by 10.5% of participants in the varenicline group, 12.6% in the bupropion SR group, and 7.3% in the placebo group. The most common adverse event with varenicline was nausea, which occurred in 101 participants (29.4%).

CONCLUSIONS: Varenicline is an efficacious, safe, and well-tolerated smoking cessation pharmacotherapy. Varenicline's short-term and long-term efficacy exceeded that of both placebo and bupropion SR.

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Upcoming Meeting

1-3rd October 2007

5th National Conference on Tobacco or Health

Shaw Conference Centre

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Contact: Canadian Council for Tobacco Control

Tel.: 613-567-3050

Website: www.ncth.ca

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