



Tobacco Smoke: Break the Chain with Nicotine Replacement Therapy

Authors

Dr. Gauri Motiwale¹, Dr. Shradha Jaiswal², Dr. Ashok Vikey³, Dr. Tejas Motiwale⁴

¹PG Student, Dept. of Oral Pathology & Microbiology, Sri Aurobindo College Of Dentistry Indore
Email- gaurimotiwale@gmail.com, Phone no: 9713894842

²Reader, Dept. of Oral Pathology & Microbiology, Sri Aurobindo College Of Dentistry Indore
Email- drshradhajaiswal@gmail.com, Phone no: 9827022332

³Professor & HOD, Dept of Oral Pathology & Microbiology, Sri Aurobindo College Of Dentistry, Indore
Email- drvikey@yahoo.co.in, Phone no: 9425977174

⁴Reader, Dept. of Oral & Maxillofacial Surgery, Sri Aurobindo College Of Dentistry, Indore
Email- doctej@yahoo.com, Phone no: 8085580951

Corresponding Author

Dr. Gauri Motiwale

Shalimar Township, PT 4 Flat no.603 A.B. Road, INDORE INDIA

ABSTRACT

Today's world is facing the epidemic of smoking tobacco. It is one of the greatest threats to global health. Smoking is a major preventable cause of premature death and is an important cause of several general diseases ranging from oral ulcers, xerostomia to lung cancers. Tobacco has been consumed from historical times & has got long history. Many varieties of smoked and smokeless forms of tobacco products are available, to which people get addicted even though they contain many carcinogens. To fight this global agent of death, government & different organizations are coming up with strict policies. This paper reviews tobacco, its constituents & various treatment modalities available for cessation of the habit.

Keywords: *nicotine replacement therapy, carcinogens.*

Introduction

India is one of the major producer & user of tobacco. The Global Adult Tobacco Survey (GATS) estimated that more than one-third (35% or 274.9 million) of adults in India use tobacco in some form or the other.⁽¹⁾ In spite of the overwhelming evidence of health hazards

resulting from smoking tobacco, many health professionals, including physicians, fail to treat smokers. This reluctance probably stems from an inadequate medical training & a lack of awareness of literature on the subject. Most health professionals believe in the "will-power" theory of smoking, which should also be supplemented

with a "supportive alternative therapies." two clear treatment-related options have emerged from the available data.^{(2),(3)}

1. The use of approved medications for cessation, this doubles the likelihood of quitting,
2. The effects of medications for cessation are increased twofold when coupled with behavioral interventions

History of tobacco smoking

On October, 1492 Christopher Columbus was offered dried tobacco leaves as a gift from the American Indians that he encountered. Soon after, sailors brought tobacco to Europe, and the plant was being grown all over Europe. The major reason for tobacco's growing popularity in Europe was its healing properties as supposed by the farmers. They believed it could cure almost anything, from bad breath to cancer. First commercial plantation was done in Virginia (USA) in 1612. During the 1600's, tobacco was so popular that it was frequently used as money and was literally "as good as gold!". Wilhelm Heinrich Posselt & Karl Ludwig Reimann isolated & analysed alkaloid in tobacco called as 'nicotine', which he found as a dangerous poison.

Tobacco was first introduced in Indian subcontinent by the kingdom of Adil Shahi, in the capital city of Bijapur, presently in Karnataka of south India, along the trading route of the Portuguese.^{(4),(5)}

Chemical composition of cigarette

Cigarette smoke is a complex mixture of chemicals. Some smoke components, such as carbon monoxide (CO), hydrogen cyanide (HCN), and nitrogen oxides, are gases. Others, such as formaldehyde, acrolein, benzene, and certain N-nitrosamines, are volatile chemicals contained in the liquid vapor portion of the smoke aerosol. Still others, such as nicotine, phenol, polyaromatic hydrocarbons (PAHs), and certain tobacco-specific nitrosamines (TSNAs), are contained in the submicron-sized solid particles that are suspended in cigarette smoke.⁽⁶⁾

Nicotine & its effects

Nicotine enters the bloodstream from the oral cavity, nose and is carried to every part of the body. It affects many parts of the body including heart, blood vasculature, hormones, basal metabolism and central nervous system. In pregnancy, nicotine freely crosses the placenta and has been found in amniotic fluid and the umbilical cord blood of newborn infants.⁽⁷⁾

Nicotine acts on central nervous system in dose dependant manner. Its biphasic activity pattern can be used by the smoker as an effective "coping response" to the demands of daily living: arousal, alertness during smoking followed by relaxation. Particularly in stressful situations nicotine induce temporary improvements in working efficiency and memory, few persons use it as a laxatives, anxiety relief, & pain reduction.

These positive effects provoke the smokers to smoke by taking more puffs, larger puffs or inhaling deeper than usual resulting in repeated "shoots" of high cerebral nicotine concentration,

so that the smoker finally becomes nicotine-addicted.⁽⁸⁾

Nicotine, stimulates the release of endogenous neuroregulators, like beta-endorphins, acetylcholine, catecholamines, dopamine, etc, which have important behavioral effects and that advantage can be used by smokers to regulate the body's normal adaptative mechanisms in response to stressful stimulations. Once an addiction to nicotine being established, the smoker needs a cigarette in order to get released from the withdrawal symptoms appearing when the cerebral nicotine level is dozing off.⁽⁹⁾

Addiction can be defined by the World Health Organization as “repeated use of a psychoactive substance or substances, to the extent that the user is:

- Periodically or chronically intoxicated,
- shows a compulsion to take the preferred substance(s),
- has great difficulty in voluntarily ceasing or modifying substance use,
- exhibits determination to obtain psychoactive substances by almost any means, and
- Tolerance is prominent and a withdrawal syndrome frequently occurs when substance use is interrupted

Pharmacological measures to quit smoking

There are three types of treatment available^{(3),(11)}

1. Psychotherapy
2. Nicotine replacement therapy
3. Second line agents

1) Psychotherapy

[Soben Peter, 1999; World Health Organization, 2014]

The “5 A’s” Model for counseling intervention⁽¹²⁾

1. Ask about tobacco use - every patient/ every visit
2. Assess willingness to a quit
3. Advice (those willing) to quit tobacco use. Those unwilling will need motivation to return to the topic at a later time
4. Assist in quit attempt - set a quit date, emphasize total abstinence, prompt support seeking, provide supplementary material and recommend pharmacotherapy
5. Arrange follow up and refer to a specialist clinic if the quit attempt has failed.

Effective nonpharmacologic interventions include brief physician advice and more intensive counseling, such as proactive telephone counseling, group and individual counseling, and use of quit lines. High-intensity counseling (> 10 min) produced a quit rate of 22.1% as opposed to 10.9% for no contact as studied at Mayo clinic nicotine dependant centre USA.

2) Nicotine replacement therapy

Five types of NRTs for quitting smoking are:-

1. Transdermal nicotine patches
2. Nicotine polacrilex chewing gum (7 - 21 mg)
3. Nicotine lozenge (2 - 4 mg)
4. Nicotine nasal spray
5. Nicotine oral inhaler

Currently, five agents have been approved by the FDA for smoking cessation: four nicotine replacement preparations (nicotine gum, transdermal nicotine patches, nicotine nasal spray,

and nicotine inhaler) and sustained-release bupropion hydrochloride.

1. Transdermal nicotine patches

This patch (fig.1) is available both with and without prescription & uses a concentration-dependent, continuous low-level delivery of nicotine through the skin. Dosage is based on the number of cigarettes smoked per day. The 16- and 24-hour patches demonstrate similar efficacy; however, patients with patch-related sleep disturbances (abnormal dreams, insomnia) sometimes better tolerate the 16-hour patch, and patients with strong cravings might have more success with a 24-hour patch. Patients who have substantial withdrawal symptoms or cravings should consider a higher dose^{(13),(14)}

Patients may complain of side effects like dizziness, perspiration, nausea, vomiting, diarrhea, headache, abdominal pain. Reactions to patch adhesives are common (up to 50%) and can be treated with 1% hydrocortisone cream or oral antihistamines. Because the adhesives vary among products, patients who have a skin reaction may consider switching brands. Patients with dermatologic conditions (eg, psoriasis, eczema, atopic dermatitis) are more likely to have skin irritation and should consider other NRT formulations.⁽¹⁵⁾

How to apply

- Apply the patch to a clean, dry, hairless area of skin on the upper body or the upper outer part of the arm.

- Do not apply patch to skin that is inflamed, burned, or irritated; this may alter nicotine absorption. When applying the patch, press firmly on the skin with the palm of the hand for 10 sec to create an adequate seal.
- Wash hands immediately after patch application; nicotine on hands can get into eyes or nose and cause stinging or redness.
- Water bathing, swimming, showering, or exercising will not harm the nicotine patch if applied correctly.
- Shortly after the nicotine patch is applied, mild itching, burning, or tingling may occur; this should resolve within 1 hr.
- After the patch is removed, the skin may appear red for the next 24 hr. If a rash develops or if the skin under the patch becomes swollen or remains irritated for >4 days, discontinue use of the patch & rotate patch application sites daily.
- Wait at least one week before applying a patch to the same site to minimize the potential for skin reactions.



Fig.1 Transdermal nicotine patch



Fig.2 Nicotine Chewing Gum

2. Nicotine chewing gum

Nicotine chewing gum (fig 2) has been introduced as a prescription only, as an aid to stop smoking in several countries, most recently the United States and Australia. In Britain it has been available since 1980, but its status has remained controversial and uncertain.

The principle of working of nicotine chewing gum is same as that of nicotine in smoking but it depends on dosage, motivation of patient and instructions followed by the patients. The withdrawal symptoms produced after quitting can be best managed by these gums.

This gum is a resin complex of nicotine and polacrillin in a sugar-free chewing gum base. Buffering agents (sodium carbonate, sodium bicarbonate) increase salivary pH, thereby enhancing absorption of nicotine across the buccal mucosa. Patients should use the gum on a fixed schedule rather than as needed to control cravings.⁽¹⁶⁾

Nicotine gum is more viscous than ordinary chewing gum, and its use is contraindicated in patients with temporomandibular joint disease.

Furthermore, this product tends to adhere to dental materials and may not be suitable for patients

undergoing orthodontic treatment, dentures, bridges & dental restorations. The use of nicotine gum improves cessation rates by about 50% compared with control interventions. This agent may be an appropriate option for patients who desire oral stimulation during cessation, find boredom as a trigger for smoking, or are concerned about weight gain after quitting.

How to use: (Chew & Park Method)

- Use on regularly scheduled basis (eg, initially every 1–2 hr while awake) and as needed to control cravings.
- Proper chewing technique is to chew each piece slowly
- Stop chewing when peppery, minty, or citrus taste or tingling sensation becomes apparent (approx.15–30 chews are required)
- Park between cheek and gum (to allow absorption of nicotine across buccal mucosa)
- Resume chewing when taste or tingle fades
- Repeat chew-park steps until most of nicotine is gone (taste or tingle does not return; generally 30 min)
- Park in different areas of mouth (to prevent mucosal irritation like buccal mucosa of both sides, floor of mouth, labial mucosa)
- No food or acidic beverages like juice, coffee, wine, soft drinks should be consumed 15 min prior, during & use (may decrease absorption of nicotine.)

3. Nicotine inhalers

Inhalers are available only by prescription. The nicotine inhaler (fig.3) is a thin plastic tube with a nicotine cartridge inside. It looks a bit like a cigarette with more dimensions and a mouthpiece attached. When patient takes a puff from the inhaler, the cartridge puts out a pure nicotine vapor. Unlike other inhalers, which deliver most of the medicine to the lungs, the nicotine inhaler delivers most of the nicotine vapor to the mouth where it's absorbed into the bloodstream. Nicotine inhalers are the FDA-approved nicotine replacement method. The method is similar like smoking a cigarette, which some smokers find helpful.⁽¹⁷⁾

The recommended dose is between 4 and 20 cartridges a day, slowly tapering off over 6 months. The most common side effects, especially when first time using the inhaler, include:

- Coughing
- Mouth and/or throat irritation
- Upset stomach

How to use:

- Initially use 6 cartridges a day, and increase as needed to a maximum of 16 cartridges per day.
- Inhale vapor into back of throat or puff in short breaths; do *not* inhale into the lungs (like a cigarette), but “puff” as if lighting a pipe
- Deep pulmonary inhalation can result in symptoms of nicotine excess like nausea, vomiting, lightheadedness.
- Do not eat or drink acidic beverages—juice, coffee, wine, or soft drinks—15

minutes before and while using the inhaler (may decrease absorption of nicotine)

- Best results are achieved with frequent continuous puffing for 20 min
- Nicotine in cartridge is depleted after 20 min of active puffing
- Titrate therapy to control nicotine cravings; eg, use the inhaler for a few minutes; put it down, and use later for a total of 20 min of active puffing per cartridge
- Open cartridge retains potency for 24 hr; once opened, each cartridge whether fully used or not should be replaced after 24 hr.
- Mild irritation of the mouth or throat or cough may occur when first using the inhaler
- Regular use during the first week will help to adapt to the irritating effects of the inhaler
- The inhaler may not be as effective in very cold temperatures (eg. the delivery of nicotine vapor is compromised in temperatures <15°C [$<59^{\circ}\text{F}$])

This form of NRT poses an extra risk to small children and pets because the used cartridges still have enough nicotine in them to cause harm if it gets on skin or mucous membranes (for instance, if licked or touched to the eyes, mouth, or other mucous membrane). Care should be taken to store and dispose of the cartridges away from children and pets.⁽¹⁸⁾

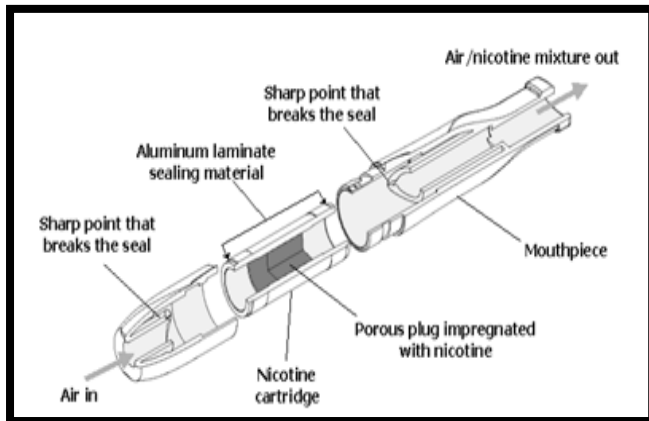


Fig. 3 Nicotine Inhaler



Fig.4 Nasal Spray

4. Nicotine lozenges:

Nicotine-containing lozenges can be bought without a prescription. Like nicotine gum, the lozenge is available in two strengths: 2 mg and 4 mg. Smokers choose their dose based on how long after waking up they normally have their first cigarette.

Lozenge makers recommend using them as part of a 12-week program.⁽¹⁹⁾ The recommended dose is 1 lozenge every 1 to 2 hours for 6 weeks, then 1 lozenge every 2 to 4 hours for weeks 7 to 9, and finally, 1 lozenge every 4 to 8 hours for weeks 10 to 12. The lozenge makers also recommend:

- Stop smoking completely when switching to lozenges

- Do not eat or drink for 15 minutes before using a lozenge.
- Suck on the lozenge until it is fully dissolved, about 20 to 30 minutes. Do not bite or chew it like a hard candy, and don't swallow it. The nicotine is absorbed through the mucous membranes of the mouth.
- Do not use more than 5 lozenges in 6 hours, or more than 20 lozenges per day.
- Stop using the lozenge after 12 weeks. If you still feel you need to use the lozenge, consult to specialist.
- Do not use the lozenge if nicotine patch or nicotine gum is already being used by the patient.

5. Nicotine nasal spray

Nicotine nasal spray (fig 4) is an aqueous solution of nicotine for nasal administration. Each spray delivers a 0.5-mg bolus of nicotine that is absorbed rapidly (<10 minutes) across the nasal mucosa. Initially, most patients will have nose and throat irritation (peppery sensation), watery eyes, sneezing, or coughing. However, with regular use, tolerance generally develops, and after the first week, most patients have minimal difficulty tolerating the spray.

This spray is not recommended for patients with chronic nasal disorders (rhinitis, polyps, and sinusitis) or patients with severe reactive airway disease because of the spray's irritant effects. Drug absorption may be reduced in patients with rhinitis or the common cold. Cessation rates associated with the nicotine nasal spray range

from 1.8 to 4.1 times higher than in controls. Because of its rapid onset of action, the spray is a possible option for patients who prefer a medication to rapidly manage withdrawal symptoms.^{(20),(21)}

Sustained-release bupropion

In 1997, sustained-release bupropion was approved as the first non-nicotine medication for smoking cessation. The mechanism of action for this agent, originally marketed as an antidepressant, is thought to be due to its capacity to block neural reuptake of the neurotransmitters dopamine and norepinephrine, reducing cravings for nicotine and symptoms of withdrawal.

Patients should initiate bupropion therapy 1 to 2 weeks before their quit date, starting with 150 mg once a day for 2 days, then increasing to 150 mg twice a day. The medication is started before the quit date because steady state therapeutic concentrations are reached after about 7 days of therapy.⁽²¹⁾ Adverse effects associated with bupropion therapy include insomnia (30%-40%) and dry mouth (11%); these usually lessen with continued use. Less common side effects include tremors (3.4%) and rash (2.4%). Because seizures have been reported in about 1 out of every 1,000 patients, bupropion is contraindicated in patients with a history of seizures or factors known to increase the risk of seizures, including a current or previous diagnosis of bulimia or anorexia nervosa, central nervous system tumors, and concurrent use of medications known to lower the seizure threshold. Because seizures are dose-related, patients should space doses at least 8 hours apart,

and the total daily dose should not exceed 300 mg. Studies of healthy smokers suggest that bupropion may be safely used in combination with NRT. Cessation rates in patients who use sustained-release bupropion are generally 2.1 times higher than those observed in patients receiving placebo. The advantages of bupropion include an oral formulation with twice-a day dosing, no risk of nicotine toxicity if the patient continues to smoke, can be used in combination with NRT, and may be beneficial for use in patients with coexisting depression.⁽¹⁷⁾

3) Second-Line Agents

Although not FDA-approved specifically for smoking cessation, the prescription medications clonidine hydrochloride and nortriptyline hydrochloride are recommended as second-line agents. Clonidine is a centrally acting agonist antihypertensive agent that about doubles cessation rates. Initial recommended dosage include 0.1 mg orally twice a day or the 0.1 mg/day patch applied weekly. Effective doses have ranged from 0.15 to 0.75 mg daily (orally) and 0.1 to 0.2 mg daily (transdermally) for 3 to 10 weeks. The likelihood of quitting is about tripled with the use of nortriptyline, a tricyclic antidepressant agent, compared with that of placebo.

The recommended initial dose is 25 mg at bedtime, gradually increasing to a target dose of 75 to 100 mg daily for 12 weeks. Lack of an FDA approved indication for smoking cessation, as well as undesirable side effect profiles, currently

prohibit these agents from achieving first-line classification.⁽²¹⁾

Conclusion

Nicotine addiction can be successfully treated with pharmacological and other non-pharmacological means. Only nicotine replacement therapy and bupropion are recognized as standard drugs for smoking cessation therapy. New therapies have evolved with a better understanding of the pathogenesis of the addiction process but need more clinical trials to validate their claims. The doctor's advice if given with authority and conviction, accompanied by a straightforward explanation, is probably the most effective method of helping the smoker to stop smoking. To achieve a smoke free society, a comprehensive health program is required which includes effective information, education activities, legal action, and smoking cessation programs.

References

1. Lal, P., Nevin, C., Wilson, L., Gupta, P C., (2012) Attributable deaths from smoking in the last 100 years in India. *Current Science*.103 (9, 100),1085-90.
2. Prignot, J. (1989) Pharmacological approach to smoking cessation. *Eur Respir J*.(2), 550-560.
3. Gawali, S.M., Vaidya, S.M.(2012). Quitting smoking – How to go about it. *JIAACM*,13(4), 311-15.
4. Gokhale, B. G. (1974). Tobacco in Seventeenth-Century India. *Agricultural History*,48(4) 484-492.
5. Kshetrimayum, N., Bennadi, D., Sibyl S. (2014) *Indian Journal of Research in Pharmacy and Biotechnology*, 2(6), 1446.
6. Talhout, R., Schulz, T., Florek, E., Benthem, J., Wester, P., Opperhuizen A. (2011) *Hazardous Compounds in Tobacco Smoke. Int. J. Environ. Res. Public Health*, 8, 613-628.
7. Osadchy, A., Kazmin, Gideon Koren, A. (2009) *Nicotine Replacement Therapy During Pregnancy: Recommended or Not Recommended? J Obstet Gynaecol Can*, 31(8),744–747.
8. Ebert, R.V., McNabb, M.E., McCusker, K.T., Snow, S.L. (1983) *Nicotine cigarettes. JAMed Assoc*, 250, 2840-2842.
9. *Nicotine and addiction* (2014, June). *ASH Fact Sheet on nicotine and addiction* Planned review.
10. Reichert, V., Talwar, A., Fein, A.M., *Treating Tobacco dependence. Medical Clinics of North America. Saunders publication*.
11. Allen, J.(2013) *Oklahoma Dental Association Journal*, 104 (9), 36-36.
12. Yudkin, P. L., Jones, L., Lancaster, T., Fowler, G. H. (1996) Which smokers are helped to give up smoking using transdermal nicotine patches? Results from a randomized, double-blind, placebo-controlled trial. *British Journal of General Practice*,46, 145-148.
13. Lancaster, T., Stead, L., Silagy, C., Sowden, A.(2000) *Effectiveness of interventions to help people stop smoking:*

- findings from the Cochrane Library. *BMJ*, 321,355–8.
14. Mills et al. (2010) Tobacco Induced Diseases, 8,8-10.
 15. <http://www.accessdata.fda.gov/scripts/cder/dissolution> April 20, 2015
 16. Fiore, M.C., Bailey, W.C., Cohen, S.J. (2000) Treating Tobacco Use and Dependence: Clinical Practice Guideline. Rockville, MD: US Dept of Health and Human Services, Public Health Service.
 17. ASH (2007 February) Nicotine Replacement Therapy Guidelines for Healthcare Professionals on using Nicotine Replacement Therapy for smokers not yet ready to stop smoking.
 18. Schiffman, S., Dresler, C., Hajek, P., Gilbert, S.J.A., Targett, D., Strahs, K., (2002) Efficacy of nicotine lozenge for smoking cessation. *Arch Intern Med*,162,1267-1276.
 19. Corelli, R., (2002) Medications for smoking cessation. *West J Med*,176,131-13
 20. Mahvan, T., Namdar, R., Kenton, V., Smith, P., (2011) Which smoking cessation interventions work best? *The Journal of Family Practice*, 60(7), 430-431.
 21. Gourlay, S.G., Stead, L.F., Benowitz, N.L., (2008) Clonidine for smoking cessation. *Cochrane Database Syst Rev*,(3), CD000058.