

## REVIEW ARTICLE

# Role of Tobacco & its Nicotine content on Oral Tissues with its Pharmacologic & Non-pharmacologic Interventions with special emphasis on Nicotine Replacement Therapy

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### ABSTRACT

Tobacco use is increasing globally and its dependence is recognized as a life threatening disorder with serious oral health consequences which responds to treatment in the form of behavioral support and medication. Tobacco kills nearly 6 million people each year, unless urgent action is taken, the annual death toll could rise to more than 8 million by 2030. Tobacco comes in different forms and all contain nicotine, the addictive substance. Pharmacological agents have been used successfully in the cessation of smoking which includes nicotine replacement therapies and nicotine medications to reduce cravings for tobacco and relieve the withdrawal symptoms while trying to quit. We oral health professionals should educate and advise patients on tobacco cessation. This article reviews the background of tobacco and its nicotine addiction with special emphasis on tobacco cessation programmes and nicotine replacement therapy.

**KEY WORDS:** Tobacco, Nicotine, Oral Health Professional, Interventions, Nicotine Replacement Therapy

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### INTRODUCTION

One of the most pervasive and destructive drugs known to mankind is "tobacco" and it is legal.[1]. Tobacco was introduced in India by the Portuguese traders during 16<sup>th</sup> century. Today India is the second largest producer of tobacco in the world <sup>67</sup> and the Indian tobacco industry is one of the largest commercial sectors and an important source of direct and indirect employment to more than 60 lakhs people [2].

Tobacco consumption harms every organ of the body including oral tissues causing various pre-cancerous lesions and carcinomas of the mouth and pharynx. It is estimated that tobacco kills nearly 6 million people each year and the annual death toll could rise to more than 8 million by 2030, unless strict actions are taken. Tobacco is consumed in various forms. Smoking forms of tobacco are bidis, cigarettes, cigars, chuttas, dhumti, pipe, hooklis and hookahs. Smokeless forms of tobacco include chewing pan (betel quid) with zarda (tobacco), gutkha, pan masala, mawa, khaini, tobacco leaves, mishri, gul, snuff, tobacco tooth paste and as tobacco water [3-7].

## **TREND OF TOBACCO CONSUMPTION AMONG YOUNG GENERATION and DIFFERENT STRATA OF THE SOCIETY**

The independent work of various researchers indicate that in this era of modernization there has been a rising trend of smoking in early age in India. Chadda RK *et al*<sup>8</sup> and Singh Vinita *et al* [9] in their independent studies highlighted that there is an increase in smokeless tobacco use by the youth and the prevalence of consumption of tobacco in adolescent school children of low-income group of National Capital Territory (NCT) of Delhi respectively. Rani M *et al* also concluded that tobacco consumption was significantly higher in poor, less educated, scheduled castes and scheduled tribe population and had a strong association with individual's sociocultural atmosphere [10].

Dhirendra N *et al* stated that tobacco use including smoking is very high among 13-15 year old students especially girls in Bihar (India) [11]. Malhotra *et al* concluded from their study that majority (83%) were in the 15-19 years age group, Hindu (80%), educated till high School (52%), were single (94%), from nuclear family (69%) of urban background (69%) [12].

## **NICOTINE AND ITS CONTENTS**

Nicotine was derived from burned tobacco leaves smoke (Posselt and Reimann in 1828), and contains more than 4 thousand chemicals approximately [13]. It is the principal naturally occurring alkaloid ingredient acting as a botanical insecticide called as "Nicotina tabacum". It is also found in low levels in vegetables such as potatoes, tomatoes, and eggplants.

Nicotine concentration is about 1.5% by weight in commercial cigarette tobacco. Oral snuff and pipe tobacco contain concentrations of nicotine similar to cigarette tobacco, whereas chewing tobacco have only about half the nicotine concentration. An average tobacco rod contains 10–14 mg of nicotine and on average about 1–1.5 mg of nicotine is absorbed systemically during smoking [14, 15].

## **NICOTINE ADDICTION AND DEPENDENCE:**

Nicotine dependence and addiction occurs because nicotine affects mood and performance. It shows all the characteristic hallmarks of a habit forming drug and reaches the brain in seconds to alter mood, appetite and alertness. It binds to nicotinic cholinergic receptors of brain with high affinity [16, 17]. Progressively the person becomes physically dependent and emotionally addicted to nicotine and causes horrid withdrawal symptoms when tried to quit [18].

The side-effects associated with the smoking of tobacco are based on a dose-response relationship to heavy smoking, and time duration [19].

1. It is the nicotine that causes smokers to become addicted to tobacco, and the chemical itself is lethal in small doses [20].
2. When tobacco smoke is inhaled, the nicotine reaches quickly to every organ of the body. Brain and nervous system are stimulated at low dose while a larger dose causes suppression [21].
3. Nicotine increases the heart rate and blood pressure, and may contribute directly to the excess of thrombosis and atheroma in smokers [22].
4. There is evidence for nicotine crossing the placental barrier and its accumulation in fetal serum and amniotic fluid in concentrations slightly higher than in maternal serum [6].

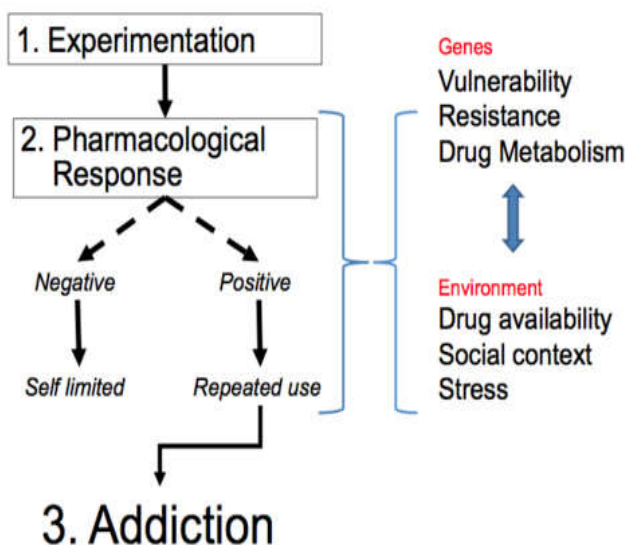
## **THE WIDESPREAD AND VARIED USE OF TOBACCO AND NICOTINE**

There are various factors that predispose to the initiation of tobacco use like family influence and experience, Peer factor, availability, psychological /emotional factor [23-27]. In long standing smokers, nicotine reduces the symptoms of confusion, restlessness, insomnia, anxiety, disturbs metabolism and suppress appetite. Bhatt S *et al* studied the effect of smokeless tobacco on the growth of cariogenic microorganisms and concluded that it exhibits anti-microbial activity against *Candida*, *Actinomyces* and *Lactobacilli* species suggesting an anti-cariogenic effect [28]. The use of tobacco products (mishri, dry snuff, tobacco water etc) as dentifrices despite its detrimental effects is still prevalent in various parts of India like Bihar, Orissa, Uttar Pradesh, in Uttaranchal in Manipur, Mizoram, Sikkim, and Tripura [29, 30].

## **NEUROBIOLOGY OF NICOTINE ADDICTION**

Nicotine addiction is due to loss of control over drug which causes premature disability and death. Based on molecular biology studies evidence the  $\alpha 4\beta 2$  nicotinic acetylcholine receptor subtype is the main receptor which mediates nicotine dependence (Picture-1) [31].

Picture-1: NEUROBIOLOGY OF NICOTINE ADDICTION



### ORAL MANIFESTATIONS OF TOBACCO USE

Various harmful oral health effects due to consumption of tobacco are mentioned in literature. Jitendra K and Sangeeta J highlighted the cause of oral changes 1) irritations of oral mucosa by toxins, and carcinogens, 2) desiccation of mucosa, 3) high intraoral temperature, 4) change in intraoral pH, 5) local alteration of membrane barriers 6) alteration in the immune response 6) altered resistance to fungal and viral infections.<sup>32</sup> Mubeen K et al reported that salivary antioxidant capacity is altered due to consumption of tobacco and creates an environment for potentially malignant and malignant disorders of oral cavity.<sup>33</sup> The various oral manifestations are tabulated below (Table 1).

**Table 1: ORAL MANIFESTATIONS OF TOBACCO USE**

<b>ORAL PRECANCEROUS LESIONS</b>	Leukoplakia, Erythroplakia, Smokeless Tobacco keratosis
<b>ORAL CANCERS</b>	1. Squamous cell carcinoma of tongue, floor of mouth, lip and gingiva 2. Verrucous carcinoma of buccal mucosa, gingiva and alveolar ridge
<b>PERIODONTAL DISEASES</b>	Increased deposition of plaque and calculus Gingival inflammation Gingival recession Periodontal pocket Alveolar bone loss
<b>ROOT CARIES</b>	
<b>PERI-IMPLANTITIS</b>	
<b>HALITOSIS</b>	
<b>TASTE DERANGEMENT</b>	
<b>STAINED TEETH AND RESTORATION</b>	

### ADVANTAGES OF QUITTING TOBACCO [18, 34]

- No Halitosis and no tobacco stains
- No attrition or abrasion and no mouth ulcer formation or burning sensation
- No propensity for potentially malignant or malignant disorders
- Financial returns- Reduced health care & life insurance costs, increased on-the-job productivity and employee productivity and a smoke-free environment

The **five R's** is recommended in the event that tobacco quitting is not being contemplated [35]:

- **Relevance:** Encourage the patient to indicate why quitting is personally relevant

- **Risks:** Dentist can help the patient to identify potential negative consequences of tobacco use. Suggest and highlight those that seem most relevant to the patient.
- **Rewards:** Dentist should ask the patient to identify potential benefits of stopping tobacco use.
- **Roadblocks:** The clinician should ask the patient to identify barriers or impediments to quitting and note elements of treatment.
- **Repetition:** The motivational intervention should be repeated every time an unmotivated patient visits the clinic setting.

#### **VARIOUS INTERVENTIONS TO PREVENT TOBACCO USE:**

**Educational intervention:** The various non-governmental organizations (NGOs) are conducting tobacco intervention programme and training courses under the guidance of WHO, UNICEF, and the Ministry of Health & Family Welfare of the Indian Government.<sup>36, 37</sup> The early educational programs for school children are meant to make them aware of the harmful effects of tobacco consumption.[38] Vaidya et al reported that school children at Ernakulam (Kerala) and Srikakulam in India after receiving health education on tobacco and training in intervention methods led to a hike in stoppage rate. [39]

**Tobacco cessation clinics intervention:** Shastri S et al [40] and Sham ASK et al [1] emphasised that medical and dental teams should encourage tobacco cessation counselling and prevention programs routinely. Gupta PC and Ray CS reported in their study that there is sufficient evidence for cancer risk reduction through tobacco cessation and anti tobacco educational programme [41].

**Media advertisements for tobacco promotion roll back intervention:** Tobacco sales and use in public places should be under firm surveillance by the government. To reduce the number of tobacco users among the young generation, stopping the sale of tobacco to children can be a helpful and significant step [42]. In 1990, information about the detrimental effects of tobacco was broadcasted on All India Radio in 16 languages from 84 stations which in turn led to decrease in use of tobacco effect by 6 % in Karnataka and by 4.3% in Goa as reported by Chaudhry K et al in their survey [43].

**Community intervention for tobacco use:** Gupta PC et al highlighted that anti tobacco messages can be spread by documentaries, slides, posters, exhibitions, folk dramas, radio messages and newspaper articles [44]. Jhunjhunu on World No Tobacco Day earned the distinction of being the first smoke-free district in the state. The district collector prohibits smoking in public places like railway station, bus stands, banks, government offices, schools, colleges and other public places and has declared it as a punishable offence [45].

**Economic intervention:** Panchamukhi P R et al suggested that counselling and financial support for tobacco farmers for starting new source of livelihood helps them to switch to the cultivation of other crops and other farm activities [46]. During the Union Budget for the fiscal year 2013-14, the Indian Government drastically raised the excise duty on cigarettes by 20 times from Rs 168 per 1,000 sticks in 2007 to Rs 3360 per 1,000 sticks in 2012 with an additional duty on unfiltered cigarettes because they are considered to be more harmful than filtered ones [2].

**Government intervention:** It is categorically stated in the Article 47 of Constitution of India (1950) that "State shall endeavor to bring about prohibition of the consumption, except for medicinal purposes, of intoxicating drinks and drugs which are injurious to health." [47] In May, 1999, WHO formulated an international legal treaty, called the Framework Convention on Tobacco Control (FCTC), that could address cross-country issues like tobacco advertising and promotion, agricultural diversification, smuggling, taxes and subsidies [48-49].

Lucid health warnings are made mandatory on all packages in local languages and in English, along with tar and nicotine content [50]. Packing must also convey printed warnings in native languages, such as "Tobacco causes a slow and painful death". These warnings need conquer at least 50% of the front and back cover of cigarette packs. Furthermore, all cigarette packs are demanded to carry a statutory warning "Cigarette smoking is injurious to health".

**Social organizational intervention:** Various social organizations recommend government to put a ban on tobacco. "The state government should not mull over about revenue from gutkha products and prohibit it for the sake of health of the people," stated state secretary of the Welfare Party of India (Rajasthan). Organizations such as Gayatri Shakti Peet Vatika, Jamat-e-Islami Hind, Indian Asthma Care society, Rajasthan Jan Manch, Welfare Party of India (WPI), Rajasthan, Volunteer Health Association (VHA), and Jain Samiti took part in signature campaign against tobacco on World No Tobacco Day [45].

#### **NICOTINE REPLACEMENT THERAPY (NRT):**

Nicotine replacement Therapy involves the use of products which contain nicotine and replace the nicotine received from tobacco and thus controls the craving for tobacco by providing nicotine at levels usually lower than those obtained through smoking. Nicotine-polacrilex chewing gum was the first

available acute dosage form. More recent add-ons are patches, vapour inhaler, sublingual tablet, lozenge and nasal spray [3]. The patch provides a continuous source of nicotine over 16–24 hours.

**Assessment of patient for NRT:**

All hospitalized patients are assessed for their smoking status via the Admission Assessment Tool [52]. Smoking statuses shall be recorded on patient records, discharge summaries and referral forms by noting the relevant International Classification of Disease (ICD-10) code for tobacco use. Current Tobacco Use is coded as Z72.0 (excluding tobacco dependence) Mental and Behavioural Disorders due to Tobacco are coded as:

F17.1 for harmful use

F17.2 for dependence syndrome

F17.3 for withdrawal state

**Duration for use of Nicotine replacement therapy:**

In order to achieve satisfactory results at least eight weeks use of NRT is recommended. Smokers are advised to continue the use of NRT for as long as they require to feel 100% sure that they can give up smoking. A period of two weeks without cravings, withdrawal symptoms or strong temptations to smoke is sometimes used to assess if someone is ready to stop NRT [52].

**Types of NRT:** The products differ in terms of the speed of nicotine delivery, the frequency and ease of use, type of local sensory side effects, amount of “behavioral” substitution they provide and the extent to which they enable the user to titrate their dose as and when needed. Based on the rate of delivery NRT can be divided into two main types[17]:

a. Constant dose (transdermal patches)

b. More flexible, self-administered dosing (gum, lozenge, sublingual tablet, inhalator, nasal spray).

**Transdermal Nicotine Patches:** Nicotine patches are applied to the skin and deliver nicotine through the skin at a relatively steady rate. Currently commonly used four patch formulations are NicoDerm CQ patch (GlaxoSmithKline Consumer HealthCare), Nicotrol patch (Pfizer), Habitrol patch (Novartis).<sup>53</sup>

**Advantages of the patch over the other NRTs:**

1. Compliance is high as it is easy to use. It gives therapeutic levels on nicotine from first day of use without having to master any special technique and has a few local side effects
2. No social acceptability problem as it is worn out of sight
3. It is extremely unlikely to give rise to problems of long-term use and dependence due to the very slow rate of nicotine delivery.

**Nicotine chewing gums:** These are available in two strengths 2 mg and 4 mg. Twelve to fifteen pieces of gum are taken per day to start with (about one per hour). [54] Studies have indicated that the permeability of nicotine across the buccal mucosa is faster than across the skin and slowly generates a steady plasma level rather than a sharp peak as experienced when smoking.<sup>51</sup>

**Nicotine lozenges:** It is of use for those who do not chew gums. Lozenges are available in 3 doses (1, 2 and 4mg nicotine). The lozenge should be sucked until the taste is strong and then parked in the mouth until the taste has faded, repeating the cycle until the lozenge has completely dissolved after about 20min or so.<sup>28</sup>

**Nicotine sub-lingual tablets:** It is a tablet formulation containing 2mg of nicotine which is easily placed under the tongue and left to dissolve. One or two may be taken every hour for about 3months and absorption rate is similar to the other oral NRTs.[55, 56]

**Nicotine inhalator/inhaler:** Nicotine inhaler comprises a small plastic mouthpiece about the size of a cigarette into which a replaceable nicotine cartridge is inserted which resembles a cigarette. Each cartridge provides up to three 20-min sessions. About 6-12 cartridges a day are used for 8 weeks, and then the frequency is gradually reduced over the next 4 weeks. [55, 57]

**Nicotine nasal spray:** The nicotine nasal spray delivers nicotine far more rapidly than any of the other NRT's as the nasal mucosa is a very efficient delivery route and peak venous nicotine levels after dosing are achieved in 5–10 minutes mimicking a cigarette. Moyses C et al evaluated the effect of a nicotine spray and a nicotine patch on smoking cessation for 12 months and found in their study that the nicotine mouth spray plus nicotine patch showed significant improvements in prolonged abstinence for all measures to 6 months or the combination versus placebo and nicotine patch.

**Combined therapy:** The common combination is an NRT patch (which gives a regular background level of nicotine) with gum or a nasal spray (taken every now and then to top up the level of nicotine to ease sudden cravings). Evidence from research studies suggests that this kind of combination provides a small but significant increase in success rates, compared with a single product. [58]

**Limitations of NRT:**

- It is expensive, low available and side effects of commonly used NRTs like Bupropion and Varenicline are insomnia, headache, dry mouth, convulsions and dizziness.[35]
- A few medical contraindications for use of NRT such as unstable angina, recent MI, serious arrhythmia, accelerated hypertension.[14]
- The major side effects usually by nicotine gum includes hiccoughs, GIT disturbances, jaw pain; patch includes skin sensitivity and irritation, nasal spray leads to nasal irritation and running nose, sublingual tablets cause hiccoughs, burning and smarting sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers.[59]

#### Nicotine withdrawal symptoms:

The symptoms of nicotine withdrawal include 2 or more of the following within 24 hours of cessation which includes anxiety, malaise or weakness, irritability or restlessness, reduced concentration, mouth ulceration, increased appetite, dysphoria, insomnia, dizziness (which may last a day or 2 after quitting); depression, irregular sleeping, headache, tiredness and restlessness. [3, 18, 60]

#### Non-pharmacologic interventions:

Non-pharmacologic methods are viable and their use should be on especially adolescents and pregnant women for whom medication use is difficult. Aggressive, rigorous and concentrated approach by behavioral and cognitive therapy is useful for patients to recognize, avoid and cope with difficult situations in which they are most likely to smoke.[61] (Table-2, 3)

**table-2: non-pharmacologic interventions**

THERAPY	REFERENCES
<b>Individual and Group counseling</b>	Offers individuals the opportunity to learn behavioral techniques for smoking cessation and to provide each other with mutual support. [34]
<b>Telephone counseling</b> (Nicorette, manufacturer of tobacco cessation products, announced the launch of a National Tobacco Cessation Quit Line-1800 227787 to mark the World No Tobacco Day)	Rao J et al [62] and Aubin HJ et al [63] concluded from their study that offering free nicotine replacement therapy or additional (proactive) counseling to standard helpline support had no additional effect on smoking cessation
<b>Self-help materials</b>	Pamphlets, videotapes, audiotapes, helplines and information on websites. Such materials may be more effective than no intervention in motivating people to quit
<b>Serotonin enhancing diet</b>	Diets that are rich in serotonin content, like high carbohydrate diet or tryptophan have been shown to cause reduction in negative effects associated with withdrawal symptoms. [64]

**Table-3: NEW DRUG THERAPY**

Drug	Mode Of Action	References
<b>Varenicline</b>	A partial agonist of nicotinic acetylcholine receptor (nAChR)	Kishore SP et al [65] and Hollis JF et al [66] in their respective studies reported Varenicline has superior effectiveness over Bupropion-SR for achieving abstinence from smoking and notably delay smoking relapse
<b>Rimonabant</b>	Selective cannabinoid receptor antagonist which blocks the CB-1 receptor	Prochazka AV et al [67] in their study concluded that it regulates endocannabinoid system and reduces craving for nicotine, thus maintaining abstinence.
<b>Mecamylamine</b>	A nicotine antagonistic agent which blocks the gratifying effect of nicotine	In most trials a combination of mecamylamine with nicotine patch has been found to be more effective than mecamylamine alone [12]
<b>Nortryptiline</b>	Active and potent metabolite of amitryptiline	Can be used as the first line smoking cessation agent.[68]
<b>Nicotine Vaccine</b>	Stimulates the development of antibodies specific to nicotine and restricts its entry to brain	Development of nicotine vaccine by many companies like Xenova (TA-NIC), Nabi (NicVAX), and Cytos (Nicotine-Qbeta) [53, 69]

#### ROLE OF THE ORAL HEALTH PROFESSIONAL:

There is upsurge in tobacco cessation by the patients when they are given counseling through oral health professional by emphasizing on the deleterious effects of tobacco use and its terrible consequences. Dental health personnel should inquire precise and detailed questions about tobacco use and give instructions to the patients about the signs of breakdown of the hard and soft tissues and the initial stages

of oral potentially malignant and malignant disorders. If there are any signs of malignancy to the oral tissues with the history of tobacco consumption, therefore biopsy of the mucosal lesion should be performed to eliminate the possibility of dysplasia or carcinoma.<sup>35,70</sup>

## CONCLUSION

During the recent years, there has been a rising trend in tobacco use often starting in early life, more in smoking forms in India and is one of the biggest threats to current and future generation health. We oral health professionals along with government cooperation should educate and counsel youth about ill effects of tobacco and discourage them from tobacco consumption. NRT, preferably in conjunction with behavioural and other types of non-pharmacological cessation interventions should be planned for tobacco users.

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