

Pharmacotherapy of smoking cessation and the Indian scenario

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Received: 22.12.2005

Revised: 24.4.2006

Accepted: 21.5.2006

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ABSTRACT

Tobacco smoking is a leading cause of preventable diseases and deaths, both in India and the rest of the world. Various effective methods are now available which can help a person to quit smoking. However, the awareness of such interventions and the will to implement them are lacking both among tobacco addicts and healthcare providers in India. This article reviews the various pharmacological interventions currently available, the Indian scenario with regard to smoking cessation and the impact of smokeless tobacco use.

KEY WORDS: Bupropion, nicotine dependence, NRT.

Introduction

There are over 3 billion cigarette smokers world wide, of which 112 million are in India. India is the third largest producer and consumer of tobacco in the world.^[1] Morbidity and mortality is continuously on the rise, in the Indian population, from tobacco use. Besides cigarettes, Indians smoke 'bidis' (tobacco rolled inside tendu leaves). However, the use of smokeless tobacco like 'gutkha' (a chewable flavoured tobacco product) and 'khaini' (tobacco rubbed with lime and put in between the cheek and gums), almost equals cigarette/bidi smoking and is more prevalent among females (smoking: male 29.4%, female 2.5%; smokeless: male 28.3%, female 12.4%).^[2]

Impact of smoking on health

Tobacco smoke contains over 1,000 identifiable chemicals of which nicotine and tar are the most important. Nicotine in tobacco smoke is responsible for dependence and tar is linked to various cancers affecting the lungs, stomach, urinary bladder and kidneys.^[3] Sufficient data exist, which links cigarette smoking to cardiovascular diseases such as coronary artery disease, hypertension, stroke and peripheral vascular disease.^[4-6] Smoking is related to respiratory diseases such as chronic obstructive pulmonary disease (COPD) and chronic bronchitis. It also worsens bronchial asthma^[7] and increases the risk of cancer of the cervix, especially in women suffering from HPV infection.^[8]

The risk of smokers developing tuberculosis is significantly high and is a point of concern for a developing country like India. Smokers face a 2-3 fold increased risk of developing influenza. So the influenza vaccine is

recommended for heavy smokers.^[9] Plasma fibrinogen level, which is an independent risk factor for cerebrovascular disease (CVD), remains high in smokers compared to non-smokers. The elevated fibrinogen remains high even for 15 years after a person quits smoking.^[10] There is a bidirectional association between smoking and erectile dysfunction (ED). Smokers have a higher risk of ED than non-smokers and those with ED were found more likely to be smokers.^[11] Smoking is also associated with hearing loss, as is evident from a meta analysis of 15 observational studies.^[12] Smoking can cause Crohn's disease, but on the contrary some improvement is seen in the course of illness of ulcerative colitis.^[13] Due to its antiestrogenic effect, cigarette smoking can induce early menopause and osteoporotic changes in women.^[14] Women smokers (>35 years), on oral contraceptives, are more prone to thromboembolic disorders.^[15]

Benefits of smoking cessation

Timely intervention for smoking cessation not only reduces the risk of major diseases, but also modifies the clinical course and outcome of certain disorders. In smokers with Crohn's disease, stopping smoking saw a 65% reduction in the risk of relapse, which was of same magnitude as that of immunosuppressive treatment. Hence, smoking cessation was recommended as the primary therapeutic aim in such cases.^[13] In a cohort study involving Canadian women, it was observed that the risk of lung cancer mortality among those who quit smoking before the age of 50 or in the previous 10 years, was significantly lower than that of current smokers.^[16]

Stopping smoking is beneficial in lung cancer patients prior to surgery, while continued smoking at the time of operation

met with poor prognosis.^[17] Smoking after cancer diagnosis shortens survival time and increases the risk of recurrence and development of another primary tumour, reduces treatment efficacy and increases complications of treatment.^[18] There can be potential interactions of smoking with antitumour therapy which might prove detrimental to surgery, radiation and most importantly chemotherapy.^[19] Smoking cessation is the most effective intervention to reduce the risk and progression of COPD.^[20] However, the increased airway epithelial and T cell apoptosis in COPD remains, despite smoking cessation, contributing to local inflammation.^[21] Stopping smoking can improve erectile dysfunction in a large number of patients. The age and severity of erectile dysfunction, before stopping smoking, are inversely related to the chance of improvement.^[22] Smoking is a well-known cause of atherogenesis and increased tendency towards thrombosis. A study found that even two weeks of smoking cessation greatly improves platelet aggregation and intra-platelet redox imbalance, thereby decreasing oxidative stress.^[23]

Barriers to smoking cessation therapy

The nature of nicotine dependence itself is the single most important factor affecting smoking cessation interventions. Even smoking a single cigarette can cause nicotine dependence.^[24] Subjective well-being is a remarkable effect of nicotine on mood.^[25] There is also reinforcement with each puff. Development of tolerance to the subjective effects of nicotine naturally increases the use of number of cigarettes smoked per day. The cause of tolerance is the avid, longer duration of the binding of exogenous nicotine to acetylcholine receptors, leading to down regulation of CNS ACh receptors, needing nicotine reinforcement to maintain the elated mood and thus causing dependence. In dependent smokers, low blood nicotine level produces typical craving and withdrawal symptoms such as irritability, anxiety, depression, restlessness, poor concentration, increased appetite, weight gain and insomnia, leading to 'negative reinforcement'.^[26, 27] One of the reasons offered by smokers for not quitting is weight gain.^[28] Weight gain after smoking cessation largely depends on genetic factors and occurs mostly due to an increase in subcutaneous body fat.^[29] The actual mechanism of weight gain is not well understood, but the carriers of DRD2 A-1 minor allele exhibit a significant increase in the rewarding value of food, following abstinence from smoking.^[30] Moderate calorie restriction produces a small but significant increase in smoking and dieting may actually increase smoking behaviour, which can interfere with attempts of smoking cessation.^[31]

Smoking cessation interventions – Guidelines and goals

The WHO expert committee on smoking control had formulated certain guidelines in 1979 which recommended the following.

1. Non-smoking should be regarded as normal social behaviour and all actions which can promote the development of this attitude are taken into consideration.
2. There should be a total prohibition of all forms of tobacco promotion.

3. Promotion of the export of tobacco and tobacco products should be discouraged. Tobacco-growing and manufacturing industries should be progressively reduced in size as rapidly as possible.
4. Governments should recognise the serious dangers for smokers in certain industrial occupations and develop special programmes to eradicate smoking from these industries, introducing legislation, where necessary. The synergy between smoking and certain occupations implies the need for careful monitoring in industries where toxic inhalation is a problem and indicates the need for research in this area.
5. Upper limits should be established for appropriate emission products of cigarettes. These limits (currently for tar, nicotine, and carbon monoxide) should be progressively lowered as rapidly as possible.^[32] However, there still exists a big gap between the recommendations and the actual implementation by the respective governments.

As per the US Public Health service report, the aims of the smoking cessation treatment should be as follows:

1. The achievement of long-term or permanent abstinence.
2. Effective treatment should be offered to all tobacco users.
3. There should be consistent identification, documentation and treatment of every tobacco user at each visit to the hospital.
4. Brief tobacco dependence treatment is also effective and thus should be offered.
5. A strong relationship exists between the intensity of tobacco dependence, counselling and its effectiveness.
6. Practical counselling and social support, arranged outside of treatment, are helpful.
7. Of all the effective pharmacotherapies, at least one of these medications should be prescribed in the absence of contraindications.
8. Tobacco dependence treatments are cost effective and should be covered by health insurance plans.^[33]

There are two types of interventions, namely non-pharmacological and pharmacological.

Non-pharmacological interventions

Non-pharmacological interventions are important as they are cost effective and, when combined with pharmacological interventions, give better abstinence rates, even in resistant cases with frequent relapses.^[34]

1. *Counselling by medical practitioners:* In a study conducted at a Singapore General Hospital with 394 out-patients and 425 in-patients, it was found that 41% achieved immediate quit rates for counselling, compared to 36% for bupropion. This quit rate was sustained at 35% after 12 months of follow-up. A quit rate of 32% was achieved even with one-time in-patient counselling.^[35] It is also recommended that child health care clinicians help parents quit smoking by counselling and prescribing medications.^[36]
2. *Smoking cessation strategies delivered by nurses and support organisations:* As compared to physicians, nurses and social workers are more in touch with the patients. The cessation strategies delivered by them can

have a much better and wider impact. Considering the magnitude of the benefit, it is recommended that nurses and social workers receive formal training in all the currently available interventions for smoking cessation including follow-up.^[37]

3. *Telephonic call back and follow-up*: This is an effective way to monitor patients who undergo treatment for smoking cessation as it also provides the necessary motivation to continue abstinence. Active calls made within the first 3 months of quitting produce a higher quit rate even at 12 months.^[38]
4. *Health education*: The ill effects of smoking and its impact on the society and environment should be taught at school, at work places and to the various special sections of society, who are at risk, by way of lectures, seminars and symposiums. This will create an environment of opinion where smoking ceases to be socially acceptable and those who smoke can be persuaded to quit smoking.
5. *Heavy taxation on tobacco products*: Levying heavy taxes on tobacco and tobacco products could result in a significant decrease in tobacco consumption.

Pharmacological interventions

Various effective pharmacological methods of smoking cessation are now available and should be advised to all smokers in the absence of contraindications.^[32]

(A) *Nicotine replacement therapy (NRT)*: NRT is an effective treatment to reduce cravings associated with smoking cessation. The methods used in NRT do not produce the same peak levels of nicotine in the blood as seen with cigarettes and thus do not cause the same subjective effects. They, however, suppress the symptoms of nicotine withdrawal. Smokers can now shift their dependence to an alternative nicotine delivery system which can be gradually withdrawn.^[39] Various formulations of NRT are available such as chewing gum, transdermal patch, inhalator, nasal spray, nicotine sublingual tablets and lozenges.^[40]

1. *Chewing gum*: This is available in 2 and 4 mg strengths. The nicotine is present in the form of a complex with methacrylic acid polymer (nicotine polacrilex). Individuals who smoke 20 or less cigarettes per day should start with the 2 mg strength gum, to be chewed slowly over 30 min when there is an urge to smoke. Those smoking more than 20 cigarettes per day, should use the 4 mg gum.
2. *Sublingual tablets*: They are the equivalent of 2 mg nicotine as β cyclodextrin complex. The recommended dose is 1-2 tabs sublingually, increased to a maximum of 40 tabs daily if necessary, for at least 3 months. The dose should be gradually reduced and then withdrawn.
3. *Lozenges*: They contain 1mg of nicotine (as tartrate). Lozenges are not suitable for individuals with strong dependence or those who failed to quit smoking with the aid of other NRT. The initial dose is one lozenge every 1-2 h, increasing up to a maximum of 25 lozenges daily. The treatment should continue for at least for three months after which it is gradually withdrawn.
4. *Adhesive transdermal patch*: Transdermal patches are designed to be applied for 16 or 24 h and are available in different strengths, delivering 5-22 mg nicotine during

the recommended wear time. One patch is to be applied daily to the hip, trunk or upper arm, usually beginning with the highest dose or with a dose determined by the previous daily consumption of cigarettes. A different site of application should be used each day, with several days gap before the patch is applied to the same area of skin. A gradual withdrawal is recommended by reducing the dose every 2-8 weeks.

5. *Nasal spray*: The suggested initial dose for a nasal spray (500 μ g per actuation) is one spray into each nostril, twice an hour, up to a maximum of 80 sprays daily for the first 8 weeks and reduced thereafter.
6. *Nicotine inhalator cartridges*: They contain 10 mg nicotine for use in an inhaler. The initial dose is 6-16 cartridges per day for 12 weeks and reduced gradually over 6-12 weeks.

NRT should be reviewed if abstinence is not achieved in 3 months. The choice of formulation is based on the patient's preference, tolerance and previous treatment, if any. The transdermal patch is the easiest to use and compliance is the greatest with this route. However, local untoward effects such as itching and irritation may occur. The gum has an unpleasant taste initially and some people find chewing difficult. It requires frequent dosing and also causes jaw pain and soreness of the mouth. Nasal spray has a faster onset of action, but may cause local irritation. A lozenge has an advantage in that it can be sucked discretely. A nasal spray can cause irritation of the nose and eyes. An inhalator produces mouth and throat irritation. Combination therapy of various NRT can be used without any increase in significant adverse effects.^[41]

NRT is usually continued for about 3 months before being withdrawn. Although manufacturers advise a gradual withdrawal, others have found that it offers no advantage and recommend abrupt withdrawal. NRT has also been advised for long-term use in patients who fear relapse if NRT is stopped or in those who have persistent withdrawal symptoms.

There are concerns over the use of NRT in patients with cardiovascular disease, but clinical experience and experiments show that NRT can be used with some precaution.^[42] However, NRT use in cases of recent MI or arrhythmia is contraindicated.^[43]

Nicotine is readily absorbed through the mucous membrane and skin. Bioavailability of oral nicotine is low due to extensive first pass metabolism. Nicotine is widely distributed, crosses the placenta and is found in breast milk. The elimination half life is about 1-2 h. Nicotine is metabolised, mainly in the liver via cytochrome P-450 isoenzyme CYP2A6 to cotinine and nicotine oxide. Nicotine and its metabolites are excreted in urine. Since CYP2A6 has a significant role in nicotine metabolism and population distribution of CYP2A6 alleles is important as it can affect the dependence trend in various ethnic groups.^[44]

Craving intensity follows the circadian rhythm with the lowest intensity in the morning and peak intensity on the evening. Nicotine delivered *via* the patch had no impact on these circadian variations. These observations suggest that craving and withdrawal symptoms may be sustained by different physiological pathways and only selected

components of cigarettes are influenced by NRT.^[45] Using a higher dose of transdermal nicotine than usual can reduce the craving and decrease the number of cigarettes smoked per day, even in heavy smokers.^[46]

(B) Bupropion hydrochloride: Bupropion hydrochloride is given as a modified release preparation (Bupropion SR), as an aid to smoking cessation, in an initial dose of 150 mg once daily for 6 days, increasing to twice daily on Day 7. The maximum recommended dose for patients with predisposing risk factors for seizure is 150 mg per day. Treatment should be started one week before the patient attempts to stop smoking, to allow steady state blood levels of bupropion to be reached, and is normally continued for 7-12 weeks. If there is no significant progress towards smoking abstinence by the 7th week, then the therapy should be stopped.

Bupropion is well absorbed from GIT, but may undergo extensive first pass metabolism. Several metabolites are pharmacologically active and have longer plasma half life and achieve greater plasma concentration than the parent compound. Bupropion is metabolised through CYP2B6 and hydroxyl bupropion is the active metabolite, with comparable potency as the parent compound. Several different CYP enzymes are likely to be involved to a clinically significant degree in the biotransformation of bupropion. *In vitro* drug metabolism studies have shown that several different CYP enzymes (i.e., CYP2B6, 3A4, 2A6, 2E1 and 1A2) can mediate the biotransformation of bupropion.^[47]

Metabolites are excreted in urine, and less than 1% of the parent drug is excreted unchanged. Bupropion and its metabolite cross the placenta and are distributed in breast milk.^[48] No significant differences between smokers and non-smokers or between male and female volunteers were seen for bupropion pharmacokinetics. Hence, there is no need for dosage adjustment with respect to gender.^[49]

The mechanism of action of bupropion in smoking cessation is not clear, but may involve central adrenergic and dopaminergic systems.^[50] 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.^[51]

The A1 allele of the dopaminergic D₂ 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.^[52]

The side effects of bupropion include agitation, anxiety and insomnia. Other less frequently reported side effects are fever, dry mouth, headache or migraine, nausea, vomiting, tremors, sweating and skin rashes. Tachycardia, chest pain and hypertension (sometimes, severe) and occasional postural hypotension have been reported.

Seizures, which are partially dose related, are particularly noted in patients with anorexia nervosa or bulimia nervosa and patients with past history of seizure disorder. Over all, seizure risk is 0.1-0.4%.^[53]

Bupropion should not be given with MAO inhibitors. Its use, along with nicotine transdermal patches, has been associated with hypertension. Bupropion is also an inhibitor of CYP2D6 and drugs metabolised by this enzyme should be given carefully, for instance, beta blockers. Prescribers should reconsider the dose of bupropion when starting or stopping a CYP enzyme inducer or inhibitor, for instance, fluoxetine, carbamazepine, since such an action could change the clearance of bupropion and/or one or more of its metabolites.^[54] Bupropion does not increase the rate of major malformation in foetuses above the baseline. However, a higher rate of spontaneous abortions are similar to the other studies examining the safety of antidepressants in pregnancy.^[55] Bupropion is effective for smoking cessation during pregnancy.^[56]

New agents and therapeutic adjuncts

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^[57] 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.^[58] Rimonabant also participates in the regulation of the impaired endocannabinoid system and reduces nicotine self administration.^[59] 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.^[60]
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.^[61]
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.^[62]
4. **Varenicline:** Varenicline tartrate 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.^[63] 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 (RR = 2.4, 95% CI 1.7 to 3.6; 95% CI 0.07 to 0.15). The drug was well tolerated and its use as a first

line agent in smoking cessation is recommended, considering its efficacy and low cost.^[64-66] One randomised trial evaluated the efficacy of nortriptyline combined with nicotine transdermal patch to a placebo. The cessation rates were 23% (n = 79) and 10% (n = 79), respectively (absolute difference 13%, 95% CI 1.3 to 24.5% p = 0.52). Most frequent adverse effects were dry mouth (38%) and sedation (20%). There was no significant effect on withdrawal symptoms.^[67]

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.^[68]
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.^[69]
8. **D₃ receptor ligands:** Pharmacological and behavioural evidence implicates dopamine D₃ receptors in the mechanisms underlying stimulus controlled drug seeking behaviour. BP 897 (a D₃ receptor partial agonist) and ST 198 (a D₃ 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 D₃ 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.^[70]
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 (n=16) with the placebo (n=15), 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.^[71] 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.

Cost effectiveness of various therapies

A study conducted by Javitz *et al*, shows that the cost per

life year and quality adjusted life year saved were sufficiently low for 300 and 150 mg doses of bupropion and are among the most cost effective of life saving medical treatments. Bupropion 150 mg, combined with either proactive telephone calls or tailored mailing, was the most cost effective regimen.^[34] A cost benefit analysis by Neilson *et al*, comparing bupropion 300 mg with the nicotine patch, concluded that bupropion 300 mg/day for 9 weeks is a more cost beneficial smoking cessation intervention than the nicotine patch.^[32] Data on the cost effectiveness of other pharmacological measures are currently not available.

Predictors of success in smoking cessation interventions

Successful treatment depends on the individual, social, demographic and genetic factors. Education is a strong socio-epidemiologic predictor of smoking cessation. Effectiveness of smoking cessation therapy can be measured from a decrease in the number of cigarettes smoked per day, Fagerstrm questionnaire, carbon monoxide measure in expired air, measurements of thiocyanates and cotinine (metabolite of nicotine) in biological fluids. However, urinary cotinine level measurement is most useful for the follow-up of smoking cessation.^[72] In one study, only 6% of smokers with less than a high school degree quit smoking during a 4 year-study period in comparison to 17% smokers with high school education and 28% of smokers with at least a college degree.^[73] Sometimes, it is argued that by increasing the prices of cigarettes, smokers can be forced to at least cut down on the number of cigarettes smoked per day. But a survey conducted among 3,602 smokers in the US suggested that most smokers are price sensitive and seek out measures to purchase less expensive cigarettes.^[74]

The CYP2B6 gene has been implicated in the biotransformation of both bupropion and nicotine. Smokers on bupropion with decreased activity CYP2B6 variant are more vulnerable to abstinence symptoms such as cravings and relapse easily. However, in females, bupropion may attenuate this genotype effect.^[75] A relapse is more likely seen in smokers with strong nicotine dependence and, in such cases, a combination of nicotine and bupropion along with counselling can achieve higher abstinence rates.^[76]

Sleep disturbance is a regular feature of smoking abstinence, which may be in the form of frequent arousal with negative day-time consequences and dysphoric moods. Sleeplessness can disturb sympathetic activity and cause cardiovascular and CNS changes. These changes could be the cause of a relapse seen following NRT and bupropion treatment, especially in women.^[77]

Mentally ill patients smoke twice as much as other patients. There is evidence that smoking cessation among psychiatric patients is more difficult to achieve than other patients and thus special strategies such as forceful smoking prohibition might be necessary along with pharmacotherapy.^[78] Achieving smoking cessation in depressed women is also quite challenging because quitting is difficult during certain phases of the menstrual cycle, which are also associated with a greater level of dysphoria. These women are also less likely to seek medical attention for smoking cessation.^[79]

COPD patients show a similar efficacy and adverse effect profile with various pharmacological interventions as in smokers without the disease. However, efficacy seems to depend on the follow-up period used to define the success, as the abstinence rate declined with longer follow-up.^[80]

A cross-sectional study of smokers, who attended a smoking cessation clinic for combined medical and cognitive behavioural group therapy, showed that smokers who fully comply with the treatment and abstain during the first week are more likely to remain abstinent even after 6 months.^[81]

The pharmacokinetic disposition of various forms of NRT contributes to the success rate of this form of treatment. The nicotine in a cigarette is absorbed from the pulmonary venous blood and reaches the brain in 10-20 sec and produces positive effects on mood and cognition. These positive effects contribute to addiction. Compared to tobacco smoking, only a few reinforcing effects are seen with NRT as with most of them, the delivery and rise in blood nicotine level is slower than with smoking. These differences in pharmacokinetics explain why some patients find it difficult to quit smoking even after using NRT.^[82] In such patients, a combination of NRT with other pharmacologic therapies or a higher dose of NRT can be used.

Nicotine is inactivated to cotinine mainly by CYP2A6 which mediates 90% of this conversion. Some studies suggest that the CYP2A6 gene polymorphism can exert a differential effect on nicotine kinetics during various stages of smoking such as initiation, conversion to dependence, amount smoked during dependence and quitting.^[83]

Depressed patients, in euthymic state maintained on selective serotonin reuptake inhibitor (SSRIs), can be given bupropion to prevent the relapse of smoking following cessation. There is also an improvement seen in the SSRI associated sexual dysfunction.^[84] Bupropion is very effective in relapsed smokers too. An open multicentre study examined 321 patients who had relapsed after a smoking cessation attempt with bupropion SR or NRT. They were given bupropion SR (300 mg/day) lasting 7 weeks with an initial run in of 150 mg/day for the first 3 days. Motivational counselling was also provided. The continuous abstinence rates for week 4-7 were 29.6% and the point prevalence rates for week 26 were 30.5%. Patients who relapsed had reduced their daily consumption to nearly one-third.^[85]

There are conflicting reports of the different response to bupropion among males and females.^[86] Meta analysis of data from 4,421 participants in 12 randomised smoking cessation trials of bupropion SR 300 mg Vs. placebo, showed the former as an effective cessation aid in women (OR = 2.47, 95% CI = 1.92 to 3.17) with no gender specific response. However, women were less successful at quitting than men, regardless of the treatment.^[87] The reason for this could be the fear of weight gain. Dietary interventions plus nicotine gum showed an increase in the success rate in terms of smoking cessation and prevention of weight gain.^[29, 88] Weight gain after smoking cessation is not dependent on obesity or drug taken. Further, a beneficial lipid profile was seen with both bupropion and NRT, in obese and lean subjects.^[85]

A randomised trial, involving 1,524 adult smokers willing to quit, evaluated the effectiveness of bupropion SR.

A significantly ($P=0.005$) higher rate of non-smoking was observed in those receiving a larger dose of 300 mg, but with a slight increase in symptoms such as difficulty in sleeping, difficulty in concentration, tremors and gastrointestinal problems with decreased craving ($P=0.001$). Thus, bupropion can be safely given, in a higher dose of 300 mg, when better results of smoking cessation therapy are expected.^[89]

A double blind randomised trial, involving 244 current smokers, observed that the achievement of 1 year quit rate as validated by saliva cotinine or spousal proxy, was not significant with bupropion as compared with placebo (19% bupropion group Vs. 24% for placebo, $P=0.36$).^[90] Thus, while commenting on a particular intervention, it is always prudent to concentrate on the achievement of the long-term quit rate. Low levels of nicotine dependence, high motivation, absence of smoking related diseases, long duration of previous quit attempts, male gender, low levels of current alcohol problems and marital status are strong predictors of the successful outcome of smoking cessation treatment.^[91] A change in the quality of cigarettes can lower the number of cigarettes smoked per day such as the switch from plain to filtered ones which deliver low tar and nicotine.^[92]

The Indian scenario of smoking cessation interventions

Surveys conducted in 2000 indicate that India has more than 184 million tobacco users. In India, tobacco is used not only in cigarettes and 'bidis,' but a great majority use tobacco in non-smoking forms such as 'gutkha' and 'khaini'. The direct consequence of these non-smoking forms of tobacco is oral cancer, which accounts for nearly 1,60,000 cases annually. As per the Indian Council of Medical Research (ICMR), 4.5 million people develop angina or other heart diseases and 3.9 million develop COPD as a result of tobacco use. According to the WHO, by 2020 tobacco will be solely responsible for 13.3% of all deaths in India.^[93]

Magnitude of the tobacco problem in India

The pattern of tobacco use greatly varies between the urban and rural population. The consumption of tobacco and tobacco products is more among the rural population and currently shows an upward trend in females in both groups. [Table 1] Literacy and living status also affect the tobacco abuse pattern. [Table 2]

Table 1

Prevalence of tobacco use in India during 1987-1999

	Prevalence %					
	1987-88		1993-94		1998-99	
Sex	Urban	Rural	Urban	Rural	Urban	Rural
Males	26.5	35.3	23.2	33.6	20.8	31.3
Females	5.9	11.1	4.0	8.8	8.8	13.8

Source: International Institute for Population Sciences (IIPS) and ORC Macro. National Family Health Survey (NFHS-2) 1998-99: India, Mumbai: IIPS 2002.

Table 2

Percentage of household members who chew pan masala/tobacco or smoke in India during 1998-1999

Background characteristics	Males		Females	
	Chew pan masala or tobacco	Currently smoke	Chew pan masala or tobacco	Currently smoke
Education				
Illiterate	38	44.8	17.4	4
Literate<Middle school completed	31.5	33.1	10.2	0.8
Middle school completed	23.2	21.2	3.8	0.3
High school completed	18.9	15.9	1.8	0.1
Standard of living index				
Low	37.6	39.4	18.7	4.2
Middle	27.7	29.1	11.7	2.2
High	17.2	16.9	5.2	0.6
Total	28.2	29.4	12.4	2.5

Source: International Institute for Population Sciences (IIPS) and ORC Macro. National Family Health Survey (NFHS-2) 1998-99: India, Mumbai: IIPS 2002.

The Cigarettes and other Tobacco Products (Prohibition of Advertisement and Regulation of Trade and Commerce, Production, Supply and Distribution) Act, 2003.

This act (then bill) was first introduced in the parliament on March 7, 2001.^[94] It was reintroduced in 2003 and passed by the Rajya Sabha on April 9, 2003 and in the Lok Sabha on April 30, 2003. It became an Act on May 18, 2003 after receiving the Presidential assent. The salient features of the Act include:

1. Prohibition of smoking in a public place.
2. Prohibition of advertising (direct and indirect) of cigarettes and other tobacco products.
3. Prohibition of sale of any tobacco products to minors and in an area within a radius of 100 yards of any educational institution.
4. Restrictions on trade and commerce in, and production, supply and distribution of cigarettes and other tobacco products.

The rules under the cigarettes and other tobacco products Act, 2003 are in the process of being formulated.

Cessation programmes

There are two types of cessation programmes currently in operation.^[95]

- a. *Clinic based:* There are 13 smoking cessation clinics across India, to provide counselling, psychosocial support and pharmacotherapy for all tobacco users who want to quit the habit. A scientific approach is adopted at these clinics, while treatment and data regarding the use of tobacco is meticulously maintained for further reference.
- b. *Community interventions:* There are various NGOs working on tobacco related issues, including the implementation of government directives and prevention of use of tobacco products by adults and children.

Awareness among physicians is lacking regarding smoking cessation interventions available today. Physicians normally advise smoking cessation only when patients have severe bronchitis, COPD and pulmonary tuberculosis. Counselling for smokers who are otherwise healthy is generally lacking.

India is a developing country with most of the population belonging to the low socio-economic strata. Tuberculosis is rampant among this population and the government has been spending millions of rupees on tuberculosis control programmes. Quitting smoking and even reducing it could be an effective measure in the control of tuberculosis, since smoking directly and indirectly (through passive smoking) affects the course of this devastating disease.^[96]

Conclusion

Both NRT and bupropion are effective and established pharmacotherapies for smoking cessation. Benefit risk assessment, assuming a 30% one year quit rate, demonstrates that for every 10,000 smokers treated with bupropion SR, 19 lives are saved and 86 cases of smoking attributed morbidity are averted in a 5 year period, while the risk of experiencing severe adverse events (seizure, hypersensitivity) is 0.22%.^[97]

The role of willingness to quit cannot be undermined. It is seen that bupropion may be more effective as an antismoking treatment in people who are motivated to quit because low doses of bupropion produce a nicotine-like effect that serves as a suitable substitute.^[98] The choice of the NRT to be used depends on comorbid conditions, previous use and the need for rapid delivery of NRT. In highly dependent patients, measures delivering a higher dose of nicotine, such as a nasal spray or an inhaler, would be preferred. Also, in such subjects a combination of bupropion with NRT is recommended, but there is some risk of hypertension with this combination. Patients should be warned and examined before-hand and there should be suitable follow-up. The most important aim of any intervention for smoking cessation should be the prevention of a relapse after successful therapy. A return to smoking after 1-2 weeks of abstinence is very common, which is more so in previously depressed patients or patients dependent on alcohol.^[99] There is an increase in depressive symptoms after abstinence, prompting resumption. Bupropion is effective in such patients and it also effectively abolishes nicotine withdrawal symptoms.^[100]

Some studies, however, recommend NRT as the first line therapy for smoking cessation because of the amphetamine-like nature of bupropion, with some structural similarities, and similar side effects such as suppression of appetite, insomnia, weight loss and hypertension.^[101] But several other studies claim that bupropion is a safe and efficacious drug^[97, 102-104] and should be prescribed with consideration, especially to patients with hypertension. Study on self-administered treatment for smoking cessation revealed that self-help manuals do increase quit rates when combined with individualised adjuncts such as written feedback and telephonic counselling. It is also difficult to evaluate the efficacy of NRT and bupropion when self-administered. It is predicted that though they increase the initial quit rate, in the long-term, there is poor compliance and early discontinuation.^[105] Counselling is an effective and cost-effective method for smoking cessation, but counselling alone may not be useful for chronic smokers and its effectiveness can be improved by simultaneous pharmacotherapy.

Other strategies such as low tar filter cigarettes to reduce cancer risk are clearly ineffective and should be discouraged.^[106] Physicians are in a unique position to advise patients, who smoke, about the ill effects of smoking. The use of smokeless forms of tobacco affect the individual in the form of oral cancers, but a smoker pollutes his environment, putting at risk not just himself but other people too. Thus, a ban on public smoking should be strictly enforced with heavy penalties.

The tobacco industry is a multibillion-dollar industry, which provides revenue to the government. It is difficult to compensate for the loss that would befall the industry, following a complete ban. Jobs are also at stake. Thus, most governments adopt a balancing act policy of imposing stricter laws over the use of tobacco products, on the one hand, while patronising tobacco industries on the other.

In India, a large part of the tobacco industry is engaged in bidi-making, which enjoys the status of a cottage industry and draws incentives from the government. This is in direct contradiction to the recommendation of the WHO expert committee on smoking control, which recommends the discouragement of the development of tobacco and tobacco related industries.^[32] Therefore, effective intervention lies in educating the masses about the ill effects of the tobacco use right from the school level, to prevent the youth from adopting this harmful habit. Physicians, nurses and primary healthcare workers should also accept their responsibility and counsel their patients. The government should encourage antitobacco strategies such as increasing the price of cigarettes and other tobacco products, while limiting their availability, albeit at the risk of losing revenue. But this loss of revenue would be much less when compared to the costs incurred on the treatment of tobacco related diseases. Only a concerted effort could realise the dream of a tobacco-free world.

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