
An Update on Pharmacotherapies of Smoking Cessation

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Smoking can be ranked as the most serious risk factor in terms of its impact on the well being of an individual and society. Factors such as withdrawal symptoms, abstinence levels achieved, quit failures associated with particular nicotine replacement product decides success of any smoking cessation therapy. Often, individual preferences play a crucial role in selecting particular intervention program. Today, several dosage forms of nicotine (gum, inhaler, patch, spray) are available in the market, which claim to meet varied clinical demands of smokers in terms of nicotine intake during treatment. There is a strong scientific rationale behind development of these products, and each product aims to reinforce the treatment. However, there is a clear need for new dosage forms and more effective therapy so as to persuade a large number of smokers for treatment, thereby enhancing cessation rates and improving public health. The present manuscript is a compilation of products available for smoking cessation program and discusses their usefulness, advantages and limitations.

Smoking, a social evil, affects economy as well as health of people throughout the world. Tobacco addiction is known to affect individuals across all segments and is the leading cause of many diseases. Smoking is the single largest preventable cause of ill health in world. In spite of several new therapies and behavioral models being developed for treating nicotine dependence, none has succeeded in bringing about smoking cessation. Though smoking affects all age groups, it is particularly on rise in younger generation. For example, in India, it has been found that nearly half the males above the age of 15 y smoke tobacco. The country has 240 million tobacco users, which is nearly one-third of the tobacco users in developing countries of the world¹. Nicotine is consumed in various ways throughout the world; however, cigarette remains the most sought after form of consuming tobacco. A cigarette contains 6-11 mg of nicotine of which smoker gets 1-3 mg.

The smoker consumes tobacco mainly for nicotine, the

main addictive constituent, however, takes in poisonous substances in addition to it. Nicotine *per se* does not cause death, but smokers die of disorders caused by the harmful constituents (tar and other compounds) present in cigarette smoke. Tar constituents are largely unabsorbed and are deposited in the respiratory tract leading to carcinomas. Smoking has wide spread effects on several body parts and is the cause behind cancers of various tissues². Smoking affects women causing premature births and has teratogenic effects on babies³.

Overall drug therapy for smoking cessation includes three modules, namely: (a) no - drug therapy, (b) non-nicotine pharmacotherapy, and (c) nicotine replacement. Nicotine replacement therapy (NRT) is the most successful therapy available today for smoking cessation program. It has better acceptance and success record as compared to other two modules. It releases nicotine in an amount sufficient to reduce withdrawal symptoms, without developing addiction to it. After a steady state, nicotine intake is progressively reduced to zero over a period of time. The major products of NRT in United Kingdom represent

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either prescription or non-prescription products and include nicotine gum, transdermal patches, nasal spray, vapour inhaler, sublingual tablet as well as lozenges⁴.

Though, NRT alone is successful in reducing incidences of smoking significantly, concurrent use of NRT and non-pharmacological aids has been found to be more successful in clinics⁵. In addition, there are various factors including individual preferences that strongly influence the overall success of smoking cessation program, thus, selection of a particular therapy for clinical use acquires a lot of significance. The choice of therapy depends on the patient preferences; the severity of nicotine dependence, past quit attempts, and the psychological vulnerabilities of individuals seeking smoking cessation.

SMOKING- AN ADDICTION

Nicotine leads to dependence, both of behavioral and pharmacological types. It enhances the emotional well being

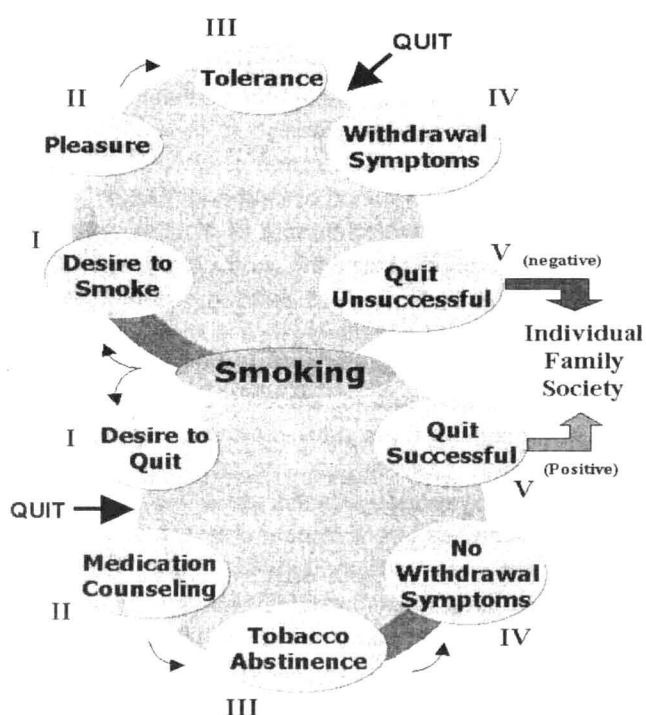


Fig. 1: Factors behind smoking – initiation and cessation.

Roman numerals – Stages involved in smoking initiation and quitting, upper sphere signifying initiation events and lower sphere represents smoking cessation events. Quitting tobacco has positive effect on society (positive) while continuing it has adverse effects (negative).

of an individual and brings about relaxation as well as relief from anxiety and depression⁶. It causes neuroadaptation, which is manifested as the development of tolerance and physical dependence. It stimulates the release of various excitatory mediators such as noradrenaline, acetylcholine, and dopamine. Withdrawal symptoms are expressed as psychological distress such as irritability and anxiety, impaired cognitive performance, weight gain, and tobacco craving, whose severity depends upon the amount of nicotine accumulated in body, number of cigarettes smoked etc. In general, chronic smoker faces more severe withdrawal symptoms than a casual smoker and requires careful planning and execution of smoking cessation programme. Fig. 1 depicts the essential elements involved in initiation/continuation of smoking and factors that help an individual quit smoking.

NICOTINE, THE DRUG AND ITS PHARMACOKINETICS

Nicotine is an alkaloid obtained from the dried leaves of tobacco plant, *Nicotiana tabacum* and *N. rustica* as well as other related species (Fam. Solanaceae). It is a tertiary amine compound consisting of a pyridine and a pyrrolidine ring as shown in fig. 2⁷. It is chemically known as S-3- (1-methyl-2-pyrrolidinyl) pyridine, has a molecular formula $C_{10}H_{14}N_2$ and a molecular weight of 162.23⁸. The knowledge of physicochemical and pharmacokinetic properties of nicotine informs about clinical choice of route of administration for delivery of nicotine. It also provides cross-disciplinary framework that facilitates better understanding of various approaches available for smoking cessation.

Physicochemical properties:

Nicotine is oily, volatile liquid obtained from tobacco plant. It is a weak, water-soluble and lipid-soluble base. It is lipophilic at salivary pH and has a characteristic pungent odour and turns brown on exposure to air or light. Though high partition coefficient of nicotine suggests nonpolarity of

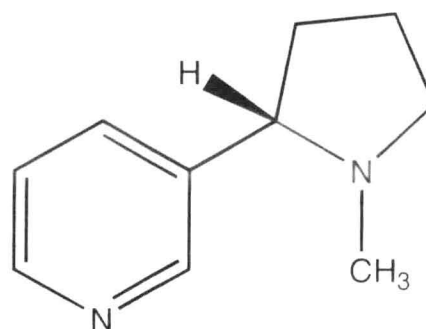


Fig. 2: Chemical structure of (-) Nicotine.

the molecule, however, it is highly water soluble due to the ability to form strong hydrogen bonds.

Absorption:

The absorption of nicotine across biomembranes depends on pH. At acidic pH (gastrointestinal tract), nicotine is ionized and minimally absorbed while alkaline pH favours its absorption. Russell *et al.* studied absorption of nicotine vapour from smoke-free cigarette and concluded that it resembles absorption of nicotine from gum. Smoke-free cigarette results in deposition of nicotine in the oral cavity, throat, and large airways, from where the absorption is slow and pH dependent⁹. At the same time, due to its lipophilicity, free alkaloid gets freely absorbed through the skin and from sites having near physiological pH.

Distribution:

Pulmonary route serves as the major port of entry for nicotine from cigarettes. Following a cigarette, nicotine enters brain within seconds and undergoes rapid distribution to body tissues leading to reduction in the brain-nicotine levels. The drug crosses placenta easily and has been found in amniotic fluid and the umbilical-cord blood of neonates. It is also secreted in milk of the lactating mothers. However, the concentrations are quite low to cause any physiologic trouble to the infant¹⁰.

Metabolism and elimination:

Nicotine is metabolized mainly in liver to pharmacologically inactive metabolites and these further undergo glucuronidation reactions. A considerable variability in the metabolism of nicotine has been reported. The metabolism of nicotine to cotinine is a two-step process via the intermediate, nicotine iminium ion¹⁰. The renal clearance of nicotine depends on the pH and flow of urine and accounts for 2 to 35% of the total elimination.

Mechanism of action:

Pharmacodynamics of nicotine exhibits a complex dose-response relationship and development of tolerance produced by exposure to nicotine. A biphasic pattern of response has been observed with nicotine during *in vivo* as well as *ex vivo* animal experiments, in which low doses cause ganglionic stimulation but in high doses the drug causes ganglionic blockade¹¹. It also activates several neurochemical pathways, one of, which is associated with the enhancement of mesolimbic dopaminergic function. Additional central actions lead to increase in arousal, attention and reaction time, and decrease in anxiety and

stress reactions¹². Detailed pharmacological effects of nicotine in humans have been described elsewhere^{10,13}.

NICOTINE REPLACEMENT PRODUCTS (NRTS)

The first NRT approved by the United States Food and Drug Administration (US FDA) in 1984 was a transmucosal product, nicotine gum containing 2-mg nicotine, intended for absorption through the mucosal lining of the oral cavity. The 4-mg form was approved later in 1992¹⁴. Since then, a number of NRT products have been introduced in the market. These include nicotine gum, transdermal patch, nasal solution, and nasal spray etc. A list of available smoking cessation products containing nicotine is given in Table 1. Patented formulations of nicotine and other smoking cessation aids have been listed in Table 2.

Nicotine gum:

Nicotine gum is also known as "nicotine polacrilex" and is official in USP 24¹⁵ as well as USP 25. Polacrilex, is a weak carboxylic exchange resin prepared from methacrylic acid and divinyl benzene that is complexed with nicotine. The complexation ensures that the contents of the gum are released slowly over a period of time so that irritation to the throat is minimized. The dosage form is buffered with alkalizers to enhance absorption of nicotine. The gum is slowly chewed over a period of time and "parked" near the buccal membranes until the taste of nicotine fades away. Variable absorption of nicotine may occur depending on whether the gum is actively chewed throughout the usage or it is stationary. The advantages associated with nicotine gum are several. Nicotine gum is the most widely studied dosage forms available for smoking cessation¹⁶. A large number of clinical trials have indicated success of this dosage form in achieving smoking cessation¹⁷⁻¹⁹. Some of the side effects reported with the use of nicotine polacrilex are oral blisters and sore throat²⁰, however they are mild and reversible once therapy is discontinued. Nicotine gum is associated with few drawbacks. It requires slow and continuous chewing of gum over a period of 30 minutes. Consumption of acidic fluids such as coffee or soft drinks during usage of the dosage form reduces availability of nicotine. Unpleasant adverse effects such as throat and mouth irritation, nausea, vomiting, hiccups and stomach upset were also reported due to involuntary swallowing of the gum contents. Several users have reported dependence potential on the gum after discontinuation of treatment. At the same time, the consistency of gum formulation makes it unsuitable particularly for elderly users having dentures. Palpitation was also reported in 0.5% of the users of the

TABLE 1: MARKETED NRT PRODUCTS.

Marketed name (Dose, mg)	Duration of Application (h)	Delivery System (Delivery Control)	Route of delivery	Manufacturer / Distributor
Habitrol (21, 14, and 7)	24	Patch (Rate controlling membrane)	Transdermal	Novartis Consumer Health, Canada Inc.
Nicoderm CQ (21, 14, and 7)	24	Patch (Rate controlling membrane)		Transdermal Glaxo SmithKline, USA.
Nicotrol 16 (15, 10, and 5)	16	Patch (Adhesive)	Transdermal	Pharmacia Corporation, NJ, USA.
ProStep (22 and 11)	24	Patch (Gel Matrix)	Transdermal	Perrigo Co., USA.
Nicotrol® 10 mg/cartridge	-	Inhaler (4 mg /inhalation)	Oral inhaler	Pharmacia Corporation, NJ, USA.
Nicotrol NS (10 mg/ml spray solution)	-	Nasal Spray (0.5 mg per spray)	Nasal	Pharmacia Inc., Sweden.
Nicorette (2); Nicorette DS (4)	30 min or till the taste fades	Nicotine gum	Oral	Glaxo SmithKline, USA.
Stoppers	-	Lozenge (0.35 per lozenge)	Oral	Stoppers, UK
Nicorette Microtab (2 and 4)	-	Sublingual tablet	Oral	QPharma AB, Malmo, Sweden.

gum and it has no beneficial effect on weight gain, which is one of the key withdrawal symptoms of smoking cessation.

Though, this form of nicotine replacement has wide acceptance, a study by Hughes *et al.* have indicated inability of nicotine gum to diminish the intense craving experienced by newly abstinent smokers²¹. This happens due to slow concentration build up of nicotine in body. At the same time, 4-mg gum was more effective than the 2-mg gum in helping heavy smokers (>20 cigarettes a day) to quit²². Therefore, to overcome these problems, new formulations of nicotine giving rapid release were introduced and novel routes of administration such as transdermal, and nasal were explored.

Transdermal nicotine:

Drug delivery through skin has great potential for some

indications and due to the excellent pharmacokinetic parameters of nicotine; it can be successfully administered by transdermal route for smoking cessation. Transdermal delivery of nicotine has been able to eliminate oral discomfort and minimize side effects observed with nicotine gum. The abstinence rates of 30-41% have been reported in first 21 d of treatment as against 4-21% in placebo treatment¹². A complete design of a transdermal system (TDS) or patch incorporates a drug loaded matrix or reservoir totally covered by a rate-controlling membrane²³. This dosage form is listed as "nicotine transdermal system" in USP 24¹⁵. The integrated dose of nicotine delivered by most of the commercially available transdermal patches in 24 h is approximately equivalent to that absorbed by 'one-pack-a day' smoker (=20 mg)²⁴.

A 24 h patch (US patent 4,839,174) comprising of an

TABLE 2: PATENTED SMOKING CESSATION AIDS.

Patent number	Title	Inventor (Assignee)
US5935604	Nasal drug delivery system containing bioadhesive ion exchange resin	Danbiosyst UK Ltd.
US6102036	Breath activated inhaler	Smoke-stop Ltd. Toronto
US6165497	Subsaturated Transdermal therapeutic system	Alza Corporation
US6183775	Buccal delivery system (lozenges)	Novartis consumer health. SA
WO0971263A1	Nicotine inhaler	Zamel, Noe
WO09945902A1	Nicotine inhaler	Piskorz Hanna, CA, USA.
US06082368	Nicotine candy cigarette	Brawn-Grahm, USA
WO00030641	Nicotine containing pharmaceutical preparation composition giving rapid transmucosal absorption	Pharmacia-Upjohn
US5147654	Oral osmotic device for delivering nicotine	Alza Corporation (Palo Alto, CA)
US5362496	Method and therapeutic system for smoking cessation	Pharmetrix Corporation (Menlo Park, CA)
US5536503	Controlled, sustained release delivery system for smoking cessation	DynaGen, Inc. (Cambridge, MA)
US5549906	Nicotine lozenge and therapeutic method for smoking cessation	Pharmacia AB (SE)
US5721257	Method and therapeutic system for smoking cessation	Pharmacia & Upjohn AB (SE)
US5834011 University	Method for aiding in the reduction of incidence of tobacco smoking	The Regents of the of California (Oakland, CA)
US5893371	Non-nicotine smoking cessation aid	Duke University (Durham, NC)
US6197827	Nicotine addiction treatment	Cary Medical Corporation Bethesda, MD)

impermeable backing membrane, a polyurethane matrix containing 5 to 50% of nicotine along with a skin contacting adhesive layer has been developed. A major disadvantage associated with a 24 h nicotine transdermal patch is sleep disturbance associated with it. To improve compliance, a 16 h transdermal patch has also been formulated so that the subject can have 8 h of nicotine-free period to avoid any sleep problems. Dermatological reactions are the major adverse effects seen with nicotine TDS. These consist of mild to moderate erythema and transient itching at the site of application. Few cases of severe skin irritation and sensitization have also been reported. Systemic adverse effects such as CNS and sleep disturbances, sweating, paraesthesia, cough, and palpitation have also been

reported. There is little potential for dependence because of slow onset of action, smaller fluctuations in the plasma nicotine concentrations, and infrequency of administration¹². Though this dosage form is capable of reducing some of the withdrawal symptoms during smoking cessation, the severe urge for tobacco is not relieved due to the slow release of drug from the system and therefore has very little patient compliance in case of heavy smokers. For satisfactory clinical results, this system has to be coupled with a dosage form that releases nicotine within 10-30 minutes of administration. It has been recommended that a patch used along with nasal spray is much more effective for smoking cessation than the patch used alone⁴. Kornitzer *et al.* studied combination of nicotine gum with nicotine TDS

in subjects smoking 10 cigarettes or more a day, and reported increased levels of abstinence upto 24 w²⁵.

Due to its basic $pK_a \sim 8.0$, the drug has a positive charge at the physiological pH and can be administered by anodal iontophoresis. The feasibility of the same was studied using hairless skin of a mouse as a model membrane and results indicated that a rapid input of nicotine could be achieved across the skin by this method²⁴. Several reports are available indicating success of nicotine TDS in smoking cessation programme^{25,27}.

Nasal solution:

Nicotine is rapidly absorbed from the nasal mucosa when administered as dry powder snuff. However, this type of dosage form is messy to be administered in appropriate and accurate doses and might be embarrassing for the subjects. A nasal solution consisting of 0.1 ml of a 2% aqueous solution of nicotine (2 mg) at pH 5.0 without any added buffer was developed for use as a nasal snuff. This formulation has an advantage of better patient compliance in those having dentures, or peptic ulcers and for those who complain of nausea and dyspeptic symptoms by using gum. A study conducted to compare the absorption of the drug from this novel formulation, the nicotine gum (Nicorette 2 mg) and the cigarette showed that the solution exhibited an intermediate rate of absorption as compared to the nicotine gum (lower absorption) and the cigarette (higher absorption). Hence the investigators concluded that it could be a promising product to be used clinically as a NRT²⁸, however, this product was not pursued further for several reasons.

Nasal spray:

Nicotrol NS is an aqueous solution of 100 mg nicotine adjusted to a pH of 7. Though it is intended for use as a metered spray, it does not contain chlorofluorocarbons. Each actuation of the unit delivers a metered dose containing approximately 0.5 mg of nicotine. One Nicotrol NS unit delivers around 200 applications. This medication has an advantage of achieving abstinence rates upto 3.5 y over the placebo²⁹. It has a dependence potential reported as 32%, which is intermediate to that of other nicotine-based therapies and cigarettes. The side effects are also mild and local.

Oral inhaler:

Nicotine is readily and rapidly absorbed from the buccal mucosal lining. The smoker is usually habituated to the

psychological feeling of holding a cigarette in the mouth during smoking. A dosage form that can simulate hand-to-mouth feeling is expected to have a better patient compliance and acceptance for the therapy. An inhalation system of such a kind is available commercially from Pharmacia Inc. under a brand name of Nicotrol inhaler. It has a mouthpiece and a plastic cartridge enclosing porous, pharmacologically inactive plug impregnated with 10-mg nicotine, 40% of which is available for inhalation. This system typically produces a 6-8 ng/ml plasma level of drug, which corresponds to that achieved after smoking a single cigarette. The cartridge is loaded into mouthpiece before use. Each inhaler package is supplied with 42 cartridges pre-loaded with 10-mg nicotine.

A double blind randomized clinical trial conducted to study the efficacy of nicotine inhaler showed that after 4 mo of therapy, 26% and 9% of volunteers showed abstinence from smoking in the active and placebo groups, respectively³⁰. In a separate study, local irritation in mouth and throat was reported in about 40% of the patients as compared to 18% of those on placebo. The frequency of irritation and cough subsided on continued use. It is also being marketed as an OTC product (Nicorette inhaler) in Italy, Sweden and UK³¹. A major problem associated with the inhaler is the potential fear of under-dosing. Hence, the technique needs to be explained to user in an elaborate manner to deliver required amount of nicotine.

Aerosolized nicotine:

The rapid absorption of nicotine from the respiratory tract is mainly due to the deposition of nicotine in the distal lung region and it has shown to achieve plasma levels of 15-70 ng/ml after 1-2 min of finishing a cigarette. Hence, use of nicotine, as an aerosol dosage form could be beneficial for nicotine replacement therapy. Such a dosage form has been developed and been investigated³². In the form of a dosimeter, which was calibrated to deliver 0.0062 ml/s. This leads to the delivery of 0.5 mg of nicotine per puff. Each puff was 0.6 sec long in duration. The only limitation was that it caused cough due to the irritant effects of aerosol vehicle in the upper airways of the respiratory tract. More studies are required to decide the success of such a dosage form for achieving optimal smoking cessation before it is included in the smoking cessation regime.

Lozenges:

Nicotine lozenges are available as OTC products in the UK market for over a decade³³. "Stoppers" are the licensed

OTC lozenge formulations prepared from the purified extract of tobacco, which contain 0.35 mg of nicotine per lozenge³. The other unlicensed lozenges present in the market include "Super 25" (A1 Pharmaceuticals, London) and "Stubit" (J Pickels & Sons, Knaresborough)³³. These are used whenever the patient craves for cigarette during smoking cessation program. Though the likelihood of dependency on these lozenges is low, there have been reports for the same and hence the possibility of addiction cannot be completely ruled out. Recently, a study conducted by Shiffman *et al.* on efficacy of nicotine lozenge (2-mg and 4-mg) showed that the treatment resulted in 28-day abstinence at 6 w and the effects were maintained for a y. Based on this result, it was concluded that the nicotine lozenge to be safe and effective new treatment for smoking cessation in low- and high-dependence smokers³⁴.

Sublingual tablets:

During smoking cessation programme, dosage forms giving immediate nicotine release are highly desirable especially in case of heavy smokers. The acute craving for nicotine during abstinence period encourages smoker to continue with the smoking habit, hence, complete smoking cessation can be brought about by providing doses of nicotine in a manner such that these relapses are prevented. A sublingual tablet containing 2-mg and 4-mg of nicotine has been developed and is available in Sweden. This product makes use of cyclodextrin as vehicle and releases nicotine immediately. Researchers have studied the effect of orally administered nicotine on the mucosal lining of the mouth and have concluded it to be safe for human use. Reversible lesions occurred when subject used 2 tablets per hour, however condition was restored to normalcy during tapering off period of the treatment³⁵. Most of the sublingual formulations are designed in a way such that the heavy smoker can get a drug in case of acute need during smoking cessation therapy.

Nicotine water:

"Nicotine Water" a new preparation available over the internet, is designed to provide a source of nicotine to individuals that is safer than conventional tobacco products, and that can be used by smokers who are either unable to smoke in particular settings or who wish to quit altogether. Nicotine water contains nicotine equivalent to about 2 cigarettes, dissolved in regular bottled water. The manufacturer claims it to be a dietary supplement, however a recent petition has been filed against this claim, asking

US FDA to classify this preparation under category of "food" containing hazardous, unapproved food additive (<http://www.nicotinewater.com>, accessed on February 8, 2002). A heavy smoker may consume 2 bottles per hour whereas requirement of a light smoker is less than a bottle per hour.

When so many delivery systems are available for nicotine, the selection of one particular dosage form becomes difficult. Many factors govern the choice of delivery system and deserve consideration before designing optimum therapy and dosage regimen for smoker. At the same time, long-term efficacy and therapeutic equivalency of various delivery systems should be proved in clinics. Silagy *et al.* carried out meta-analysis of 53 randomized controlled clinical trials of NRT (42 trials on nicotine gum, 9 on transdermal patches, 1 intranasal spray, and 1 inhaler). The odds ratio (OR) for individual therapies indicated that currently available nicotine replacement systems are efficacious and can be successfully used in the clinics³⁶.

NON-NICOTINE PHARMACOLOGICAL AIDS

Mecamylamine:

Mecamylamine is a ganglion-blocking agent and has various pharmacological effects. The oral absorption of drug is incomplete and erratic. The slow excretion of drug by the kidney results in relatively long duration of action³⁷. Being a ganglion blocker, it antagonises the action of nicotine at the ganglia and thus has been found to be effective for smoking cessation therapy.

A combination of oral mecamylamine (2.5 to 5.0 mg twice a day) and transdermal nicotine patch has been studied. It is assumed that when mecamylamine would block the specific nicotinic receptors at the ganglia, nicotine delivered by patch would attenuate the positive reinforcing effects of cigarette smoking and suppress withdrawal symptoms. In such a study, marked enhancement of 50% and 38% abstinence rates with short and long-term treatment⁵ were observed, though the intolerable adverse effects of constipation and urinary retention led to very high (36%) dropout rate among the subjects. Mecamylamine also relieved the key withdrawal symptoms such as craving for cigarette and appetite for food⁵. A commercial TDDS of the same has been developed by the Sano Corporation and is undergoing phase III clinical trials³⁸. Pre-treatment with mecamylamine and NRT significantly prolonged duration of continuous smoking abstinence and therefore can be used as an adjunct for NRT³⁹.

Clonidine:

Many studies have confirmed the involvement of central adrenergic overactivity causing withdrawal symptoms during smoking cessation⁴⁰. Clonidine, a nonreceptor nicotine antagonist, acts by its central sympatholytic action and found to be useful when given orally (0.075 mg/tablet, 3 tablets a day) for smoking cessation⁴¹. Clonidine reduces anxiety, tensions, and irritability thus showing promise as a smoking cessation aid⁴². It has also been administered for the same, in the form of transdermal patch incorporating a maximum dose of 0.2 mg and abstinence rate of 62 % has been observed after 6 w treatment⁴³. In spite of usefulness of clonidine for smoking cessation, it is associated with several drawbacks such as dry mouth, sedation, dizziness, symptomatic postural hypotension, and a risk of 'rebound hypertension' once therapy is discontinued. This makes it an unsuitable candidate as a first-line treatment for most patients⁴⁴.

Antidepressants, bupropion:

The smokers with the history of depression are more prone to the withdrawal symptoms and usually have lower success rates during smoking cessation⁴⁵. Hence, drugs that can relieve the individuals of their depressive disorders may contribute to counter tobacco addiction. The combination of antidepressants such as fluoxetine⁴⁶, bupropion⁴⁷, nortriptyline and doxepine¹⁶ with nicotine have been investigated and have been found to be effective in smokers with depressive disorders.

Bupropion has been investigated for smoking cessation therapy extensively and is the only non-nicotine FDA approved medication for smoking cessation and is believed to produce its effect via mediating through dopaminergic and noradrenergic neurotransmitters involved in nicotine dependence⁴⁸. "Zyban" (bupropion), is the only non-nicotine drug available in India for smoking cessation therapy and is being widely prescribed. A pivotal study carried out by Hurt *et al.* showed that sustained-release form of bupropion was effective for smoking cessation and did not possess side effects such as weight gain etc⁴⁹. Many studies have also demonstrated that combination therapy of nicotine with bupropion has greater abstinence potential than either drug given alone^{50,47}. The drug is contraindicated in subjects with history of seizures. Subjects receiving a combination of bupropion SR and the nicotine patch should be closely monitored for treatment of emergent hypertension. Other adverse effects include dry mouth and insomnia that are reported to be well tolerated and reversible. Few cases of

convulsion have also been reported in Netherlands⁵¹.

Fluoxetine:

A clinical study to assess the abstinence rate of smoking was conducted for combinations of fluoxetine and nicotine inhaler, and placebo and nicotine inhaler. The percent abstinence from smoking after 12 Mo from the initiation of treatment was found to be 21% and 23% for the two combinations, respectively⁴⁶. Hence, no conclusive evidence of use of fluoxetine as an adjuvant to NRT could be drawn. But it could be beneficial for the patients with depressive disorders as substantial increase in the abstinence rate was observed in clinical trials involving such patients⁵². Furthermore, it prevented weight gain associated with reduced nicotine intake by diminishing the caloric uptake⁵³.

Nortriptyline:

Nortriptyline is a tricyclic antidepressant, which is known to inhibit the neuronal uptake of noradrenaline. The use of nortriptyline in smoking cessation is based on the fact that smoking cessation precipitates depression as a major withdrawal symptom. In a placebo controlled clinical study, nortriptyline showed significant reduction in withdrawal symptoms such as anxiety, irritability, difficulty in concentration, restlessness etc. The abstinence rates at 6 mo were 14% and 3% for treatment and placebo group, respectively⁵⁴. Hence, it may be concluded that the drug does hold a future as an aid to smoking cessation therapy either alone or as an adjuvant to the NRT⁴².

Moclobemide:

Moclobemide is a monoamine oxidase (MAO) inhibitor with an antidepressant activity and is associated with enhanced dopaminergic activity. Cigarette smoke has MAO inhibitory properties and smokers have low MAO activity as compared to non - smokers. The outcome of a study, which included 88 heavy smokers, showed that moclobemide increased the cessation rate in heavy smokers. However, the role of MAO inhibitors in smoking cessation needs to be evaluated⁵⁵.

Anxiolytics:

Often, smoking is initiated or continued to relieve anxiety and irritability. Haxby has reported a higher prevalence of anxiety in cigarette smokers than in non-smokers². This finding has led to the use of anti-anxiety drugs as potential aid for the smoking cessation therapy. Buspirone is one such drug tested for treating withdrawal symptoms. However, it has shown poor results in clinical trial

and offered no relief from withdrawal symptoms in case of heavy smokers⁵⁶.

Buspirone:

It is a selective agonist at the serotonin 5-HT receptor sites. It has a lesser dopamine D2 receptor activity. The trial enrolled healthy volunteers who lacked any mood/anxiety disorders. 15-45 mg of buspirone was administered over 4-12 w period. The drug offered only short – term benefits and had adverse effects such as dizziness, nausea, headache, nervousness and light-headedness. Although, it may be useful for the smokers with high degree of anxiety; however, conclusive data needs to be generated to support the use of drug in this direction⁴².

Lobeline:

Lobeline, an alkaloid similar to nicotine has also been tried in the form of 2 mg and 2.5 mg capsules and nicotine gum for smoking cessation. Lobeline is the FDA category III drug, which is safe and is available without prescription⁵⁷. A US patent (US 5,41,4005) has been granted for a sublingual tablet containing lobeline in the form of a soluble salt at a dose level of 0.6 to 0.75 mg. While overdose is a potential problem with this drug, reports showed that there was no significant benefit over the placebo treatment⁵⁸.

Silver compounds:

Silver compounds have also been used for smoking cessation in the form of mouthwashes, chewing gums and mouth sprays. The contact of saliva with these compounds leads to the formation of silver chloride that produces unpleasant metallic taste in presence of cigarette smoke. This is also known as an "aversive treatment". The mouthwash contains silver nitrate while the gum contains silver acetate, ammonium chloride and co-carboxylase. However, clinical trials conducted with silver compounds showed a little advantage in promoting smoking cessation⁵⁹.

Dextrose:

Use of oral dextrose for smoking cessation is based on the fact that the urge to smoke arises in part from a mislabeling of a physiological desire for carbohydrates. The serotonin enhancing substances such as tryptophan and high carbohydrates are used to relieve the negative effects associated with smoking cessation⁶⁰. The outcomes of the clinical trial conducted by West *et al.* showed 49 % abstinence when 3 g of dextrose tablet was co-administered with 15 mg of nicotine patch while 30 % abstinence was observed with placebo and nicotine patch combination⁶¹.

Nicobrevin:

A formulation containing menthyl valerate, quinine, camphor and eucalyptus oil has been formulated and evaluated for its usefulness for smoking cessation. Quinine helps to alleviate the adverse effects of withdrawal symptoms, camphor helps to eliminate the undesirable effects of smoking on the respiratory system, menthyl valerate is a mild sedative, and eucalyptus oil helps to relieve accumulation of mucus, which occurs during smoking cessation. The placebo-controlled, double blind trial carried out with this product has shown it to be superior to placebo in quitting smoking³.

Methoxsalen:

Recently, inhibitors of cytochrome P450 2A6 have found a useful role in smoking cessation program. The enzyme cytochrome P450 2A6 is responsible for the metabolism of nicotine in the body and also for the activation of carcinogens present in the cigarette smoke. Inhibition of this enzyme reduces metabolism of nicotine and thus prolongs its therapeutic action. This reduces the number of cigarettes smoked and also the carcinogenic effect of tobacco smoke even if subject continues with this habit while on therapy. Methoxsalen is one such drug reported to have inhibitory action on the enzyme and is currently being used in the treatment of psoriasis. One odd trial of the drug in this therapy has been reported to increase nicotine levels in plasma⁶². However, further investigations to study the toxicity and safety of drug for the same needs to be carried out.

CONCLUSIONS

Smoking poses a major threat to the individual human and the society in terms of both health and economy. Hence, the development of a rationale therapy regimen is essential for smoking cessation. Various delivery systems of nicotine and other pharmacological agents have been investigated for smoking cessation. Each therapy has certain advantages in terms of abstinence rates but also suffer from one or the other limitations. Selection of particular therapy is a complex process and is influenced by various factors. Although both NRT as well as non-nicotine therapy are efficacious in clinics, but better cessation rates are usually achieved when they are used concurrently. Combining above-mentioned approaches with effective patient counseling and other behavioral methods, success of smoking cessation can be enhanced. Since, every individual exhibits distinct pattern of nicotine requirement during the cessation therapy, there is a need to simulate this pattern for higher success rates. In order to achieve this concept, novel formulations of nicotine that are safe, efficacious, and able to meet the require-

ments of smokers, should be developed and tested. By understanding interrelated factors behind smoking, patient psychology, and optimization of therapy, higher rates of smoking cessation can be obtained.

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