The following sections will review the available behavioural and pharmacological therapies for smoking cessation.

Rationale

Behavioural and pharmacotherapy for tobacco dependence and withdrawal can contribute substantially to improved health by enabling cessation of tobacco use. Even among persons who might ultimately achieve tobacco abstinence without therapy, the benefits can be profound if treatments help people to achieve tobacco abstinence earlier, because the risk of disease is strongly related to the duration of tobacco use. Several concepts are discussed that can contribute to understanding the place of therapy in tobacco-disease-control efforts.

The first concept to understand when contemplating the provision of treatment for a disease in general is the nature of the disease and factors that can impede the efficacy and utilization of a treatment. In the case of tobacco dependence there are at least three important considerations. The first is that tobacco dependence is a powerful biological and social process that strongly impedes achieving and sustaining cessation. The second is that tobacco dependence is often accompanied by unrealistic fears about treatment as well as the assumption that treatment really is not needed. This is typical across addictions and is sometimes referred to as the “denial” or “rationalization” factor because of the tendency of addicted persons to deny that they are truly addicted and need help, and because they may assume that treatment is riskier than the disease. Third is that this disease is promoted to an unprecedented extent by the tobacco industry, which engages all manner of economic, social, political and regulatory pressures to enable it to establish and sustain tobacco dependence.

Treatment can make it possible, but rarely makes it easy, to achieve cessation from tobacco. Whereas tobacco products are designed and marketed for maximum appeal, treatment medications for addiction are designed with greatest consideration to safety and efficacy, including attention to reduce overuse or addictive use of the products. This means that treatment is, by design, less appealing than tobacco, and whereas the main problem with tobacco is enabling and sustaining cessation, a major problem with most treatment is to foster compliance and adequate use to achieve
and sustain tobacco abstinence. Furthermore, whereas the tobacco industry ensures that tobacco products are readily available, attractive, and highly affordable, pharmacotherapy is frequently out of reach, available often only by prescription or from limited points of sale, and is often more expensive on a daily basis and point of sale basis because it is generally distributed in packages that include behavioural treatment guidance and sufficient units to discourage simple occasional use as a temporary substitute for tobacco. Behavioural therapy similarly is often not readily available, is human-resource intensive, and has been found to appeal only to sub-populations of tobacco-users.

Evidence-based pharmacotherapy offers a variety of options for individuals that are important to match with the wide variations in individual preferences. These include several forms of nicotine-replacement therapy (gum, lozenge, patch, nasal spray and oral inhaler) and bupropion. The general efficacy of the evidence-based medicines is similar in providing an approximate doubling of the probability of long-term smoking cessation. Behavioural treatment can be effective in its own
right and can also substantially increase the success of pharmacotherapy.

Efficacious and highly cost-effective treatments have been reviewed in many countries and institutions and they advocate that all health-care personnel and clinicians should consistently deliver smoking cessation interventions to their patients. Behavioural treatment ranges from brief opportunistic interventions by health professionals to encourage and support cessation, to highly structured programmes to address withdrawal, cope with cravings, and avoid relapse to tobacco use.

Major challenges for the twenty-first century include making treatments culturally relevant and appropriately tailored to individuals and populations, and making treatment as readily accessible as are the tobacco products themselves.

Treatment should ideally be offered as one component of comprehensive tobacco-control efforts that include increased taxes on tobacco, restrictions on public smoking, education emphasizing the dangers of tobacco and benefits of cessation, and restrictions on tobacco-product marketing; these are critical for cessation efforts, treatment utilization and the maintenance of tobacco abstinence.

**Behavioural interventions**

The efficacy of behavioural therapies for the treatment of tobacco dependence has been comprehensively reviewed in the United States' *Clinical Practice Guideline: Treating Tobacco Use and Dependence* (Fiore et al., 2000), reports from the US Surgeon General (United States Department of Health and Human Services, 2000) and the Royal College of Physicians; United Kingdom (Royal College of Physicians, 2000) and in the online treatment resource, treattobacco.net (see [http://www.treattobacco.net](http://www.treattobacco.net)). A variety of behavioural therapies have been shown to be efficacious for many smokers. Behavioural therapy ranges in complexity from simple advice offered by a physician or other health-care provider to much more extensive
therapy offered by counsellors or specialized smoking cessation clinics. Clearly, as the level of complexity of the therapy increases, the cost to the smoker or third-party provider increases, and the availability of the therapy, particularly among developing countries, decreases.

**Physician advice**

Simple advice from a physician has been shown to increase abstinence rates significantly (by 30%) compared to no advice (Fiore et al., 2000). Although there have been no systematic studies of advice by other clinicians, it is plausible that a similar increase in abstinence rates would be observed (Fiore et al., 2000). United States guidelines recommend the “Five A’s approach”: ask about tobacco use; advise all users to quit; assess willingness to make a quit attempt; assist the patient to quit; and, arrange follow-up contact (Fiore et al., 2000). Whereas the absolute effect of brief advice is relatively small, this intervention can have considerable global impact because of the large number of people who visit their physicians (http://www.treatobacco.net). Physicians are in a unique position because of their ability to advise patients who would like to quit, as well as smokers who do not intend to quit (Jackson et al., 2001). For smokers who do not intend to quit smoking, physicians should inform and sensitize patients about tobacco use and cessation, especially by personalizing the benefits. For smokers who are insecure about their ability to quit, physicians may use motivational strategies, such as discussing barriers to cessation and their solutions. The benefits of such interventions can be enhanced by critical points, such as helping the patient to select a specific day to quit and personalizing the potential benefit. For smokers ready to quit, the physician can offer strong support, help set a quitting date, prescribe pharmaceutical therapies for nicotine dependence, such as replacement therapy and/or bupropion (with instructions for use), and suggest behavioural strategies to prevent relapse.

**Self-help materials**

Generic self-help materials are no better than brief advice from a health professional, but are more effective than no intervention, and they have the advantage of being able to reach large numbers of people at relatively low per-person cost; thus they can be cost-effective, even though not as efficacious as medication (Stead and Lancaster, 2000). For example, a Cochrane review meta-analysis found that self-help materials with no face-to-face contact had a small benefit (OR=1.2) over no self-help materials (Stead and Lancaster, 2000). Materials intended to encourage smokers to attempt to quit and to help them in their efforts are increasingly becoming widely available in
developed countries, and need to be available in regions where they are presently difficult to obtain. In choosing particular materials to provide or recommend, it is important to take account of the accessibility of the material (http://www.treatobacco.net). It is especially important that the materials are appropriate in language, literacy level and cultural approach. For example, in some cultures it is important to tie the benefit and rationale for cessation to the family. Printed materials are most common and may range from a brief guide and tips sheet to a structured manual with exercises to guide quit attempts. Resources may include audiocassettes, videos or computer programs, as well as those widely available on websites. The increasing accessibility of the Internet should increase opportunities for individually tailored self-help therapies.

Approaches that are more recent have concentrated on making self-help materials appropriate to the needs of individuals (Stead and Lancaster, 2000). In eight trials included in a Cochrane review meta-analysis, individually tailored materials were more effective than generic materials (OR=1.4). Individually tailored materials are based upon the individual response of smokers at baseline, and can then provide smokers with interactive feedback about their stage of change, decisional balance considerations regarding the pros and cons of quitting smoking, temptations that might develop in the most important smoking situations and techniques for coping with specific situations (Prochaska et al., 1993).

Telephone contact is an economical way of adding personal contact to self-help materials. Six trials examined by the Cochrane review, included the benefit of proactive calls from a counsellor.

**Behavioural and psychological interventions**

Behavioural support, with multiple sessions of individual or group counselling, assists smoking cessation. Both individual and group therapy have been shown to improve quit rates beyond those seen with self-help materials alone (Stead and Lancaster, 2000). There appears to be no difference between individual and group therapy in terms of quit rates; therefore, either therapy may be of benefit (Stead and Lancaster, 2000). Groups are theoretically more cost effective, but their usefulness may be limited by difficulties in recruiting and retaining participants (Stead and Lancaster, 2000).

Three types of counselling and behavioural therapies have been shown to produce higher abstinence rates: 1) providing smokers with problem-solving/skills training (e.g. avoiding situations where other people are smoking, identifying triggers to
smoking; 2) providing social support as part of treatment; and 3) helping smokers to obtain social support outside of treatment (Fiore et al., 2000). Another type of behavioural therapy shown to be associated with positive outcomes is aversive smoking (Hajek and Stead, 2000). Aversive smoking involves guided smoking, where the patient smokes intensively, often to the point of discomfort, nausea and/or vomiting. Aversion therapy pairs the pleasurable stimulus of smoking a cigarette with some unpleasant stimulus. The objective is to extinguish the urge to smoke. Such therapy can be effective but requires more extensive staff support than other behavioural therapies and it appears not to be widely acceptable.

A main tenet of therapy with person-to-person contact is “more is better.” Whereas minimal contact (i.e. less than three minutes), as with physician contact, can increase abstinence rates by 30% over no contact, more intensive counselling (more than 10 minutes) can more than double abstinence rates (Fiore et al., 2000) compared to no contact. A dose-response curve also has been observed for both total amount of contact time and the number of person-to-person treatment sessions (Fiore et al., 2000).

Mass media communication campaigns

The impact of mass media has been extensively studied in Australia, Canada, Finland and the United States. Mass media campaigns can increase knowledge about the health effects of smoking and the benefits of stopping. They can also change and reinforce attitudes towards stopping, provide cues to simple action and influence smoking behaviour.

Telephone Quitlines/Internet-based services

Quitlines are a low-cost and easily accessible smoking cessation service. They provide confidential and anonymous support to smokers wanting to quit. Quitlines can be available for extended hours, including evenings and weekends, and will often be on a freephone or low-call rate.

Telephone help lines use two main approaches: reactive, in which smokers can simply telephone the line, and proactive, in which counsellors ring callers back and give ongoing telephone support. The effectiveness and cost-effectiveness of proactive telephone counselling for smoking cessation is now widely recognized (US Department of Health and Human Services, 2000a). The effectiveness of reactive telephone counselling is harder to demonstrate because of the difficulties in undertaking randomized controlled trials with a reactive service. However, there is an increasing understanding that other evaluation methods may be more appropriate for reactive
services, although reactive telephone counselling can also be an effective and cost-effective intervention (Owen, 2000; WHO Europe).

Quitlines are a popular and easily accessible intervention that can reach large numbers of smokers. The study of the United Kingdom’s Quitline concluded that for a single intervention to reach 4.2% of the total population of adult smokers in England was a major achievement (Owen, 2000). Quitlines can also reach groups who have difficulty accessing mainstream smoking cessation services. The United Kingdom’s Asian Quitline receives 20,000 calls per year and is reaching 10% of South Asian tobacco users in the country (South Asia Social Researcher’s Forum, 2001). For the vast majority of callers, the line is their first contact with any form of smoking cessation service. Sweden’s Sluta Rota Lingen has had a similarly positive experience in attracting ethnic minority smokers.

Quitlines are increasingly developing a range of quality smoking cessation counselling services using the Internet, which are integrated with the telephone helplines. A number of quitlines in European countries such as Denmark, Germany, the Netherlands and Sweden are developing innovative services building on their mainstream service.

There are now many “quit smoking” sites currently available on the Internet to offer smokers help and support. Two of the better known sites are www.quitnet.org (run in association with Boston University Department of Public Health) and www.stop-tabac.ch (set up by the University of Geneva). Other more generic sites may also include smoking cessation pages e.g. www.netdoctor.com. Research into the use and effectiveness of these sites is just beginning (Etter, et al., 2001; Takahashi, et al., 1999; Yuasa, et al., 2000; West, et al., 2001). In the United Kingdom smoking is concentrated particularly amongst unskilled manual workers and it is this group which has least access to the Internet (27% compared to 70% of professionals). However, with the advent of newer and faster technology it is likely that the problem of lack of access will soon be overcome. As a means of delivering health care
information and support the Internet has the potential to reach a wide range of smokers and tobacco-users.

Quitlines have an important role to play as part of an overall comprehensive smoking cessation programme. They provide a low-cost, easily accessible, popular and effective service. Quitlines are increasingly incorporating online counselling as part of a flexible range of services for smokers. The Internet offers the potential to reach large numbers of smokers at low cost and the challenge is to develop a range of innovative and effective web-based services which smokers will want to use.

**Quit and Win competitions**

Quit and Win is a cost-effective, evidence-based smoking cessation method for population-wide public health use that also more broadly supports national tobacco-control work. The Quit and Win campaigns use innovative communication methods, partnerships, community organization and health service involvement to bring about cessation rates of around 20%. Conservative evaluation methods of one-year follow-up evaluation of the participants have shown that 10%-30% of the participants have stayed completely smoke-free during the whole year following the Quit and Win campaign.

Quit and Win is a rapidly growing smoking cessation campaign that contains a positive message for smokers. The participants stop using tobacco for at least the
contest period of four weeks and, if they succeed, they are eligible to win prizes. The Quit and Win organizers in the countries provide the financial means and the prizes for their local campaigns and follow an internationally standardized protocol. Prior to the contest all participants have been using tobacco daily for at least one year and have to be 18 years of age or older. The International Quit and Win Coordinating Centre is situated at the National Public Health Institute in Finland and the campaigns are carried out in close collaboration with WHO.

**Smoke-free places**

The smoke-free workplace is a cost-effective public-health approach that encourage the important long-term goal of de-normalizing tobacco use. Furthermore, taking a public-health approach can affect large numbers of individuals at minimal cost (National Cancer Institute, 1991; US Department of Health and Human Resources, 2000c). Working with individual smokers to change their smoking behaviour is an important goal, but has limited impact if the environmental factors that promote and support smoking are not also addressed. The creation of smoke-free places, especially smoke-free work sites, is thus an essential component of any successful strategy to promote smoking cessation.

The United States has over 20 years’ experience with changing public policy to promote smoke-free places. The creation of public and private policies to restrict smoking has been found to be an extremely effective approach to promoting cessation (US Department of Health and Human Services, 2000c). Numerous studies have documented the effects of these restrictions on employee smoking behaviour. Studies have been conducted in health-care settings, government agencies, insurance companies, telecommunications companies, and among other random samples of the workforce. These studies found reductions in average daily consumption of cigarettes and lower overall prevalence rates. The percentage of smokers contemplating quitting was also higher in smoke-free work sites, and such sites also seemed to promote long-term quitting (Emont et al., 1993; Stillman et al., 1990; Borland et al., 1991; Wakefield et al., 1992).

The tobacco industry’s own internal documents have revealed that smoking restrictions were considered to be a major threat to their profitability since they found that, "Smokers facing workplace restrictions have a 84% higher quit rate than average" and it was expected that a “10% decline in consumption” could be expected if smoking was banned in all workplaces (Heronimus, 1992).
Legislation to restrict smoking in public places is also an effective strategy to support cessation, since an additional benefit of this regulation is a reduction in smoking among the general public. Clean indoor air laws are associated with lower smoking prevalence and higher proportions of quitters. States that impose more tobacco-control smoking restrictions along with higher taxes have the lowest consumption rates (Gilpin et al., 2000; Stephens et al., 2001). Just passing a law or establishing a restrictive policy does not accomplish these reductions. The policy has to be implemented with care, along with the provision of supportive services for cessation and enforcement procedures should be established.

**Pharmacologic interventions: tobacco dependence and withdrawal**

Many people are able to successfully quit smoking on their own and with behavioural self-help guidance (World Bank, 1999; Fiore et al., 2000). However, most smokers are nicotine-dependent and could benefit from interventions to address the physiological aspects, specifically the disorders of tobacco dependence and tobacco withdrawal, which are recognized by the ICD-10 – International Classification of Diseases (World Health Organization, 1992).

The development of pharmacotherapies to treat nicotine dependence has focused on the alleviation of tobacco-withdrawal symptoms. For example, as noted in the next section, nicotine-replacement medications reduce withdrawal symptoms by partially replacing the nicotine normally achieved by smoking. Antidepressants such as bupropion and nortriptyline may be efficacious for smoking cessation because of their reduction of the cessation-induced depression that is related to nicotine withdrawal. Clinical trials to promote cessation by pharmacologically reducing other withdrawal symptoms such as anxiety have also been attempted (Henningfield, Fant and Gopalan, 1998).

**Efficacy across products**

There are currently two categories of medication that are available for smoking cessation: nicotine replacement medications and non-nicotine medications. Among the non-nicotine medications, one, bupropion, has been specifically approved for smoking cessation whilst others discussed in this review are considered effective even though they have never been specifically approved by regulatory authorities as smoking cessation treatment products. Bupropion and the various nicotine replacement therapy (NRT) products have been most widely studied, and this research supports the conclusion that all are effective under a broad range of conditions, and all may
be concluded to approximately double the rate of abstinence compared to placebo (Royal College of Physicians, 2000; US Department of Health and Human Services, 2000; Fiore et al., 2000; www.treatobacco.net). Comparing efficacy across products is problematic because there has been very little direct within-study comparison of the products and because success rates vary so widely across products. However, it can be concluded that the products are effective with guidance provided in their labelling, but that improved outcomes can be achieved with more intensive behavioural support (Royal College of Physicians, 2000; US Department of Health and Human Services, 2000; Fiore et al., 2000; see also www.treatobacco.net). There is no validated system for matching cigarette smokers to the treatment form that will produce the most successful outcomes; however, people do vary in the form that is most acceptable (e.g., gum versus patch) and persons who have tried to quit smoking and failed with one product might find another product more effective. Therefore, it is important to make available as many of the products as possible. The following sections will review those medications within each category that have been clinically proven to be effective.

**Nicotine replacement medications**

The most direct way to help people manage the symptoms of nicotine dependence and withdrawal is therapeutic use of nicotine medication (Fiore et al., 2000; Henningfield, 1995; Henningfield, 1995; American Psychiatric Association, 1996). Nicotine medications make it easier to abstain from tobacco by replacing, at least partially, the nicotine formerly obtained from tobacco and thereby providing nicotine-mediated neuropharmacologic effects such as increased expression and reduced turnover of nicotine receptors in the brain and other parts of the body, alteration of brain EEG and regional cerebral glucose metabolism, and activation of dopaminergic reinforcement systems in the brain (US Department of Health and Human Services, 1988).

There appear to be at least three major mechanisms by which smoking cessation efforts are enhanced (Henningfield, 1995; Benowitz, 1993). First, medications may reduce either general withdrawal symptoms or at least prominent ones, thus enabling people to function while they learn to live without tobacco-use. Second, medications may also reduce the reinforcing effects of tobacco-delivered nicotine. Finally, nicotine medications may provide some effects for which the patient previously relied on cigarettes, such as sustaining desirable mood and attention states and making it easier to handle stressful or boring situations. For most people who use replacement medications, discontinuation from the medication occurs within a few months following smoking cessation. Some people need to use the medications longer in order to avoid
resumption of cigarette smoking, but it is not clear how to determine, prior to cessation, which people will need longer-term use and how long they will need to use the medication.

**Current forms of nicotine replacement therapy**

**Transdermal patch**

There are currently four patch formulations on the market that vary widely in their design, pharmacokinetics, and duration of wear (i.e., 24- and 16-hour wear). The diversity in patch systems has been described in reviews (Benowitz, 1995; Gorsline J, 1993), and the differences in pharmacokinetics has been illustrated in a head-to-head clinical trial (Fant et al., 2000). Because it is not possible to predict which smokers would find which particular patch characteristics most desirable or effective, it is useful to ensure access to several if not all types. For example, some smokers may require a patch that delivers higher and faster levels of nicotine whereas others may prefer a patch that delivers lower levels of nicotine more gradually.

All of the patch types are available in a range of dosages, which permits higher-dependent smokers to use the strongest patches and lower-dependent smokers to use a lower dose according to the guidance provided for each brand. The range of dosages for each brand also means that users can gradually decrease their nicotine intake over a period of several weeks or longer to enable a gradual adjustment of their bodies to lower nicotine levels and ultimately to a nicotine-free state.

The main advantage of the nicotine patch over acute NRT formulations is that compliance is based on whether or not the patient places the patch on the body in the morning, rather than on the patients’ actively using a product throughout the day. For this reason, compliance with patch therapy tends to be higher than for other NRT products (Hajek et al., 1999). The nicotine patch delivers nicotine more slowly than acute NRT formulations, although nicotine plasma concentrations can get higher during the day with patch use than with acute NRT use, especially if the patient does not use the acute NRT product as many times during the day as recommended (Benowitz, 1993; Henningfield, 1995).

The most frequently reported side effects occurring with nicotine patch use are local skin reactions, with up to 50% of patients experiencing this effect (Fiore et al., 2000). Moving the site of patch application daily as instructed can reduce the incidence of skin reactions to the patch. Sleep disturbances have also been commonly reported with 24-hour patches, and a dose effect has been noted, with 21-mg patches producing
higher rates of sleep disturbance than 14- or 7-mg patches (Transdermal Nicotine Study Group, 1991). Physicians may recommend that persons who have sleep disturbances either use a lower dose patch or remove the patch after 16 hours and do not wear it while sleeping.

**Acute dosing**

**Gum**

The first NRT that was made available to consumers was transmucosally-delivered nicotine polacrilex ("nicotine gum"). This was initially approved for prescription marketing in several European countries, Canada and the United States in the early 1980s and many other countries later in the 1980s. By the 1990s, many countries had approved availability of the gum without prescription either from pharmacies or in many countries as an over-the-counter or general sales product. Mint and orange flavours of nicotine gum have been introduced in an effort to increase compliance with use instructions among patients who found the original ("peppery") flavour to be unpalatable. Hundreds of basic and clinical research studies have been done documenting the safety and efficacy of the product for smoking cessation and for treating withdrawal symptoms, including craving (Royal College of Physicians, 2000; US Department of Health and Human Services, 2000; Fiore et al., 2000).

Nicotine gum is not chewed like ordinary confectionary gum, but is intermittently chewed and held in the mouth over about 30 minutes, as needed, to release its nicotine. It is available in both 2-mg and 4-mg dosage forms, each of which typically deliver approximately 50% of their nicotine over a 15-30 minute period of oral use (Benowitz et al., 1987). Thus, when gum is chewed on a fixed schedule of 10 pieces per day, a smoker receives about 10 mg or 20 mg of nicotine per day using the 2-mg or 4-mg gum formulations, respectively. The average systemic intake of nicotine from cigarettes is about 30mg per day (Townsend, 2002). Thus, most gum chewers do not match the nicotine levels achieved daily through the smoking of a cigarette. Furthermore, because of the relatively slow absorption of nicotine from gum compared to smoke inhalation, individual doses do not produce the extremely high arterial levels of nicotine produced by smoke inhalation (Henningfield, 1995). Smokers who use fewer pieces of gum achieve much lower concentrations of nicotine, which may reduce the efficacy of the treatment.

Due to the importance of replacing nicotine in adequate quantities, success with nicotine gum treatment depends in part on how many pieces of gum the smoker chews per day (Russell et al., 1983). Smokers that are more dependent have been
shown to improve their chances of achieving abstinence with the 4-mg than the 2-mg gum (Tonnesen et al., 1988). After a few weeks or months, the number of doses per day is reduced gradually until it is no longer required. This tapering phase is several weeks in duration for many users but should be continued as long as needed to permit gradual adaptation of the body to reduced nicotine and to avoid relapse to smoking.

**Lozenge**

The nicotine lozenge is the most recent NRT to receive approval for smoking cessation in the US, and is available in many European countries as well. The lozenge is available in 2-mg and 4-mg formulations. Instructions for use and dosing are similar to nicotine gum, but the lozenge is not chewed; it dissolves in the mouth over approximately 30 minutes with some variation across individuals. As with nicotine gum, nicotine from the lozenge is absorbed slowly through the buccal mucosa and delivered into systemic circulation. The lozenge provides an alternative to the gum for persons who need intermittent and controllable nicotine dosing, but who do not find gum chewing acceptable.

The amount of nicotine absorbed per lozenge appears to be somewhat higher than that delivered by gum. Single dose studies demonstrated 8-10% higher $C_{\text{max}}$ values and 25-27% higher $AUC_{0-\infty}$ values from lozenges compared to gums at both 2-mg and 4-mg dose levels, which is probably due to the residual nicotine retained in the gum (Choi et al., 2003).

**Sublingual tablet**

A small nicotine tablet has been developed, and is currently being marketed in many European countries. The product is designed to be held under the tongue where the nicotine in the tablet is absorbed sublingually. Like the lozenge, the tablet has the advantage of not requiring chewing. The levels of nicotine obtained by use of the 2-mg lozenge and 2-mg nicotine gum are similar (Molander and Lunell, 2001).

In a randomized, double-blind, placebo-controlled trial of 2-mg sublingual tablets, success rates for complete abstinence for active versus placebo were 50% vs. 29% at 6 weeks, 42% vs. 23% at 3 months, 33% vs. 18% at 6 months and 23% (Wallstrom et al., 2000). This doubling of quit rates is comparable to the doubling seen with other forms of NRT. In this trial, adverse events were mild and tolerable, the most common being irritation and soreness in the mouth and throat.
Oral inhaler

The nicotine vapour inhaler, which consists of a mouthpiece and a plastic cartridge containing nicotine, was first marketed in the United States in 1998 as a prescription smoking cessation medication. The vapour inhaler was designed to satisfy behavioural aspects of smoking, namely, the hand-to-mouth ritual, while delivering nicotine to reduce physiological withdrawal symptoms produced by tobacco withdrawal. It is important to note that although termed an “inhaler” the majority of nicotine is delivered into the oral cavity (36%) and in the oesophagus and stomach (36%) (Lunell et al., 1996). Very little nicotine is delivered to the lung (4%). Because absorption is primarily through the oral mucosa, the rate of absorption is similar to that of nicotine gum.

Each inhaler cartridge contains 10 mg nicotine, of which up to 4 mg can be delivered and 2 mg can be absorbed (Molander et al., 1996) following frequent “puffing”. Patients may self-titrate with the inhaler to the level of nicotine they require. However, as with nicotine gum, success is largely dependent on the number of doses taken per day. In clinical trials, most smokers who successfully abstained from smoking used between 6 and 16 cartridges per day.

Nasal spray

Nicotine nasal spray was designed to deliver doses of nicotine to the smoker more rapidly than was possible with use of the gum or patch. The device currently available to consumers is a multi-dose bottle with a pump mechanism fitted to a nozzle that delivers 0.5 mg of nicotine per 50-uL squirt. Each dose consists of two squirts, one to each nostril (Fiore et al., 2000).

Nicotine from the nasal spray is absorbed into the blood rapidly relative to that delivered by gum or patch. Whereas the rate of plasma nicotine absorption with the spray approaches that of cigarettes and oral snuff, the magnitude of the increase in plasma nicotine concentrations is lower. According to labelling, the dose of nasal spray should be individualized for each patient based on the patient’s level of nicotine dependence and the occurrence of symptoms of nicotine excess. Patients should be started with one or two doses per hour, which may be increased up to the maximum of 40 doses per day. One dose of nasal spray per hour (1-mg nicotine) for 10 hours produces average plasma concentrations of 8 ng/ml.
Improving delivery

High-dose patches

The use of higher-dose patches would be predicted to better mimic the doses of nicotine achieved during tobacco use, particularly among heavy and more dependent users. Jorenby et al. (1995) conducted a randomized, double-blind clinical trial among 504 smokers who received 22 mg or 44 mg patches under different counselling conditions (Jorenby et al., 1995). Among those receiving minimal contact, the 44-mg dose produced greater abstinence at four weeks than did the 22-mg dose (68% versus 45%; \(P < 0.01\)). Hughes et al. (1999) conducted a randomized, double-blind trial in which 1039 smokers received 0, 21, 35, and 42 mg/day for six weeks followed by tapering over the next 10 weeks (Hughes et al., 1999). Continuous abstinence rates for the 0, 21, 35, and 42 mg doses at the end of treatment (12 weeks) were 16%, 24%, 30%, and 39%; however, there were no statistically significant differences between active treatments. Fredrickson et al. (1995) conducted an open-label study among 40 smokers to determine the safety and tolerability of a 44-mg/day dose for smoking cessation (Fredrickson et al., 1995). Subjects received 44 mg/day for four weeks followed by four weeks of 22 mg/day. Biochemically confirmed point prevalence smoking cessation rates were 65% and 55% at weeks four and eight of patch therapy. Taken together, these results suggest that there is some evidence to indicate that higher-dosage nicotine patches may improve treatment outcomes for highly dependent individuals.

Combined patch + acute forms

A strategy for further improving the efficacy of NRT is to combine one medication that allows for passive nicotine delivery (e.g. transdermal patch) with another medication that permits ad libitum nicotine delivery (e.g. gum, nasal spray, inhaler). The rationale for combining NRT medications is that smokers may need both a slow delivery system to achieve a constant concentration of nicotine to relieve cravings and tobacco-withdrawal symptoms, as well as a faster acting preparation that can be administered on demand for immediate relief of breakthrough cravings and withdrawal symptoms (Sweeney et al., 2001). This speed of onset of effects may be particularly important in the morning, when the withdrawal symptoms and craving are at a peak for many smokers. The patch provides nicotine in a steady-state and passive form while gum can be manipulated to accommodate the users’ needs. Thus combining use of the nicotine patch, which may prevent the appearance of severe withdrawal, with the gum, which can provide relief in trigger-to-smoke contexts, may provide an excellent treatment option over either therapy alone.
Clinical trials suggest incremental efficacy of patch plus gum compared to either product alone (Kornitzer et al., 1995; Puska et al., 1995). Less research is available on combinations of the patch and other acute NRT formulations. However, one study that compared the efficacy of the nicotine inhaler plus nicotine patch versus nicotine inhaler plus placebo patch for smoking cessation found a significantly higher abstinence rate at one year among those who used the combination (Bohadana et al., 2000). No studies have examined the patch in combination with lozenge, nasal spray, or inhaler, though it could be predicted that similar incremental efficacy would be observed with the combination.

Despite the possibility of increased efficacy, present NRT labelling warns against combination use. Without removal of such warnings, these strategies will be largely limited to smoking cessation specialists and clinics. The complexity of obtaining approval for combination medications, combined with the difficulty of marketing combination products, has slowed attempts by manufacturers to gain regulatory approval for combination therapies (Sweeney, Fant, Fagerstrom, McGovern, and Henningfield, 2001).

**Nicotine safety and toxicity**

Although nicotine can be toxic at very high dosages, relative to those typically delivered by use of tobacco or nicotine-replacement medications, its toxicological effects in tobacco use are generally considered modest compared to the many carcinogens and other toxins present in tobacco products and the many more produced when tobacco products are burned (Benowitz, 1998; Hoffmann and Hoffmann, 1997). For example, nicotine is not a carcinogen and nicotine replacement is not a risk.

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**Improving availability of Nicotine Replacement Therapies**

**Selected experiences**

**BRAZIL** - Brazil has been providing free support for smoking cessation services (pharmacological products and cognitive behavioural therapies) since 2002.

**CANADA** - A number of provinces and territories, including Ontario, Quebec and the Yukon cover nicotine-replacement therapies in Canada, nicotine replacement therapies are not taxable when prescribed by a physician. When purchased over the counter, taxes range from 7% to 15% but many provinces no longer impose a provincial sales tax.

**HONG KONG (SAR, CHINA)** - NRT is being provided through four outpatient facilities of the department of health.
factor for cancer. Nonetheless, nicotine delivered by tobacco products and medications is not benign. It can produce a variety of potential adverse effects depending upon the dose and pattern of administration. For example, cigarette smoking during pregnancy produces a high risk of problems that are attributed to the high levels of nicotine exposure and the additional substances available in the smoke such as carbon monoxide (Dempsey and Benowitz, 2001). At doses delivered by nicotine-replacement medications, the risk of adverse effects from nicotine during pregnancy appears substantially lower than by smoking. However, because the possibility of risks cannot be ruled out, it is generally recommended that a doctor be consulted concerning use of the medications during pregnancy (Oncken, 1996; Windsor et al., 2000). Similarly, nicotine is a presumed risk factor for coronary artery disease leading to labelling on nicotine medications advising persons with histories of heart disease to consult with a doctor before using the products (Benowitz and Gourlay, 1997).

The future

True pulmonary inhaler

As previously noted, the nicotine “inhaler” does not deliver nicotine to the lung, but rather deposits nicotine into the mouth and throat where it is absorbed through the buccal mucosa, making its delivery of nicotine more comparable to nicotine gum or lozenge than to a cigarette. Specifically, cigarettes deliver nicotine to the lung where absorption is rapid and almost complete. A true pulmonary inhaler, unlike the currently available nicotine inhaler, would delivery nicotine to the lung in a manner more comparable to cigarette smoking. This would be predicted to deliver a dose of nicotine sufficient to reduce background cravings and withdrawal symptoms, and would allow for rapid relief of acute cravings and morning craving. Because the delivery of nicotine directly to the lung would effectively mimic the effects of cigarette smoking on a physiologic level, the smoker could eliminate the need for tobacco, and subsequently taper the nicotine level over time to alleviate dependence upon nicotine altogether.

Although there are substantial technological challenges to producing an effective and acceptable lung inhaler, the greatest barrier to development may be the potential for abuse and the regulatory implications. Specifically, if the medication meets criteria for a controlled substance, its marketing could be severely restricted along the lines of morphine-like analgesics. The mechanisms of the regulatory framework are the United States Government’s Controlled Substance Act, and the World Health Organization’s Convention on Psychotropic Substances (McClain and Sapeinza,
1989). The provisions of the Controlled Substance Act were raised with respect to the nasal nicotine formulation for smoking cessation in 1994 when the FDA and other federal agencies considered whether the formulation should be regulated as a controlled substance such as morphine (US Food and Drug Administration, 1995; US Food and Drug Administration, 1996). In the final analysis, it was concluded that even though the nasal formulation met accepted criteria for a controlled substance, its abuse liability was substantially less than that of the ubiquitously available tobacco products and that prescription level of control would be adequate. Whether regulatory authorities would come to such a conclusion with a lung inhaler, if the lung inhaler were of substantially increased abuse liability is uncertain. Such uncertainties can be expected to limit commercial development of such a product because of the uncertain market for a tobacco-cessation product that is regulated as a controlled substance. This issue may require resolution if it is considered important to encourage development of NRT products that deliver nicotine to the lung or by other means that increase its abuse liability.

Non-nicotine medications and substances for treating tobacco dependence

In principle, a substance might be efficacious in treating dependence (i.e. aiding smoking cessation) without being efficacious in alleviating composite withdrawal scores and vice versa. Furthermore, a substance might be effective in treating a specific symptom of withdrawal without providing adequate relief of other withdrawal symptoms to justify its being considered efficacious for treatment of nicotine withdrawal. Whereas the ideal smoking cessation medication would be consistently effective in reducing all signs and symptoms of nicotine dependence and withdrawal, there is, in fact, wide variation in the degree to which various substances produce beneficial smoking cessation-related effects. Furthermore, substances with even narrowly limited benefits might be useful in helping people to reduce or quit smoking; however, it is important for health professionals and consumers alike to understand the benefits and limitations of substances used to treat nicotine dependence and withdrawal and to underline the degree to which various products are interchangeable.

A wide range of non-nicotine substances has been marketed for people who need help in reducing or quitting smoking and managing symptoms associated with withdrawal (Henningfield, Fant, and Gopalan, 1998). Currently, only bupropion has received regulatory approval for the treatment of tobacco dependence. However, clonidine and nortriptyline are also listed as “second-line medications” in the United States’ Clinical Practice Guideline: Treating Tobacco Use and Dependence (Fiore et al., 2000). Below is a brief summary of the evidence on these medications.


**Adherence to long-term quitting therapies**  
*a study in Hong Kong (SAR, China)*

The Hong Kong Smoking Cessation Health Centre provides smoking cessation services with trained counsellors and nicotine-replacement therapy. The services provided are free including a one week supply of NRT.

Of the 989 clients who were successfully followed up at three months, 90% (895 out of 989) were prescribed NRT.

A study was conducted on their adherence to cessation therapy, adherence being defined as self-reported use of NRT for at least four weeks.

Adherence to NRT therapy was seen to be a major factor associated with success in quitting and a significant predictor for quitting. The quit rate in the adherent group was 43% and significantly greater than the 29% in the non-adherent group.

Based on step-wise logistic regression analysis, predictors of adherence were seen to be age, sex, educational status, quitting for one day or more in the last attempt, experience of using NRT in the past, and perception of quitting as difficult. Those who were male, older, with more education and past experience of quitting or NRT use were more likely to adhere.

Overall prevalence of adherence was seen to be low, at 25% for three weeks of self-reported use and 19% for four weeks of use.

**Bupropion hydrochloride**

Negative mood is one of the symptoms of tobacco withdrawal, which may account for failures to quit smoking and relapse after cessation. For this reason, several antidepressants have been tested as smoking cessation aids. Bupropion Hydrochloride (*Zyban®, GlaxoSmithKline*) is a sustained-release formulation of the antidepressant medication. This is the first non-nicotine medication that has received approval by the United States Food and Drug Administration (FDA) for a smoking cessation indication, and is listed as a first-line therapy in the United States’ *Clinical Practice Guideline: Treating Tobacco Use and Dependence* (Fiore et al., 2000). It takes about five days or longer to achieve steady state plasma levels of the drug, thus it is suggested that a smoker begin use of the drug about one week before the quit date (Hurt et al., 1997). In a meta-analysis of two placebo trials of bupropion, the estimated odds ratio of efficacy relative to placebo was 2.1 (95% confidence interval 1.5-3.0) (Fiore et al., 2000).
There is also some evidence that a combination of bupropion and nicotine patch can increase efficacy over either product alone (Jorenby et al., 1999). However, there is currently no indication for combination use, and complexities in obtaining regulatory approval and difficulties in marketing make it unlikely that such an indication will be sought by manufacturers.

**Clonidine**

Clonidine has been shown to diminish symptoms of both opiate and alcohol withdrawal symptoms (Gossop, 1988), and may be useful for diminishing some tobacco withdrawal symptoms as well. Although not approved by regulatory authorities for smoking cessation, the United States’ *Clinical Practice Guideline: Treating Tobacco Use and Dependence* (Fiore et al., 2000) has given clonidine an “A” level of evidence indicating that there is a consistent pattern of positive findings in multiple well-designed clinical trials. In a meta-analysis of five trials in which clonidine doses varied from 0.1mg to 0.75 mg/day, the estimated odds ratio of efficacy relative to placebo was 2.1 (95% confidence interval 1.4-3.2) (Fiore et al., 2000). These results suggest that clonidine may be efficacious in the treatment of tobacco dependence, but the conditions under which it is most appropriately used are not well defined.

**Nortriptyline**

Nortriptyline is a tricyclic antidepressant that has been tested as a potential pharmacotherapy for smoking cessation. The United States’ *Clinical Practice Guideline: Treating Tobacco Use and Dependence* (Fiore et al., 2000) has given nortriptyline a “B” level of evidence indicating that there is some evidence supporting efficacy. In a meta-analysis of two trials, the estimated odds ratio of efficacy relative to placebo was 3.2 (95% confidence interval 1.8-5.7) (Fiore et al., 2000). These results suggest that nortriptyline may be efficacious in the treatment of tobacco dependence; however, because of the paucity of data, the medication should be considered a second-line therapy.

**Conclusion**

There is a wide range of treatment options that have been proved effective, including behavioural and pharmacological therapies. There is no single approach that should be emphasized to the exclusion of others because the therapies vary widely in their efficacy, their acceptability, their cost-effectiveness, and their cost on an individual
and population basis. For example, pharmacotherapies tend to require less human resource time to deliver and are more effective than many behavioural therapies, but can cost more in material resources. However, for some populations (e.g. pregnant women, and persons with heart disease), for whom there is an especially great benefit of cessation, the costs may be more readily justified. Minimal interventions by health professionals offer not only an important and cost-effective approach, such interventions can help to change the culture from one in which the health professionals are models for smoking to one in which they are models of non-smoking. Furthermore, public health approaches such as mass media campaigns, Quit and Win competitions and telephone help lines serve to play an important role in changing societal norms and promoting smoking cessation. Working with individual smokers to change their smoking behaviour is an important goal but has limited impact if the environmental factors that promote and support smoking are not also addressed. Hence, population-based interventions should be thought of as complementary approaches to individual-based behavioural or pharmacological interventions.

On the basis of the variety of proven methods and variety of needs within and across countries, it would appear that the ideal goal would be to work towards maximizing the options and occasions for smoking cessation interventions, both population- and individual-based, within and across countries.

References


Lam TH. Smoking cessation experience in Hong Kong. Presentation at the occasion of the WHO meeting on Global Policy for Smoking Cessation hosted by the Ministry of Health of the Russian Federation, Moscow, 14-15 June 2002.


Sändigstrom P Quit and Win. Presentation at the occasion of the WHO meeting on Global Policy for Smoking Cessation hosted by the Ministry of Health of the Russian Federation, Moscow, 14-15 June 2002.


POLICY RECOMMENDATIONS FOR SMOKING CESSATION AND TREATMENT OF TOBACCO DEPENDENCE


WHO Europe, [www.treatobacco.net](http://www.treatobacco.net).

Wilson E. Smoking cessation experience in Canada. Presentation at the occasion of the WHO meeting on Global Policy for Smoking Cessation hosted by the Ministry of Health of the Russian Federation, Moscow, 14-15 June 2002.


