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REVIEW ARTICLE

NICOTINE REPLACEMENT THERAPY – A BOON TO TOBACCO SMOKING CESSATION

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ABSTRACT

Nicotine replacement therapy replaces temporarily the nicotine from cigarettes which reduces motivation to smoke and nicotine withdrawal symptoms, thus easing the transition from cigarette smoking to complete abstinence. Nicotine replacement therapy replaces nicotine in blood, thus reduces urge to smoke. NRT is available as chewing gum, patches for the skin, nose spray, inhalers, and tablets. It is better to wait until the smokers feel ready to stop, and then make a quit attempt. All of the commercially available forms of NRT can help people who make a quit attempt to increase their chances of successfully stopping smoking. It is a cost effective way of reducing ill health and prolonging life.

INTRODUCTION

There are nearly 1.1 billion smokers across the world and 80 percent of them are in the developing countries. India has a total of 240 million smokers, (Shimkhada *et al.*, 2003). Despite increasing awareness to the harmful effects of tobacco, smoking continues to be a significant health risk factor. But, it has been observed that 70% of smokers want to quit and only 3 – 4% succeeded in quitting. (Fiore *et al.,* 2000) The reason can be suggested as high dependence of nicotine and poor determination of smokers for quitting. Nicotine replacement therapy abbreviated as NRT help those people who actually wants to stop smoking. The aim of nicotine replacement therapy is to replace temporarily the nicotine from cigarettes which reduces motivation to smoke and nicotine withdrawal symptoms, thus easing the transition from cigarette smoking to complete abstinence. NRT is available as chewing gum, patches for the skin, nose spray, inhalers, and tablets. The use of nicotine patches and nicotine gum have been shown in randomized clinical trials to have high quit rates for smokers than smokeless tobacco users. (Smoking cessation, 1996) However, NRT can still be effective in reducing cravings of smokeless tobacco uses, (Hatsukami *et al.,* 2000). Thus, NRT can also be a useful adjunct for behavioral treatments of smokeless tobacco cessation but the effect on cessation rates has been surprisingly small compared with that of smokers. Studies of smokeless tobacco cessation have also reported lower success rates for subjects who concurrently also smoke cigarettes than for users who only use chew or snuff, (Andrews *et al.,*1998). The first type of NRT to become widely available was chewing gum. The nicotine resin complex is presented in a buffered chewing gumbase to enable the nicotine to be absorbed directly through the buccal mucosa, resulting in plasma concentrations which are approximately half that produced by smoking a cigarette, (Russell *et al.,*1976). Although products for nicotine replacement therapy have been available for over 20 years, but still they have been excluded from use by different states or countries because of increased cost, lack of awareness and poor government supply of products. So, the aim of this review to put a light on mechanism of action, doses and the effectiveness of nicotine replacement therapy (NRT), including gum, transdermal patch, intranasal spray and inhaled and oral preparations, in achieving smoking cessation. The article chosen under this review are mainly clinical trials on the various forms of NRT and discussing its advantages and limitations.

Mechanism of action

Nicotine replacement therapy replaces nicotine in blood, thus reduces urge to smoke. It stimulates nicotinic receptors in the ventral tegmental area of the brain and causes release of dopamine in the nucleus accumbens. This and other peripheral actions of nicotine lead to a reduction in nicotine withdrawal symptoms in regular smokers who abstain from smoking. (Molyneux *et al.,* 2004). NRT may also provide a coping mechanism, making cigarettes less rewarding to smoke. It does not completely eliminate the symptoms of withdrawal, however, possibly because none of the available nicotine delivery systems reproduce the rapid and high levels of arterial

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nicotine achieved when cigarette smoke is inhaled, (Molyneux *et al.,* 2004). All the available medicinal nicotine products rely on systemic venous absorption and do not therefore achieve such rapid systemic arterial delivery. It takes a few seconds for high doses of nicotine from a cigarette to reach the brain, but NRT products achieve lower levels after a minute (for nasal spray or oral products such as gum, inhalator, sublingual tablet, or lozenge) and hours (for transdermal patches) Molyneux *et al*. (2004).

Forms of Nicotine replacement therapy

The evidence that NRT helps some people to stop smoking is now well accepted, and many clinical guidelines recommend NRT as a first line treatment for people seeking pharmacological help to stop smoking. Nicotine gum contains enough nicotine to reduce the urge to smoke. The over-the-counter gum is available in 2mg doses (for smokers of 24 or fewer cigarettes each day) and 4mg doses (for smokers of 25 or more cigarettes each day), (Herrera *et al.,* 1995; Garvey *et al.,* 2000). One piece of gum is one dose; maximum dosage should not exceed 24 pieces per day. Several factors limit the usefulness of nicotine chewing gum in some smokers, including oral and gastric side effects, (Henningfield *et al.,* 1990) impaired absorption when taken with coffee or acidic beverages, inadequate dosing, and a risk that some smokers may transfer their dependence from cigarettes to the gum, (Hughes *et al.,*1986).

nor a benefit for using patches beyond eight weeks. NRT works with or without additional counselling and does not need to be prescribed by a doctor, (Stead *et al.,* 2012).

When one should receive NRT

Ideally, it is better to wait until the smokers feel ready to stop, and then make a quit attempt. New research supporting this indication challenges this assumption and provides evidence for nicotine assisted reduction to stop. It suggests that cutting down first before NRT can increase the number of smokers who go on to stop. This finding is extremely important, as it could attract a new group of smokers into stopping.

This new indication is called "*Cut Down Then Stop*" (CDTS), (Drug Ther Bull *et al.,*1999). There is currently little scientific basis for matching particular smokers to particular forms of NRT, (Tang *et al.,* 1994). This is still a confusion between health professional to advise which form of NRT to which patient. The use of nicotine replacement therapy should be restricted to smokers who show evidence of nicotine dependence. Among such smokers the transdermal patch is probably the product of choice for most of them West *et al*, (2000). Smoking cessation guidelines for health professionals: an update: Silagy *et al.* (2000)

Table 1. Various forms of nicotine replacement therapies

TYPE	AVAILABLE DOSES[8]
Nicotine transdermal patches	5mg, 10 mg, 15 mg doses worn over 16 hours 7 mg, 14 mg, 21 mg doses worn over 24 hours
Nicotine chewing gum	2 mg and 4 mg doses
Nicotine sublingual tablet	2 mg dose
Nicotine lozenge	1 mg, 2 mg and 4 mg doses
Nicotine inhalation cartridge plus mouthpiece	Cartridge containing 10 mg
Nicotine metered nasal spray	0.5mg dose/spray

The nicotine patch releases a constant amount of nicotine in the body. Unlike smoke which passes almost instantaneously into the blood through the linings of the lung, the nicotine in the patch takes up to three hours to make its way through the layers of skin and into the user's blood. The only side effect which appears to interfere with use of the patch is skin sensitivity and irritation; this may affect up to 54% of patch users, but it is usually mild and rarely leads to withdrawal of patch use, (Fiore *et al.,* 1992).

Nicotine sublingual tablets have been reported to cause hiccoughs, burning sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers, (Wallstrom *et al.,* 1999). More recently, the observation that nicotine patches and gum do not provide 100% nicotine replacement has led to interest in increasing the efficacy of nicotine replacement by raising patch doses or by combining different forms of NRT, for example, patches and gum, or nasal spray with patches. In addition, there is growing interest in comparing NRT to newer pharmacotherapies, particularly the antidepressant bupropion, (Jorenby *et al.,* 1995). Although evidence suggests no overall difference in effectiveness between different forms of NRT,

- Smokers of 10 or more cigarettes per day should normally be encouraged to use NRT or bupropion.
- There is currently no scientific basis for recommending one form of NRT over others.
- There is no scientific basis for disallowing different forms of NRT to be combined and there may be some benefit to combinations.
- NRT can be recommended for use in patients with cardiovascular disease but only with the agreement of the patient's physician if the disease is acute or poorly controlled.
- Use of NRT by pregnant smokers may benefit the mother and fetus if it leads to cessation of smoking.
- NRT may aid smoking cessation in adolescent smokers but there is insufficient evidence yet to make a recommendation.
- No recommendation can currently be made concerning the circumstances in which bupropion should be preferred over NRT or vice versa other than those for which one of the drugs is contraindicated.

- No recommendation can be made regarding the use of NRT and bupropion in combination.
- Both bupropion and NRT should be prescribed for relatively short durations at a time and the prescriptions only repeated if the quit attempt is continuing.

Efficacy

Nicotine replacement therapy is effective in aiding smoking cessation. It reduces the urge to smoke and other withdrawal symptoms following cessation, (Silagy *et al.,* 2000). There appears to be little difference overall in the effectiveness of different types of NRT on cessation. One study which directly compared four of the six products found no difference in abstinence rates or withdrawal discomfort. Strong evidence that NRT is effective is limited to adult smokers of 10 or more cigarettes per day not suffering from manifest smoking related diseases. There is currently insufficient research on the use of NRT in light smokers, smokers under the age of 18, pregnant smokers and inpatient smokers, (Hajek *et al.,* 1999). Although NRT was more effective for men than placebo at 3-month, 6-month, and 12-month follow-ups, the benefits of NRT for women were clearly evident only at the 3- and 6-month follow-ups. Giving NRT in conjunction with high-intensity no pharmacological support was more important for women than men, (Benito *et al.,* 2004).

The relative efficacy of a single course of NRT remains constant over many years. The majority of relapse after 12 months occurs within the first or second year and is not detectable thereafter, suggesting that NRT has a permanent effect on smoking cessation, (Etter *et al.,* 2006). The efficacy of all forms of nicotine replacement therapy must rely to some extent on smokers being dependent on nicotine, and this was indeed the case. Ten trials of nicotine gum that measured nicotine dependence all showed a greater efficacy in highly dependent smokers ($P< 0.001$). The association between efficacy of the gum and nicotine dependence (measured by the Fagerstrom score) was continuous, but efficacy was low in smokers with Fagerstrom scores of 6 or less, (Tang *et al.,* 1994).

Cost-effectiveness

Nicotine replacement therapy is cost effective as compared to placebo. NRT and a package of non-price interventions other than NRT are also cost-effective in low-income and middle-income regions, at 280-870 US dollars per DALY (Disability adjusted life adjustment) and 36-710 US dollars per DALY, respectively. In high-income countries, price increases were found to have a cost-effectiveness of 83-2771 US dollars per DALY, NRT 750-7206 US dollars per DALY and other non-price interventions 696-13,924 US dollars per DALY. Tobacco control policies, particularly tax increases on cigarettes, are cost-effective relative to other health interventions, (Ranson *et al.,* 2002). Purchasing smoking cessation interventions represents an extremely cost effective way of reducing ill health and prolonging life.

Estimates of the cost-effectiveness of a global policy to make NRT freely available to smokers interested in quitting predict that 1 million smoking-attributable deaths could be averted if this policy results in a reduction in smoking prevalence by 0.5%. An increase in the price of cigarettes prompts people to quit smoking or reduce consumption and deters others from starting. A 10% increase on cigarette prices worldwide would reduce consumption by 4% in high-income countries and by 8% in low- and middle-income countries, (Novotny *et al.,* 2000).

Poor use of NRT in India

Cost is the main reason for its poor use among Indians. Those wanting to quit smoking have to shell out money to buy these chewing gums. A pack of 10 gums cost around Rs 45- 90. A chain smoker wanting to quit will need around two packs a day for a maximum of six months, (Sinha *et al.,* 2011). Since the government does not provide it, smokers have to pay for it, which is a huge deterrent. Cost is a major factor why NRTs haven't caught on in India. Reducing their price will get more Indians trying to quit smoking to use NRT. But India has to increase its tobacco cessation centers. Now, there are only 19 across India, (Sinha *et al.,* 2011). Moreover lack of awareness among the people regarding NRT also lead to its poor use which can be overcome by increasing the advertisement of various products available in the market.

Conclusion

All of the commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets/lozenges) can help people who make a quit attempt to increase their chances of successfully stopping smoking. NRTs increase the rate of quitting by 50- 70%, regardless of setting. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. Provision of more intense levels of support, although beneficial in facilitating the likelihood of quitting, is not essential to the success of NRT. NRT works with or without additional counselling. Heavier smokers may need higher doses of NRT. However, a nicotine patch (15 mg per 16 hours) along with behavioral cessation support for women who smoked during pregnancy did not significantly increase the rate of abstinence from smoking because of low adherence, participants usually stop using this therapy when they have a relapse, (Coleman *et al.,*2012). But, People who use NRT during a quit attempt are likely to further increase their chance of success by using a combination of the nicotine patch and a faster acting form. Preliminary data suggests that starting to use NRT shortly before the planned quit date may increase the chance of success, (Stead *et al.,* 2008).

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