Critical Appraisal of The Existing and Emerging Therapies for Smoking Cessation

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SUMMARY

Smoking is a major health problem of the society as it causes a wide variety of health hazards and produces a strong addictive behavior. Various pharmacological and non pharmacological treatments have been tried for smoking cessation from time to time. Some of the pharmacological treatments have been able to achieve the status of first line and second line therapy for smoking cessation by the US Public Health Service Clinical Practice Guideline. Some newer and very promising drugs have come up and are in the clinical trials for establishment of their efficacy. While some other drugs have been tried from time to time but have failed to show any consistent results. Various non pharmacological therapies like behavioural therapy are also of utmost importance in this regard. This article gives a brief review and critical assessment of the existing and the emerging smoking cessation therapies.

KEY WORDS:
Electronic cigarettes, Nicotine replacement therapy, Nicotine vaccines, Varenicline, Vaporizers

The World Health Organization estimates that there are around 1.3 billion smokers in the world, of which almost 1 billion are men. This represents about one third of the global population aged 15 and over[1] and the vast majority of these people, around 84% or 1 billion people live in developing countries[2]. 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 has been linked to various cancers affecting the lungs, stomach, urinary bladder and kidneys[3]. 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[4]. Smoking accelerates the development of coronary artery disease and other atherosclerotic vascular diseases and can greatly increase the risk of acute coronary events, particularly sudden cardiac death[5]. Smoking is related to respiratory diseases such as chronic obstructive pulmonary disease (COPD) and chronic bronchitis. It also worsens bronchial asthma[6] and increases the risk of cancer of the cervix, especially in women suffering from Human Papilloma Virus (HPV) infection[7]. The risk of smokers developing tuberculosis and influenza is significantly high. Smokers have a higher risk of Erectile Dysfunction (ED) than nonsmokers and those with ED were found more likely to be smokers[8]. Smoking is also associated with hearing loss and Crohn's disease[9]. Due to its antiestrogenic effect, cigarette smoking can induce early menopause and osteoporotic changes in women[10]. Women smokers (>35 years) on oral contraceptives are more prone to thromboembolic disorders.

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, a 65% reduction in the risk of relapse was observed on stopping smoking, which was of same magnitude as that of immunosuppressive treatment[9]. Stopping smoking is beneficial in lung cancer patients prior to surgery, while continued smoking at the time of operation is met with poor prognosis[11]. Smoking cessation is the most effective intervention to reduce the risk and progression of COPD[12]. Stopping smoking can improve erectile dysfunction in a large number of patients. Smoking is a well-known cause of atherogenesis and increased tendency towards thrombosis. A study found that even two weeks of smoking cessation greatly improved platelet aggregation and intra-platelet redox imbalance, thereby decreasing oxidative stress[13].

A variety of pharmacological and non-pharmacological treatments for smoking cessation have been proposed from time to time. Some of them have proved to be very efficacious and are considered to be the first line treatment by US Public Health Service Clinical Practice Guideline, while some others have been assigned as second line treatment. Many new treatment modalities have been developed, some of which are being looked forward to as very promising therapies. This article focuses on the critical evaluation of the existing and emerging pharmacological and non- pharmacological smoking cessation therapies.

Neurological basis of nicotine addiction

Addiction is defined as a situation in which a drug unreasonably controls behavior[11]. Drug dependence is characterized by compulsive use of a drug with psychoactive effects and the presence of drug-reinforced behavior. Additional criteria are stereotypic patterns of use, use despite harmful consequences, relapse following abstinence, and recurrent drug cravings[12]. Smoking also produces a similar addictive behavior. Approximately 40 percent of smokers attempt to quit annually, yet less than 5 percent actually do so. Most smoking cessation attempts fail within the first two weeks[13]. Even in patients with cardiovascular disease, cancer or chronic obstructive pulmonary disease where stopping smoking is essential to prevent further deterioration of their medical condition, fewer than 50 percent quit[14].

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The agent largely responsible for maintaining smoking addiction is nicotine. On inhalation, nicotine diffuses readily into brain tissue, where it binds and stimulates nicotinic acetylcholine receptors (nAChRs) and results in the release of a variety of neurotransmitters in the brain, most importantly dopamine and others being GABA, serotonin, glutamate, noradrenaline, endogenous opioid and corticotrophin releasing hormone. Dopamine is released in the mesolimbic area, the corpus striatum, and the frontal cortex. The most important areas involved in the release of dopamine are the ventral tegmental area of the midbrain and nucleus accumbens, and this pathway appears to be critical in drug-induced reward phenomenon. The release of these neurotransmitters affects many of the subjective, cognitive, and behavioral effects associated with smoking such as increase in pleasure, improved mood, increased attention, enhanced cognition, improved motor performance and weight loss[15]. Chronic cigarette smoking also reduces brain monoamine oxidase A and B activity, which leads to increase in monoaminergic neurotransmitter levels such as dopamine and norepinephrine in synapses, thus augmenting the effects of nicotine and contributing to addiction[16].

The cessation of tobacco use results in a withdrawal syndrome, characterized by depressed mood, insomnia, irritability, frustration, anger, anxiety, difficulty concentrating, restlessness, decreased heart rate and increased appetite resulting into weight gain[17]. The potential for abuse or addiction to a drug depends upon the magnitude of the positive reinforcing effects and the speed of drug delivery to the brain[15]. Generally, the more quickly the drug is delivered to the brain, the greater is the potential for abuse. Nicotine from a smoked cigarette reaches the brain in ten to twenty seconds. Such rapid delivery contributes to its high abuse potential.

TREATMENT OPTIONS FOR SMOKING CESSATION

A number of treatments have been tried, but not many have proved to be quite successful as yet. In addition to many non pharmacological approaches which may play an important role, a number of pharmacological treatments have been tried to date with variable results.

PHARMACOLOGICAL TREATMENT

Pharmacological basis for treatment

Following approaches have been tried-

- Replacement/ substitution therapy for prevention and relief of withdrawl syndrome
- Drugs acting as agonists on nicotinic acetylcholine receptor
- Drugs which prevent dopamine/norepinephrine/ serotonin reuptake
- Drugs acting as antagonists on nACh receptors, which decrease the reward associated with smoking
- Others include those acting on GABA, opioid and cannabinoid receptors

The drugs may act by more than one mechanisms of action and have been conventionally classified as first line and second line drugs for smoking cessation. There also is a large group of emerging drugs that have shown some promise as smoking cessation therapies

- **First line treatment**
  - o Nicotine replacement therapy
  - o Bupropion
- **Second line treatment**
  - o Nortriptyline
  - o Clonidine
- **Emerging pharmacotherapies**
  - o Varenicline
  - o Nicotine vaccines
  - o Cytochrome P450 (CYP)2A6 inhibitors
- **Adjuvant therapies**
  - o Selective serotonin reuptake inhibitors
  - o Opioid antagonists
  - o GABAergic agents
- **Other pharmacotherapeutic options**
  - o Rimonabant
  - o Anticholinergics
  - o Lobeline
  - o Topiramate
  - o Silver acetate
  - o Anxiolytics
  - o D3 receptor ligands

FIRST LINE TREATMENT

Nicotine Replacement Therapy (NRT)

Nicotine-replacement medications may facilitate smoking cessation in several ways. The principal action is believed to be the relief of craving and withdrawal symptoms when a person stops tobacco use. Secondly, it also provides positive reinforcement, particularly in stress situations. The degree of positive reinforcement is related to the rapidity of absorption and the peak nicotine plasma level achieved. Thus, positive reinforcement is most relevant for short-acting, rapid-delivery formulations such as nicotine nasal spray. A third possible mechanism of benefit is the potential of nicotine medications to desensitize a subtype of nicotinic acetylcholine receptors, namely $\alpha_4\beta_2$ nAChRs, which results in a reduced effect of nicotine from cigarettes. This makes the cigarette less satisfying to the person in the case when his resolve to quit smoking fails and he tries to resume back smoking[18].

A systematic review of over 100 trials[19] to determine the effects of NRT have found that the incidence of smoking cessation was increased approximately 1.5 to 2-fold with NRT. Various formulations of NRT are available such as chewing gum, transdermal patch, inhaler, nasal spray, nicotine sublingual tablet, lozenge, straw, lollipop and electronic cigarette[20]. At present, there is insufficient evidence to recommend one form of NRT over another and thus patient and physician preference should play a large role in choosing a specific NRT drug. Patients with lesser dependence on nicotine (ie, <10 cigarettes/d) may consider lower-dose of NRT. Pregnancy and acute cardiovascular conditions especially recent acute myocardial infarction require cautious use of nicotine replacement therapy.

Novel electronic nicotine delivery system

Electronic cigarette

An electronic cigarette (or "e-cigarette") is an alternative to smoked tobacco products such as cigarettes, cigars or pipes. It

Table I: Various formulations of nicotine replacement therapy (NRT)

Form of NRT	Advantages/ disadvantages	Comment
Nicotine patch	Adv- simple and easy to use. Disadv - local skin irritation (50%), increased nicotine toxicity if the patient continues to smoke as well	Approved by the US Food and Drug Administration (FDA) Available over the counter drug (OTC).
Nicotine gum	Adv- simple and easy to use. Shown to reduce or delay weight gain Disadv- need for oral manipulation, unappealing flavor, jaw fatigue, jaw and mouth soreness, headaches	FDA-approved for smoking cessation Available OTC
Nicotine lozenges	Adv- simple and easy to use Disadv- heartburn, mouth and throat irritation, hiccups, and nausea.	Approved by the FDA in 2002 for smoking cessation. Available OTC
Nicotine nasal spray	Adv- rapid method of nicotine replacement Disadv- potential for abuse, nasal airway, throat irritation, watery eyes, runny nose, coughing and sneezing	FDA-approved for smoking cessation. Available by prescription only. Suitable for acute craving episodes.
Nicotine inhaler	Adv- replaces the "oral, handling, and sensory reinforcements" of cigarette smoking Disadv- Expensive, local irritation, sneezing, coughing, hiccups. Requires more intense puffing than smoking.	FDA-approved for smoking cessation. Available by prescription only. Not available OTC.
Nicotine drops	Adv-. simple and easy to use Disadv- cannot be used as a rescue medication, potential for interaction with beverages	Novel nicotine delivery system. No published efficacy data
Nicotine straw	Adv- simple and easy to use Disadv- cannot be used as a rescue medication, potential for interaction with beverages	Novel nicotine delivery system. No published efficacy data
Pulmonary delivered nicotine	Adv- rapid relief of acute cravings, more physiological resemblance to cigarette smoking Disadv- technically difficult design, potential for abuse	Considered sufficiently abusable to merit regulation under the auspices of the CSA (Controlled Substance Act).
Nicotine lollipops	These lollipops often contained a product called nicotine salicylate with a sugar sweetener. Disadv – risk of accidental use by children	Nicotine salicylate is not approved by the FDA for pharmacy use. The FDA has warned pharmacies to stop selling nicotine lollipops on the Internet, calling the products "illegal."
Nicotine wafer and nicotine water	Adv- simple and easy to use Disadv – risk of accidental use by children	Advertised as ways to get nicotine in places where smoking is not allowed. Not approved by the FDA
Electronic cigarettes	Adv- does not contain other harmful material produced by the combustion of tobacco Disadv- technically difficult design	Objected by WHO as a legitimate smoking cessation aid

is a battery-powered device that provides inhaled doses of nicotine by delivering a vaporized propylene glycol/nicotine solution. In addition to nicotine delivery, this vapor also provides a flavor and physical sensation similar to that of inhaled tobacco smoke. A common design is the "pen-style", so named for its visual resemblance to a ballpoint pen. Nicotine concentrations in these devices range from high doses (to mimic the content of regular cigarettes) to midrange and low doses (that mimic the nicotine content of "light" and "ultralight" cigarettes). Solutions are also available without any nicotine *at all*[21].

Electronic cigarettes are marketed as a healthier alternative to tobacco smoking by claiming that most of the harmful material produced by the combustion of tobacco in traditional cigarettes is not present in the atomised liquid of electronic cigarettes. They have also been marketed as a way to keep or curtail an addiction to nicotine[22]. There has been a valid objection for the electronic cigarette to be a legitimate smoking cessation aid by WHO as no rigorous peer reviewed studies have been conducted as regards the safety and efficacy of these electronic cigarettes[23]. Various formulations of NRT have been shown in table I.

TOBACCO REPLACEMENT THERAPY

This is another way of replacing nicotine but has many drawbacks. So it is a poor way of nicotine replacement.

Tobacco lozenges and pouches

Tobacco lozenges and pouches are being sold as other ways for smokers to get nicotine in places where smoking is not allowed. The FDA has stated that these are types of oral tobacco products like snuff and chew and are not smoking cessation aids. They have never been rigorously tested to see if they can help people quit tobacco. These products contain human carcinogens and can cause mouth cancer, gum disease, destruction of the bone sockets around teeth, bad breath, staining of teeth and harmful effects on the heart and circulation[24].

Vaporizer
It is a relatively newer device without the harmful effects of irritating toxic and carcinogen by- products like CO and tar etc that has been recommended as medically justifiable delivery medium especially in the circumstances where there are public bans to smoking. The vaporizers offer the advantages of effective and direct delivery to blood through lungs and a more precise titration[25].

BUPROPION
Bupropion is an atypical antidepressant drug that is approved by the US FDA for the treatment of tobacco dependence. At therapeutic doses it can bind to striatal dopamine transporters (~20% occupancy) and potentially prevent dopamine reuptake, thereby reducing negative withdrawal symptoms. Bupropion may act as an antagonist at the nicotinic acetylcholine receptor, suggesting that bupropion may attenuate the rewarding effect of nicotine.

It may be appropriate for patients who dislike or have not achieved smoking cessation with NRT. As bupropion helps to prevent weight gain, so it may be especially beneficial for patients concerned about this problem associated with smoking cessation. The efficacy of bupropion has been confirmed in several large studies[26]. The recommended duration of treatment is 7 to 12 weeks, but this may be extended by 12 months to prevent relapse, depending on the individual's nicotine withdrawal phase[27]. Because bupropion is a non-nicotine—based therapy, there is no rebound phenomenon on abrupt discontinuation of the drug.

Major side effects observed in clinical trials include insomnia (30%–42%), headache (26%) and dry mouth (10.7%) in patients using the sustained-release formulation[28]. Bupropion SR is contra-indicated in patients with a history of an eating disorder, seizures, closed head trauma, histories of allergic responses to bupropion and among those who have recently used monoamine oxidase inhibitor. Caution needs to be warranted in children and adolescents with certain psychiatric disorders and in pregnancy.

Current status- Due to the well-documented efficacy of bupropion in increasing quit rates, it is the only first-line non nicotinic product, that has been recommended by the US Clinical Practice Guideline[29] for the treatment of tobacco abstinence.

SECOND LINE TREATMENT
Nortryptline
This tricyclic antidepressant is thought to exert its therapeutic effects via the inhibition of the re-uptake of norepinephrine and serotonin and also by acting as a weak nicotinic receptor antagonist. The efficacy of nortriptyline as a smoking cessation aid has been assessed in studies which demonstrated that nortriptyline significantly increased smoking cessation rates when compared to placebo[30]. Treatment is continued for 12 weeks. It is started 10–28 days before target quit date. Dose needs to be tapered before discontinuation. It may be used in combination with NRT.

Nortriptyline should be avoided in patients prone to arrhythmias because the drug can cause cardiac conduction delay in such patients[31]. It is not recommended during pregnancy.

Current status- Nortriptyline has been endorsed by the US Clinical Practice Guideline[29] as a second-line pharmacotherapy for the treatment of tobacco abstinence. It is not approved currently by the FDA for nicotine dependence.

Clonidine
Clonidine is an α_2 adrenergic agonist developed originally as an antihypertensive agent, but it has also been recommended for the treatment for opiate or alcohol abuse withdrawal. The exact mechanism of action of clonidine for alleviating withdrawl symptoms are not known, but may involve decreasing norepinephrine release and thus decreasing sympathetic activity associated with withdrawl states. It has also been used as a smoking cessation therapy. It has been found to be effective in both male and female smokers in some studies, while in some others, it was found to be more effective in females as compared to males[32,33]. Patients who stop clonidine use abruptly may experience withdrawl symptoms such as agitation, headache, tremor, as well as rebound hypertension. It should be used with caution in pregnancy. Situations where clonidine may be considered appropriate include the failure of NRT or bupropion, and the presence of multiple drug-abuse problems. It might be used in combination with NRT or bupropion, as its mechanism of action is different from that of either.

Current status- Clonidine has been endorsed by the US Clinical Practice Guideline[29] as a second-line pharmacotherapy for the treatment of tobacco dependence.

EMERGING PHARMACOTHERAPIES
Varenicline
Varenicline, a nicotine receptor partial agonist, is the most recently developed non-nicotine preparation. The partial agonistic activity of varenicline on $\alpha_4\beta_2$ nicotinic receptor leads to relief from nicotine craving and withdrawl symptoms caused by low levels of dopamine during cessation attempts. It is especially useful for patients who have a relapse after quitting smoking. Because of its partial agonist character, varenicline has a lower risk of adverse events and a lower abuse potential than a medication containing nicotine. Better efficacy of varenicline as compared to placebo and bupropion for smoking cessation has been seen in some double blind randomized controlled trials[34]. Some studies have reported good abstinence rates with varenicline, even after 1 year[35]. Most common adverse event due to varenicline is nausea, headache, insomnia and abnormal dreaming. But the long term (> 24 weeks) safety issues are yet to be determined in clinical trials[36]. It should be used with caution in pregnancy. Some post marketing reports of occurrence of neuropsychiatric symptoms like agitation, depression and suicidality led to addition of new safety warnings to varenicline treatment in 2008[37].

Current status- Varenicline offers a new therapeutic option for patients trying to achieve smoking cessation. It is approved by the FDA as an aid to smoking cessation[28]. It appears to be a cost effective option in the long term, inspite of higher average daily cost of therapy.

Nicotine Vaccines
A newer strategy currently being investigated for smoking cessation is the nicotine vaccine. The principle of this strategy is to prevent nicotine from entering the brain due to binding by nicotine specific antibodies, thus preventing the nicotine induced dopamine release in the brain and hence the reward phenomenon[38]. It would help in reducing relapse after smoking cessation. It can also be used in adolescents to prevent initiation of tobacco use after assessing in detail the risks and benefits of such an intervention. An advantage of nicotine vaccines is that daily administration of the drug is not required; only occasional booster shots are needed to maintain an adequate antibody titer. Presently three types of nicotine vaccines are being studied for this purpose. All of these vaccines have shown some efficacy in early phase II studies. The disadvantage with nicotine vaccine is that the titer of antibodies after active immunization may not be sufficient to bind all of the nicotine in arterial blood, and thus restricting entry of nicotine into the brain[39]. This may result in paradoxical compensatory smoking. One way to deal with the problem associated with antibody titer is through passive immunization, in which nicotine-specific antibodies are administered directly. Thus, nicotine antibodies may provide a potential alternative to active vaccines; however, the main disadvantage is high costs associated with antibody production.

Current status- It appears that nicotine vaccines may be efficacious as a tobacco dependence treatment. But still more studies are required before these drugs can be approved and marketed.

Cytochrome P450 (CYP)2A6 Inhibitors
In humans, approximately 70–80% of nicotine is metabolized to cotinine with help of enzyme CYP2A6. Thus CYP2A6 inhibitors when used along with NRT products can aid smoking cessation by inhibiting the first pass metabolism of the nicotine obtained from the NRT product. CYP2A6 inhibitors studied in experimental settings include methoxsalen (8-methoxypsoralen, 8-MOP) and tranylcypromine (TCP)[40]. There are some reports of efficacy of CYP2A6 inhibitors when given in combination with NRT[41].

Current status- There are currently no CYP2A6-inhibitors indicated for the treatment of tobacco dependence because approval for a combination product (e.g. a CYP2A6 inhibitor plus an NRT product) would require more extensive studies regarding efficacy and adverse effects of the combination[42].

ADJUVANT THERAPIES

Selective Serotonin Reuptake Inhibitors
Selective serotonin reuptake inhibitors (SSRIs) are used to treat depression and anxiety and to regulate mood. After stopping smoking, many people experience mood changes resembling subclinical depression. Thus, it is theoretically possible that SSRIs such as fluoxetine, paroxetine, or sertraline may help patients overcome these symptoms[28]. Fluoxetine is an SSRI that has shown modest, short-term efficacy as a tobacco dependence treatment in some studies along with the additional benefit of reducing post cessation weight gain[43], but others like paroxetine and venlafaxine are of doubtful value.

Opioid Antagonists
The opioid system is thought to be involved in the reinforcing properties of several drugs of abuse including nicotine. This may imply that opioid antagonists may attenuate the reinforcing value of cigarette smoking[44]. Opioid receptor antagonists, such as nalmefene and naltrexone, have demonstrable efficacy in decreasing cigarette consumption and self reported smoking satisfaction and increasing smoking cessation rates in some studies. But naltrexone therapy was associated with a higher rate of withdrawal because of an increased incidence of adverse events like drowsiness, disorientation, nausea and abdominal pain[45].

GABAergic Agents
GABAergic neurotransmission significantly abolishes dopaminergic neurotransmission and thus decreases the reinforcing effects of nicotine and its withdrawl symptoms[46]. Thus GABAergic agents could be used as a useful tobacco dependence treatment. GABAergic medications that have been tried include baclofen, gabapentin, vigabatrin and tiagabine[42]. **Tiagabine** (inhibitor of GABA reuptake) has shown a significant efficacy over placebo in one study[47].

Current status- Although there is some evidence for the role of GABA neurotransmission in the acute neurochemical and behavioral effects of nicotine, there is only a little evidence indicating a potential role of GABAergic neurotransmission in nicotine withdrawal[48].

OTHER PHARMACOTHERAPEUTIC OPTIONS

Rimonabant
Rimonabant is a cannabinoid (CB1) receptor antagonist that was thought to be a possible aid in smoking cessation particularly in patients for whom weight gain is a significant barrier to smoking cessation[49]. But recently some side-effects have been reported with rimonabant like severe depression, suicidal intent and neurodegenerative diseases[50]. As a result of these drawbacks, it is not likely to emerge as smoking cessation therapy[51].

MAO Inhibitors
Cigarette smoking has been demonstrated to inhibit MAO-A and MAO-B enzyme[52]. Thus, substituting MAO inhibitors for smoking might theoretically facilitate smoking cessation by achieving increased synaptic concentrations of dopamine, serotonin and noradrenaline. But moclobemide and selegiline have not been able to demonstrate much efficacy as a tobacco dependence treatment[53,54]. The reversible inhibitor of MAO-B lazabemide was also evaluated for smoking cessation, but the study was terminated due to concerns of hepatotoxicity[55].

Anticholinergics
Anticholinergic drugs act by blocking muscarinic sites in the cerebral cortex, which are involved in the mediation of nicotine withdrawal[56]. Drugs used are a combination of atropine, scopolamine and chlorpromazine. Some clinics claim high success rates, but the available published scientific research does not back up these claims[57].

Silver Acetate
Silver acetate is a pharmaceutical aversive therapy that leaves an unpleasant taste in the mouth when combined with

cigarettes[58]. The Cochrane Collaboration and US Department of Health and Human Services (USDHSS) Clinical Practice Guidelines review found no benefit from silver acetate[29]. Thus in light of current available information, it is not recommended.

Anxiolytics
The Cochrane Collaboration reviewed 58 trials of anxiolytics (buspirone, diazepam, meprobamate and β blockers) and concluded that none of the trials supported efficacy for improving smoking cessation. Thus they are not recommended[59].

Lobeline
Lobeline is an alkaloid, classified as a partial nicotinic agonist that is derived from Lobelia inflata, an Indian tobacco plant. It has been used widely in a variety of proprietary tobacco dependence treatments. A recent review by Stead and Hughes failed to identify any adequate long-term trials that could provide evidence that lobeline can aid smoking cessation[60].

Topiramate
Topiramate, an anticonvulsant medication, is being tried as a treatment for alcohol and cocaine addiction. It is now suggested that it may also be used as smoking cessation agent also but its utility for smoking cessation needs to be examined further in controlled clinical trials[61].

Mecamylamine
Mecamylamine is a non-competitive antagonist at the nicotinic acetylcholine receptor site. Review of 2 studies indicates that mecamylamine combined with nicotine patch produced better cessation rates than nicotine patch alone[62]. However, lack of any long term studies precludes current endorsement of mecamylamine[29].

D_3 Receptor Ligands
Dopamine D_3 receptors have been implicated in stimulus controlled drug seeking behaviour. BP 897 (a D_3 receptor partial agonist) and ST 198 (a D_3 receptor antagonist) have been shown to reduce the motivational effects in animal experiments. Thus they might be successful as a smoking cessation aid[63].

NON PHARMACOLOGICAL TREATMENT

Dietary Treatments
Many homeopathic aids and herbal supplements are being used as stop-smoking methods but they have not been proven to effectively help people quit smoking[24]. Glucose tablets which curb the hunger pangs can be used as an aid in smoking cessation[64]. Serotonin enhancing substances such as tryptophan and high carbohydrate diet reduce the negative effect, which is a classic symptom of withdrawal. Some studies have established its efficacy[65]. Thus, tryptophan and high carbohydrate diet could become an important adjuvant in smoking cessation therapy after undertaking more trials with greater number of patients.

Behavioural Therapies
Non pharmacologic therapeutic approaches that may improve smoking cessation outcomes include cognitive, behavioral and motivational therapies. The US Department of Health and Human Services (DHHS) Guideline Panel on treatment of tobacco use and dependence determined that there is a strong, positive relation between the intensity of counseling (i.e., total minutes of contact) and successful abstinence[29].

Self-help programs for smoking cessation generally consist of printed or electronic materials given to patients to increase motivation to quit smoking. They are inexpensive, are effective in different target groups and can be reused for repeated quit attempts[66]. Telephone counseling is another method which is tailored according to the personal needs[67]. Some studies depict that it is an effective way to monitor patients who undergo treatment for smoking cessation[68].

Opportunistic interventions by healthcare providers include brief advice during routine patient contact, implementation of standard screening and treatment programs for smokers and recommendation of exercise programs as an adjunct to smoking cessation interventions[69]. Hypnosis though not a scientifically proven method, might be of help by getting the smoker into a deeply relaxed state where he is open to suggestions that strengthen his resolve to quit smoking and increase his negative feelings toward cigarettes[70].

OTHERS

Acupuncture And Low-Level Laser Therapy
Both of these treatments are used to stimulate body's acupoints and release endorphins to mimic the effect of nicotine in brain but there are no scientific evidences that they help and can be recommended as a method of choice for smoking cessation[24].

Aversive Therapies
Aversive therapies like rapid smoking, smoke holding, rapid puffing, excessive smoking and electric shock involve linking a negative sensation to smoking that encourages its cessation. Hajek and Stead concluded that there was insufficient evidence to support the effectiveness of aversive therapy[71].

Light and De-Nicotinized Cigarettes
For decades now, light and de nicotinized cigarettes have been promoted with the claim that they are less harmful to smoker's health because of low nicotine content. However it has been demonstrated that low nicotine cigarettes function almost the same as typical cigarettes in terms of brain nicotine receptor occupancy[72]. Hence their value as a cessation aid is also doubtful.

CONCLUSION

Various pharmacological and non pharmacological treatments have been tried for smoking cessation from time to time. Some of the pharmacological treatments have been able to achieve the status of first line therapy for smoking cessation by the US Public Health Service Clinical Practice Guideline. These include six forms of NRT (nicotine patch, nicotine gum, nicotine lozenges, nicotine nasal spray, nicotine inhaler and nicotine sub-lingual tablets) and the antidepressant bupropion. Other newer forms of NRT like nicotine drops, nicotine straw, pulmonary delivered nicotine and nicotine containing electronic cigarettes have yet to

establish their place in therapy for smoking cessation. Other efficacious drugs that have received the status of second line drugs for smoking cessation by the US Public Health Service Clinical Practice Guidelines include antidepressant nortriptyline and α noradrenergic agonist clonidine. Varenicline is a very promising new drug that has come up as an aid to smoking cessation. Other new drugs that have come up but have yet to establish their efficacy in clinical trials include cytochrome P450 (CYP)2A6 inhibitors and nicotine vaccines. Rimonabant was being considered as a very promising new drug for smoking cessation, but now has been seen to be associated with serious adverse effects. Opioid antagonists and GABAergic agents hold a doubtful place in smoking cessation therapy. Other drugs have been tried from time to time but have failed to show any consistent results include anticholinergics, silver acetate, anxiolytics, lobeline, mecamylamine, topiramate and D3 receptor ligands. Among the non pharmacological treatments, vaporizers are the recent developments that are being considered as good optional agents. Other non pharmacological treatments that have been tried from time to time, but they lack any scientific evidence of their efficacy include light and de-nicotinized cigarettes, tobacco lozenges and pouches, glucose tablets, aversive therapies, hypnosis, acupuncture, low level laser therapy, filters, smoking deterrants, herbs and supplements. Behavioural therapies for smoking cessation constitute a very important part of treatment because they increase the smokers' will to quit, without which any of the other pharmacological or non pharmacological treatment cannot be successful.

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