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REVIEW ARTICLES

Pharmacological Therapy in Smoking Cessation

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Introduction:

Cigarette smoking is largely a 20th-century phenomenon. The introduction and promotion of manufactured cigarettes changed the nature of tobacco use to that of a regular consumer activity. The introduction of cigarettes is important from public health point of view due to 2 important reasons:[17]

1) The cigarette smoke is directly, deliberately inhaled.
2) As cigarettes are portable and convenient, tobacco smoking became a social and everyday phenomenon rather than a ceremonial and formal activity.

Regular use of cigarettes quickly leads to addiction. Tobacco smoke has been classified as a class A carcinogen[7]. The main components of tobacco smoke are:

1) Tar: As a solid irritant, tar coats the lungs, blocks the airways and causes emphysema and lung cancer.
2) Carbon monoxide (CO): CO binds to haemoglobin (Hb) and replaces oxygen. It causes heart and arterial disease. The level of CO in a smoker's body depends on the number of cigarette smoked and how they are smoked.
3) Nicotine: This is the addictive component of tobacco smoke. The nicotine in each puff of inhaled smoke reaches the brain in less than 7 seconds. The amount available in nicotine replacement therapy (NRT) is not sufficient to cause major physical harm.

Smoking is the chief avoidable cause of premature death and ill health in the world. It continues to be the dominant risk factor for cardiovascular disease (CVD) in terms of both mortality and morbidity. The total number of smokers is expected to reach about 1.6 billion by 2025.[16] The cardiovascular effects are related to the amount of tobacco smoked daily and to the duration of smoking. In presence of other risk factors (diabetes, hypertension, dyslipidaemia, overweight) smoking related risk increases even further.

Smoking has been identified as the most important of the known modifiable risk factors for CVD. The death rate for all CVD for smokers is 2-3 times that of non-smokers and between 35% and 40% of these deaths occur before retirement age.[24] Passive smoking increases the risk of heart disease by 23% (Independent Scietific Committee on Smoking and Health.[13]

Smoking cessation strategies:

Given the ongoing risk for major cardiovascular events as defined in population-based studies, repeated clinical interventions to address chronic users and relapses seems very important. Effective pharmacologic and counseling strategies are now the pillars of tobacco cessation programmes. Currently approved 1st-line pharmacological agents include nicotine replacement therapy (NRT), which is available in different formulations; bupropion, an atypical antidepressant, and varenicline, a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor receptor.

In the following section pharmacological strategies involving 2 drugs (NRT and varenicline) will be discussed in general with particular emphasis on their effectiveness and safety on patients with cardiovascular disease or those at high risk of developing cardiovascular disease.

Nicotine Replacement Therapy (NRT):

Nicotine addiction leads to alteration of brain structure with nicotinic receptor upregulation, changes in brain activity evidenced by alteration regional glucose metabolism and cognitive effects that patient rely on such as mood and sleep control.[9] The NRTs enable the person to abstain from by replacing the nicotine derived from their tobacco product use. The main 3 mechanisms NRTs can aid smoking cessation effort are:[12]

1) Physical withdrawal symptoms may be reduced.
2) It may also reduce the addiction enforcing effects of tobacco derived nicotine
3) It also helps by avoiding the mood disturbances and attention states of withdrawal.

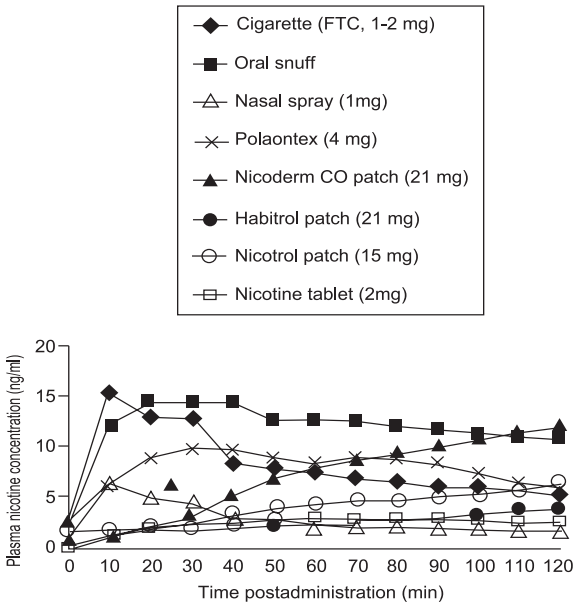

Fig.-1: *Venous blood concentrations for various nicotine delivery products (Garrett & Rose and Henningfield, 2001)*

The above figure (Fig 1) shows none of the NRTs can elevate blood nicotine levels as quickly as inhaled cigarette smoke. The average systemic nicotine intake from cigarettes is 30 mg/day. For example, a nicotine gum provided in a 2 to 4 mg tablet usually provides 10 mg or 20 mg respectively.

Relative efficacy of different NRT formulations:[27]

Table-I

Risk Ratio (RR) of abstinence with different NRT

Treatment	Risk Ratio (95% CI)
NRT: All forms, pooled (meta-analysis of 111 studies)	1.58 (1.50–1.66)
Gum	1.43 (1.33–1.53)
Patch	1.66 (1.53–1.81)
Inhaler	1.90 (1.36–2.67)
Lozenge	2.00 (1.63–2.45)
Nasal spray	2.02 (1.49–3.73)

The above table (Table 1) shows the efficacy of different NRT in clinical trials. It appears that all forms of NRT has more or less similar efficacy. This meta-analysis shows that NRTs increase the rate of quitting by 50-70%, regardless of setting. The effects were largely independent of the duration of therapy.

Table-II

Different NRT formulations: Comments, adverse effects, contraindications and dosage (Nides, 2008)

Medication	Comments	Most Common Adverse Events	Contraindications/Precautions	Dosage
Nicotine patch	FDA-approved for smoking cessation Continuous-release (long-acting) formulation Available OTCCan be worn for 24 hr or for only 16 hr to avoid insomnia	Mild skin irritation at placement site	Pregnancy category D; avoid in pregnant women due to continuous delivery formulation Use with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	>10 cigarettes/ day: 21 mg/24 hr for 6–8 wk; decrease to 14 mg/24 hr for 2–4 wk; then to 7 mg/24 hr for 2–4 wk ≤10 cigarettes/ day: 14 mg/24 hr for 6 wk; then decrease to 7 mg/24 hr for 2–4 wk

table continued

Medication	Comments	Most Common Adverse Events	Contraindications/Precautions	Dosage
Nicotine gum	FDA-approved for smoking cessation SANRT formulation allows for flexible dosing Available OTC Heavy smokers achieve greater benefit with 4-mg gum than 2-mg gum (see *Dosage*) Shown to reduce or delay weight gain	Jaw pain, mouth soreness, dyspepsia, hiccoughs	Pregnancy category C; the risk–benefit ratio may be favorable in pregnant smokers if efforts to quit without medication have failed and if the patient is continuing to smoke more than 10–15 cigarettes/dayAvoid in patients with temporomandibular joint diseaseUse with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	≥25 cigarettes/day: use 4 mg nicotine gum; <25 cigarettes/day: use 2 mg nicotine gum on the following schedule: day 1 of abstinence through week 6: 1 piece every 1–2 hr; weeks 7–9: 1 piece every 2–4 hr; weeks 10–12: 1 piece every 4–8 hrIt is suggested to use e”9 pieces/day for the first 6 wk (max: 20–30 pieces/day)
Nicotine inhaler	FDA-approved for smoking cessationSANRT formulation allows for flexible dosingBy prescription onlyHand-to-mouth use mimics action of smoking, providing a coping mechanism for conditioned smoking cues	Mouth and throat irritation, cough	Pregnancy category DUse with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	6–16 10-mg cartridges/day for 12 wk; taper dosage over next 6–12 wkEach cartridge delivers 4 mg of nicotine
Nicotine lozenge	FDA-approved for smoking cessationSANRT formulation allows for flexible dosingAvailable OTC	Mouth and throat irritation, hiccoughs	Pregnancy category DUse with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	Patients who smoke their first cigarette within 30 min of awakening should use 4-mg lozenges; others should use the 2-mg dose1 lozenge every 1 to 2 h for weeks 1 to 6; 1 lozenge every 2 to 4 h for weeks 7 to 9; 1 lozenge every 4 to 8 h for weeks 10 to 12

table continued

Medication	Comments	Most Common Adverse Events	Contraindications/Precautions	Dosage
Nicotine nasal spray	FDA-approved for smoking cessationSANRT formulation allows for flexible dosingBy prescription onlyFastest delivery system for NRT, which is useful for rapid relief of withdrawal symptoms (especially in heavy smokers)	Runny nose, throat and nasal irritation, coughSide effects usually resolve after 3 days	Pregnancy category DUse with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	1 or 2 0.5-mg doses in each nostril hourly for 3–6 mo; taper doses over 4–6 wk

The above table (Table 2) summarizes the indication, side effects, contraindication and dosage of different NRT products approved by Food and Drug Administration (FDA).

NRT appears safe in most patients, including those with CVD with stable angina. The safety of NRT has not been studied in patients with unstable angina or myocardial infarction within 2 weeks of planned treatment.[15] Thus, for those inpatients with nicotine dependence admitted for acute coronary syndrome (ACS), NRTs should be used with caution. Unlike smoking, NRT does not increase the coagulability of blood or expose a patient to CO or oxidizing gases that damage endothelium.[2] Despite the vasoconstrictor effects of nicotine, studies have failed to demonstrate an increased risk with the use of NRT in patients with CVD. The benefit of NRT appears to outweigh the risk for cardiovascular patients who continue to smoke.

In a randomized controlled trial (RCT), the results of 4 NRT products were compared. After 12 weeks of therapy, efficacy was similar (20-24%) but the compliance varied among the groups widely, with the highest use noted in the patch (82%), intermediate in the gum (36%), and lowest in nasal spray (15%) and vapour inhaler (11%). The expected 12-month abstinence for NRT is 10-16%.[11] Combining NRT products such as the patch with gum or nasal spray was associated with higher cessation rates.

Most smokers perceive NRT as less satisfying than smoking cigarettes. This is due to:

1) Slower delivery of nicotine.
2) It only partially addresses the reinforcing effects of smoking that are not associated with nicotine.

For these reasons, NRT has been shown to be less liable for abuse and low dependence potential[32]. Moreover, there is no evidence of withdrawal discomfort when patients discontinue NRT use.

Varenicline:

Varenicline is the most recently FDA approved agent for smoking cessation and has been included in the DHHS guidelines for the treatment of tobacco dependence.[8]

Nicotine dependence is believed to be mediated by activation of $\alpha4\beta2$ nicotinic acetylcholine receptor in the ventral tegmental area of the brain, and the $\alpha4\beta2$ receptor density has been proven to be much higher in smokers.[28,18] As a non-nicotinic partial agonist of the $\alpha4\beta2$ nicotinic acetylcholine receptors, varenicline binding leads to partial stimulation of receptor-mediated release of dopamine in the reward centre and competitive inhibition of receptor binding by nicotine delivered from cigarettes. As a result varenicline suppresses the symptoms of nicotine withdrawal and reduces the pharmacologic reward from cigarette smoking.[4] The following figure (Fig. 2) shows the mechanism of action of varenicline.

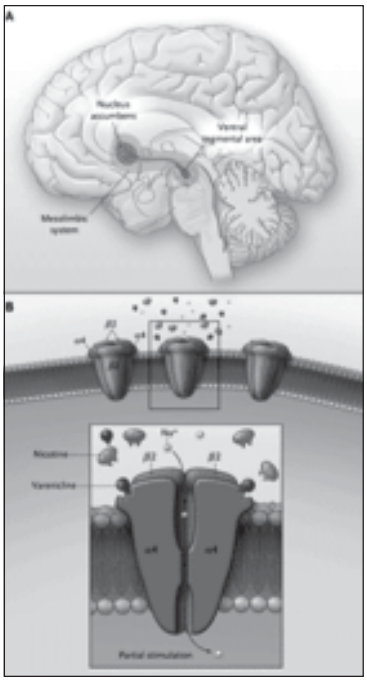

Fig.-2: *The Actions of Nicotine and Varenicline in the Brain. (Slater et al., 2003)*

Panel A: The principal site of nicotine action in the brain is the mesolimbic system. Nicotine stimulates dopaminergic neurons located in the ventral tegmental area, increasing dopamine release in the nucleus accumbens. Nicotine interacts with nicotinic acetylcholine receptors located in the mesolimbic system and elsewhere.

Panel B: The highest-affinity nicotinic acetylcholine receptors consist of two α4 subunits and three β2 subunits. Nicotine binds to and causes a conformational change in the α4β2 nicotinic acetylcholine receptor, increasing sodium (Na^+) influx. Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor that causes partial stimulation while it competitively inhibits nicotine binding.

Table-III

Dose and duration of treatment of varenicline

Dose	Duration
0.5 mg daily for 3 days , then	12 weeks
0.5 mg bid for 4days , then	
1mg bid from day 8 for 12 weeks	

Table 3: The above table (table 3) shows the dose and total duration of treatment of varenicline. The 1-week dose adjustment period reduces nausea as compared with initial therapy at 1 mg twice daily.[21]

The following table shows the adverse effects of varenicline compared with placebo.

Table 4 shows that 12% subjects discontinued varenicline due to treatment related adverse events in RCTs at a dose of 1 mg twice daily. Adverse events reported in 5% or more of subjects are included. Other gastrointestinal effects were vomiting, constipation, diarrhea, flatulence and dyspepsia. The numbers are expressed in percentage[14,10].

Table-IV

Adverse effect	Varenicline	Placebo
Nausea	35.8	11.2
Insomnia	22	12.7
Abnormal dreams	14.4	5
Headache	16.8	14.3
Other gastrointestinal effects	22.5	11.8
Discontinuation of varenicline due to treatment related adverse event	12	8.1

The overall incidence of adverse events leading to discontinuation of varenicline is similar to that observed with placebo. The ceiling effect seen with partial agonists (i.e., increasing the dose beyond a certain point does not increase the effect) suggests a low potential for abuse with varenicline.[20,22]

In 2006, Food and Drug Administration (FDA) advised consumers and physicians about psychiatric symptoms while using varenicline but provided no data about similar events among other smokers to derive a denominator. Similar events were not appreciated in the approval study and probably underscore the fact that most cessation trials exclude patients with any prior history of psychiatric condition or simultaneous use of psychologically active drugs.[14,30] The Institute for Safe Medication Practice has recommended physicians exercise caution in the use of varenicline in whom the risk of accident is high, such as those operating mass transit vehicles, trains, planes, or heavy machinery or life-sustaining devices.[29]

The meta-analysis by Cochrane review found seven trials of varenicline compared with placebo for smoking cessation; three of these also included a bupropion experimental arm. It also found one open-label trial comparing varenicline with nicotine replacement therapy. The pooled risk ratio (RR) for continuous abstinence at six months or longer for varenicline versus placebo was 2.33 (95% confidence interval [CI] 1.95 to 2.80). The pooled RR for varenicline versus bupropion at one year

was 1.52 (95% CI 1.22 to 1.88). The RR for varenicline versus NRT at one year was 1.31 (95% CI 1.01 to 1.71).[3]

Varenicline increased the chances of successful long-term smoking cessation between two- and threefold compared with pharmacologically unassisted quit attempts. More participants quit successfully with varenicline than with bupropion. Two open-label trial of varenicline versus nicotine replacement therapy demonstrated a modest benefit of varenicline.[26]

In another meta-analysis of available pharmacological therapies for smoking cessation, all therapies were better than placebo. In the trials of varenicline that included bupropion in the controlled arm, varenicline was found superior (OR, 2.18; CI 1.09-4.08).[30]

Recently a multicenter, placebo-controlled RCT compared the efficacy and safety of varenicline in smokers with stable cardiovascular disease. The primary end point was CO confirmed continuous abstinence rate for weeks 9 through 12 (last 4 weeks of treatment). The continuous abstinence rate was higher for varenicline than placebo during weeks 9 through 12 (47% versus 13.9%; OR, 6.11 (95% CI 1.93 to 5.11) and weeks 9 through 52 (19.2% versus 7.2%; OR, 3.14 (95% CI 1.93 to 5.11). The varenicline and placebo groups did not differ significantly in cardiovascular mortality, all-cause mortality, cardiovascular events or serious adverse events.[23]

Conclusion:

Smoking is best regarded as a chronic disease that requires a long-term management strategy, rather than a quick solution.[31] Smoking cessation has been valued as the single most important step that smokers can take to enhance the length and quality of their lives.[1] Most smokers mistakenly believe that stopping smoking is purely a matter of willpower and remain unaware of effective treatments to promote quitting. Smokers trying to quit have to cope with psychological, behavioral, and physical aspects of tobacco dependence. Smokers develop nicotine dependence that resembles other addictions, and may require multiple attempts and long-term treatment to sustain abstinence.

Currently approved 1st-line agents include NRT, which is available in different formulations; bupropion, an atypical antidepressant, and varenicline, a partial agonist of the $\alpha 4\beta 2$ nicotinic acetylcholine receptor receptor. All therapies are better than placebo. The multiple formulations of NRT offer smokers a choice in the route of administration, which may have a positive influence on adherence to treatment. Combination of nicotine patch with gum, inhaler, or nasal spray was more efficacious than the use of any of these products alone.[8]

Varenicline was found superior to bupropion and NRT in clinical trials. More methodologically rigorous studies comparing varenicline and NRT are needed to make any judgement about their comparative efficacy.

Both NRT and varenicline have a benign adverse event profile, with a low rate of discontinuation due to adverse events. Their safety profile appears to outweigh the risk for cardiovascular patients who continue to smoke. However their safety has not been studied in patients with acute coronary syndrome (unstable angina or myocardial infarction) within 2 weeks of planned treatment. Therefore they should be used with caution in patients with nicotine dependence admitted for ACS.

The long-term benefit of smoking cessation on cardiovascular risk suggests a 36% reduction in mortality risks.[5] The reduction in mortality due to CVD exceeds the benefits of other preventative therapies such as use of statins (29%), aspirin (15%), and β-blockers (23%).[22] Therefore, assistance with smoking cessation is a cost-effective intervention that is underused by health professionals.[6] For physicians and health care system alike, the challenge is implementing effective treatment in routine medical practice.

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