

Minireview

The Pharmacotherapy Of Smoking Cessation

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ABSTRACT

The great majority of smokers are chronically dependent on tobacco. This dependence arises from the rituals and sensory associations of smoking that are reinforced, within seconds, by a rapid burst of nicotine from the cigarette. All forms of nicotine replacement therapy (NRT) — gum, patches and inhaler — and bupropion are safe and effective for increasing smoking cessation rates in the short and long terms. Other than those who are minimally dependent, all patients willing to quit should be offered one of these therapies unless contraindications exist. The effectiveness of drug treatments is multiplied when associated with effective counseling or behavioral treatments. While NRT is not recommended during pregnancy or in patients with cardiac disease, if the alternative is smoking NRT is almost certainly safe. Combination NRT (more than one therapy) may be indicated in patients who have failed monotherapy in association with withdrawal symptoms. There are some specific contraindications to the use of bupropion. Its subsidized availability should not influence prescribers to ignore these.

Keywords : NRT, Nicotine , Bupropion

In the world, cigarette smoking is the most significant cause of avoidable health harm. To reduce this, individual clinicians should follow the so-called five A's — Ask about smoking; Advise quitting; Assess current willingness to quit; Assist in the quit attempt; and Arrange timely follow-up [1]. While this review focuses on the forms of drug therapy that assist cessation, these treatments should be coordinated with the general and specific support and counseling strategies that are also of proven benefit [2].

The great majority of regular smokers are dependent on cigarette smoking, and not simply addicted to nicotine [3]. Smoking is highly contextual and associated with certain rituals. These start with the opening of a packet, followed by the lighting process and then the sight and smell of smoke. After inhaling smoke from a modern cigarette, arterial nicotine levels increase markedly within 15 seconds [4]. This bolus of nicotine activates the brain-reward system by increasing dopamine release [5]. This brain reward system is a common pathway for pleasurable activities like sexual activity, eating and most drugs of addiction [6]. This peak in plasma nicotine level, and the transient activation of the reward system, is followed by a gradual fall in nicotine levels into a state

of withdrawal [7] that is, in turn, relieved by the next cigarette. Dependence arises from the temporal association of the rituals and sensory inputs with the repeated stimulation and relief of withdrawal [2]. This required association explains why nicotine replacement therapy (NRT) products, that deliver nicotine slowly and do not produce high plasma nicotine levels, have minimal addictive potential [8].

The aim of NRT is to assist smoking cessation by providing a near-constant level of nicotine above that which is associated with withdrawal. No form of NRT can replicate the rapid nicotine delivery from a cigarette. The NRT formulations available in India include gum, patches and oral inhaler. Nicotine nasal spray and a sublingual tablet or lozenges are not presently available in India.

Gums contain nicotine (2 mg or 4 mg per piece) in a resin base. The gum should be chewed slowly, and then left between the cheek and gum. Over the next 20–30 minutes, the gum should be chewed intermittently and repositioned. Because nicotine is poorly absorbed in an acid environment, acid drinks such as fruit juices should be avoided. As smokers may be conscious of the per-piece cost, there may also be a tendency to use an insufficient number of pieces or not to continue with treatment for long enough. It is preferable for patients to use gum on a regular basis. While extra doses may not rapidly increase nicotine levels, the process of their use is a ritual that is in some ways analogous to smoking, and this may be an advantage.

Nicotine transdermal patches are designed to release nicotine slowly. Immediately after application, there may be relatively rapid transfer of nicotine from the adhesive layer. In steady-state phase, nicotine will exist in the patch, in a skin “reservoir” and in the circulation. The presence of the skin reservoir reduces the rate of decay of plasma levels after the patch is removed. Patches come in a variety of dose strengths from 7 mg to 21 mg, and in preparations designed to be used for 16 or 24 hours. Patches are applied each morning. The 16-hour preparations are useful for smokers who experience insomnia or other nocturnal symptoms. Patches should be applied on a rotational basis to a variety of non-hairy skin sites. Local skin reactions are the commonest adverse effect. This can be minimized by rotation among a number of sites of application, but can be severe enough to require discontinuation.

The inhaler is a plastic cartridge that is inserted into a mouthpiece. Gaseous nicotine is released by deep inhalation through the mouthpiece. Twenty minutes after the first deep inhalation, the device has released about 4 mg of nicotine. This process, as with patches and gums, does not release nicotine rapidly [9], but it does replicate some of the smoking rituals. After use, the device is spent and cannot be reused or recycled.

BUPROPION

Bupropion was developed and first marketed as an antidepressant. Although it is an effective antidepressant [10], it is not marketed for this purpose. Anecdotal observation of spontaneous smoking cessation in depressed smokers [11] led to its further evaluation as an aid to smoking cessation [12] and the later development of the sustained release form. The suggested mechanism of action is inhibition of neural reuptake of dopamine or noradrenaline, but this may be simplistic [13]. Bupropion is not related to other classes of antidepressants presently in clinical use. With the exception of nortryptiline, which has a weak effect, these other antidepressants do not increase rates of smoking cessation [1]. There is no evidence that the antidepressant activity of bupropion contributes to its efficacy in smoking cessation.

The mechanism of action of bupropion in smoking cessation is not clear, but may involve central adrenergic and dopaminergic systems. In an experiment, two subcutaneous injections of nicotine to rats, on post-natal days 14-15, significantly enhanced the magnitude of functional responses in the hippocampal region, arising from the upregulation of type II and type III nACh receptors. This upregulation could be an important signal in nicotine addiction which is effectively blocked by bupropion.

The A1 allele of the dopaminergic D 2 receptor gene (DRD2) is associated with a reduced number of dopaminergic binding sites in the brain and with the increased likelihood of substance abuse and addictive behaviour. Women with at least one A1 allele will stop taking bupropion due to its side effects. This variation is not seen in men.

DOSE AND ADMINISTRATION

Treatment should commence at 150 mg daily for three days, and then decrease to 150 mg twice daily. The nominal target date for

Box 1 The Fagerström test for nicotine dependence		
Question	Answer	Score
How soon after you wake do you smoke your first cigarette?	Within 5 minutes	3
	5–30 minutes	2
	31–60 minutes	1
	Over 60 minutes	0
Do you find it difficult to refrain from smoking in places where it is forbidden?	Yes	1
	No	0
Which cigarette would you most hate to give up?	The first one in the morning	1
	Any other	0
How many cigarettes per day do you smoke?	10 or less	0
	11–20	1
	21–30	2
	Over 30	3
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0
	Score	Rating
	0 to 2	Very low dependence
	3 to 4	Low dependence
	5	Medium dependence
	6 to 7	High dependence
	8 to 10	Very high dependence

smoking cessation is Day 7 of treatment. However, some smokers lose the desire to smoke before this, and successful, long-term cessation is seen even in those who smoke beyond Day 7 [14].

SIDE EFFECTS, PRECAUTIONS AND CONTRAINDICATIONS

Nausea, insomnia and dry mouth are common early symptoms. The time to peak plasma level is three hours. Therefore, if insomnia is prominent, the evening dose may be taken early, but at least eight hours after the morning dose. Seizures are the major side effect of concern. When bupropion was initially used as an antidepressant, the seizure rate was one in 1000, similar to that with other antidepressant medications. With the slow-release formulation used for smoking cessation, seizures are even less common, but warnings associated with pre-existing conditions and concomitant medication, especially monoamine oxidase inhibitors and drugs that lower the seizure threshold, must be strictly followed.

Bupropion is absolutely contraindicated in patients with a history of epilepsy, and there is a relative contraindication in conditions that might increase the risk of seizures, such as type 1 or 2 diabetes. If it is to be used in patients with such conditions, it should only be after careful consideration of the risks and alternative treatment options, balanced against the benefits of cessation in the individual. Hypersensitivity reactions are the other adverse effects of concern. Facial edema has been reported, as has a serum-sickness-like reaction [15]. Adverse cardiovascular effects are rare. At last report, there had been 18 deaths associated with Zyban use reported to the Therapeutic Goods Administration (TGA) [16]. At present, bupropion should not be prescribed during pregnancy, as there is insufficient evidence to establish its safety.

USE OF NRT IN CARDIAC DISEASE AND PREGNANCY

There is now quite extensive evidence that NRT is safe in patients with stable cardiac disease such as angina pectoris [17,18]. Evidence is lacking in acutely unstable patients, but NRT would produce lower peak and cumulative nicotine exposure levels than smoking, without delivering the increased carboxy hemoglobin and the many other vasoactive compounds in smoke. The issue of NRT use in pregnancy is a vexed one. In one randomized study, NRT by patch did not increase cessation during pregnancy, but did increase birth weight, perhaps by reducing total smoke exposure [19]. The second issue is safety. Prenatal exposures to nicotine have important developmental effects, but, as total nicotine levels are lower with NRT than smoking, if the alternative is active smoking NRT is almost certainly safe in pregnancy [20].

Because of residual safety concerns, use of NRT in pregnant women should be aimed at those who are moderately or highly dependent and have been unable to quit by other means [19]. NRT is most likely to be effective if combined with high-intensity counselling. Careful supervision of NRT could include monitoring of urinary cotinine levels and use of non-continuous treatment — gum, spray and 16-hour, rather than 24-hour, patches. A key message here is that women contemplating pregnancy should try to quit beforehand, as pregnancy is not a time during which smoking cessation is easy to achieve [21].

CLINICAL MANAGEMENT OF THE SMOKER PREPARED TO QUIT

In counselling smokers about the optimal means to achieve cessation, clinicians should make an assessment of dependence. Box 1 shows the Fagerström test for nicotine dependence, which may be useful and is simple to administer [22]. If there is not the opportunity to apply the Fagerström test, the number of cigarettes smoked daily and the interval between waking and first cigarette will give a rough guide to the degree of dependence. Some long-term smokers do have minimal dependence. They typically smoke small numbers of cigarettes, and may cease smoking for short or longer periods without withdrawal symptoms. This group is worth identifying, as such smokers should be able to quit without pharmacological assistance.

Drug treatments address some of the biochemical aspects of smoking, but are most effective when counselling or behavioral programs are used to redress the associated contextual and ritual elements [2]. The effectiveness of programs and products for smoking cessation needs to be judged against the “natural” rate of smoking cessation that is in the range of 1.5%–3% per year [23, 24]. Placebo success rates in all published drug treatment trials are typically higher, about 10%–15% at end of treatment and 5%–10% after one year, as participants are self-selected as interested in quitting and receive at least a minimum level of counselling. Other than those who are minimally dependent, all smokers trying to quit should be advised to use one of the range of safe, effective treatments available [1,2]. All forms of NRT about double the chance of successful cessation [25]. The number of patients needed to treat to achieve one extra successful quitter is about 10. Patients report a preference for patches over gums, sprays or the inhaler and tend to use patches nearer to the fashion recommended, but these differences do not affect cessation rates [26].

If the initial treatment is a nicotine patch, 16-hour and 24-hour patches are equally effective. There is a modest increase in success for increases in delivered dose above 20 mg [27]. There is no need to adjust patch dose based on smoking level before cessation [28]. Treatment periods should be at least eight weeks. There is no medical need to taper treatment, but the process of tapering is reassuring to some patients. Smoking while using patches has a trivial safety risk, but above all predicts a very low chance of successful cessation. If a patient is still smoking after seven days, the quit attempt should be terminated, with the intention of trying again at a later time. If gum is used, 4 mg doses are associated with greater chance of cessation in smokers with higher dependency [29,30]. Other than those who are minimally dependent, smokers should be advised to use 4 mg pieces. Tapering to 2 mg doses later is intuitively logical, but of unproven benefit. If the nicotine inhaler is chosen, at least six cartridges should be used initially. Tapering the dose is recommended after three months without evidence to support this.

A range of studies have shown that bupropion increases the chance of success 2.1-fold, with the number needed to treat to achieve an extra successful quitter being 7.5[1]. The one comparative study published found that bupropion (150 mg twice daily) produced a higher cessation rate than nicotine patch alone [31]. However, the quit rate with NRT in this study was lower than that generally found in other studies. In a second study, bupropion and NRT by patch were compared for their effect on late quitting from Week 4

onwards. Late quitting was more common with bupropion than NRT but this could be predicted from other studies. The likelihood of successful cessation with bupropion is not reduced in patients previously treated with bupropion [32]. The choice of recommending NRT or bupropion will rest on individual patient characteristics and preferences.

IMPORTANT MESSAGES FOR PATIENTS

Stopping smoking will improve your health in the short term and long term, but quitting without some support is almost always unsuccessful. Drug treatments are safe and effective, especially when combined with the support of your doctor.

It is important for you to think about your lifestyle and how you might change it to help you stay off cigarettes. Many patients need to try a number of times before they are successful and you should not fear failure. If you do relapse, there will always be another chance.

FUTURE PERSPECTIVE

1. Rimonabant (SR 141716): Rimonabant is a selective cannabinoid receptor antagonist which blocks the CB-1 receptor. In animal studies, it has shown beneficial effects in treating obesity, smoking cessation[33] and metabolic syndrome. In human studies, rimonabant has been effective in the treatment of obesity and smoking cessation. To date only nausea is reported to be greater than placebo.[34]

Rimonabant also participates in the regulation of the impaired endocannabinoid system and reduces nicotine self administration.[35] In animal experiments involving rat models, cues which maintain nicotine seeking behaviour several weeks after withdrawal is reversed by rimonabant, suggesting that it is not only effective in smoking cessation, but also capable of maintaining abstinence.[36]

2. Nicotine vaccine: Currently under Phase II trials, the nicotine vaccine acts by inducing nicotine specific antibodies which can combine with nicotine in the blood and prevent nicotine's entry into the brain, thereby reducing its addictive potential and preventing a relapse following smoking cessation.[37]

3. Topiramate: It is an AMPA/kainite antagonist and thus could be of value in the treatment of addiction. A small study, comprising 13 subjects, has shown this agent of some value in the pharmacotherapy of smoking cessation.[38]

4. Varenicline: Varenicline tartarate is a selective nicotinic receptor, partial agonist. A multicentre phase II double blind trial compared varenicline with placebo and bupropion with placebo as control. The results were comparable for both the drugs in terms of efficacy and tolerability.[39] Varenicline could provide a new approach in the pharmacotherapy of smoking cessation.

5. Nortriptyline: Nortriptyline is the main active metabolite of amitriptyline, with longer $t_{1/2}$ than the parent compound. Nortriptyline undergoes extensive first pass metabolism in the liver to active compound 10 hydroxy nortriptyline. In a meta analysis of 5 trials, comprising 861 smokers, it was concluded that with

nortriptyline higher prolonged abstinence rates were seen at 6 months as compared to the placebo. The drug was well tolerated and its use as a first line agent in smoking cessation is recommended, considering its efficacy and low cost.[40-42]. One randomised trial evaluated the efficacy of nortriptyline combined with nicotine transdermal patch to a placebo. The cessation rates were 23% and 10% respectively. Most frequent adverse effects were dry mouth (38%) and sedation (20%). There was no significant effect on withdrawal symptoms.

6. Glucose tabs: Single doses of nicotine relieve hunger in smokers and hunger pangs, sometimes, are associated with a craving for cigarettes. The adaptation to long-term nicotine intake leads to the exacerbation of these sensations during periods of abstinence. A placebo-controlled study has shown that glucose tablets increase one month abstinence rates significantly when compared to placebo. The low cost of glucose tablets can make it a useful adjunct in smoking cessation treatment.[43].

7. Mecamylamine: It is a nicotine antagonist and may block the rewarding effect of nicotine, thereby reducing the urge to smoke. In a study of 48 volunteers, a combination of mecamylamine with the nicotine patch was found more effective than the nicotine patch alone (abstinence rate at one year was 37.5% Vs. 4.2%). Another study of 80 volunteers compared mecamylamine alone with nicotine alone. The combination of mecamylamine with nicotine and the placebo showed a highest abstinence rate of 40% and statistically significant benefit with mecamylamine, using the Kaplan Meir survival analysis. Mecamylamine was well tolerated and only dose reduction was required in 40% of the subjects because of constipation.[44]

8. D 3 receptor ligands: Pharmacological and behavioural evidence implicates dopamine D 3 receptors in the mechanisms underlying stimulus controlled drug seeking behaviour. BP 897 (a D 3 receptor partial agonist) and ST 198 (a D 3 receptor antagonist) have been shown, in animal experiments, to reduce the motivational effects of mechanisms distinct from those of NRT and bupropion. These findings suggest that D 3 receptor ligands would be selective for rewarding and reinforcing the effects of nicotine which contribute to tobacco smoking behaviour, without affecting subjective responses to nicotine or producing any antidepressant-like effect.[45]

9. Tryptophan and high carbohydrate diet: Serotonin enhancing substances such as tryptophan and high carbohydrate diets have been shown to reduce the negative effect, which is also a classic symptom of withdrawal. In a randomised trial comparing tryptophan with the placebo, the former group smoked fewer cigarettes daily. Reported anxiety and other withdrawal symptoms were lower in the tryptophan group as compared to the placebo group.[46] Thus, tryptophan and high carbohydrate diet could become an important adjuvant in smoking cessation therapy. However, more trials involving a larger number of patients and standard treatment are required. [47]

CONCLUSION

Tobacco dependence is a chronic, relapsing medical illness. Reasonable standard of care now requires that smokers be identified and that proven, effective strategies that will maximize the chance of safe cessation are used. Doctors must therefore

become sufficiently familiar with bupropion and one or more forms of NRT to confidently recommend suitable treatment.

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