

Nicotine: Decoding Myths and Facts

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Abstract

Nicotine despite being the addictive component in cigarettes, is not the most toxic. The increased morbidity and mortality due to cigarette smoking can be blamed on various additives which are carcinogenic and toxic in nature. To achieve zero rates of cigarette smoking is a theoretical and idealistic target, but practically, the most feasible option is to adhere to harm minimization. This concept recognizes that not all Nicotine containing products are equally harmful and the ones which are safer can be promoted to increase their utilization, eventually reducing the rates of cigarette smoking as well as its associated health hazards.

The Nicotine delivering product, along with being safe should also be satisfying and acceptable to cigarette smokers, so as to encourage them to switch to the better option. A tangible impact on public health will be created only if this change is followed by a major part of the population. An essential point to remember is that harm minimization does not substitute for tobacco prevention and cessation, rather it is a complementary plan for smokers who are unwilling or unable to quit. Nicotine replacement therapy, (remodeled or novel) Nicotine and tobacco products, psychological interventions and alternative therapies can be implemented individually or in combination for smoking cessation, depending on patient preference and comfort. This paper contains a detailed view on application, precautions and efficacy of various Nicotine delivery products.

Keywords: Nicotine; Nicotine replacement therapy; Tobacco harm reduction; Harm minimization; Novel Nicotine and tobacco products.

Key Messages: Nicotine although addictive, is not directly responsible for all the health hazards of tobacco consumption. Cigarette smoke has more than 7000 compounds that are harmful and lethal. Various compounds present in tobacco smoke such as carcinogens, toxicants, particulate matter and carbon monoxide are also responsible for the increased health risks related to tobacco smoking.

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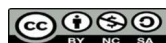
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INTRODUCTION

An overview on Nicotine

Smoking Addiction: How Does it Work?

Tobacco is the second most commonly used psychoactive substance in the world with



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Nicotine being its addictive component.¹ While smoking, the inhaled Nicotine particles enter the pulmonary circulation and reach to the brain through absorption by the blood stream.² Cigarette smokers are repeatedly exposed to rapid Nicotine delivery, promoting neurological and psychological adaptations and creating its dependence.¹ Nicotine is similar to acetylcholine, activating cholinergic systems. Long-term consumption creates a novel homeostatic equilibrium in the brain.

Non-availability of Nicotine disturbs this equilibrium and triggers the withdrawal symptoms. Pharmacodynamic effects aside, associative learning and psychology/conditioning are also responsible for Nicotine addiction. Craving and relapse are linked to internal signs/ cues of negative origin.³ Pleasure and arousal attained by smoking as well as avoidance of withdrawal symptoms associated with Nicotine addiction like irritability, anxiety, difficulty in concentration, insomnia and restlessness encourage addiction, thus making it difficult to quit.^{1,2}

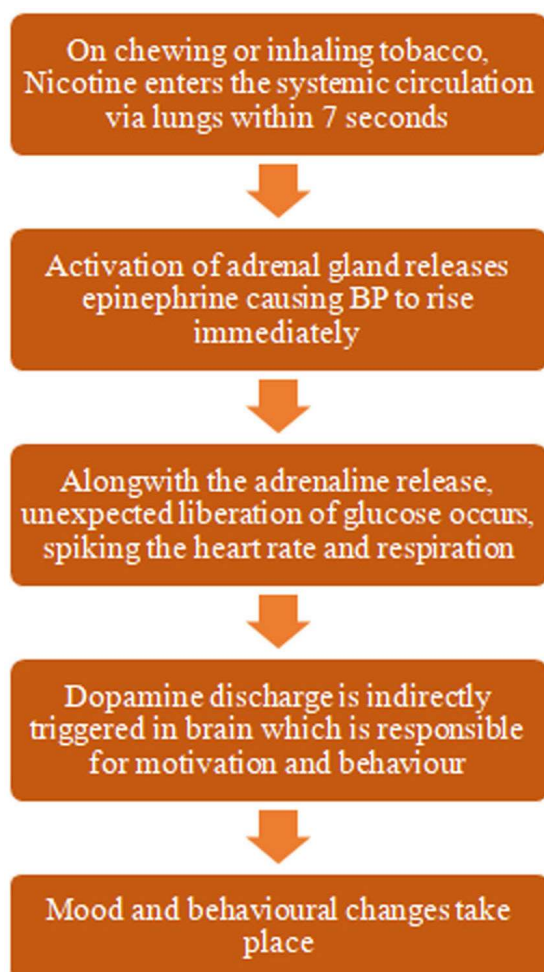


Fig. 1: Physiology of Nicotine addiction.⁴

Statistics and Hazards Related o Nicotine Addiction

Cigarette smoking is the most common form of tobacco consumption in the world, while in the Indian scenario, smoking is one of the most prevalent form of tobacco consumption at a staggering 20%.⁵ A study on prevalence of non-communicable diseases (NCD) in smokers concluded that 22% of smokers suffered from at least 1 type of NCD. On further categorization, NCD which are not related to respiratory system was prevalent in 17.8% smokers while respiratory system related NCD was prevalent in 6.6% smokers.

The rates of prevalent comorbidities among the surveyed population of smokers was as follows: 13.9% had hypertension, 6.0% had chronic bronchitis, 3.4% had type 2 diabetes, 2.1% had cancer, 0.8% had chronic obstructive pulmonary disease, 0.6% had asthma and 0.5% had coronary heart diseases. On comparing the two categories of smokers i.e. those without NCD and those with NCD, longer duration of smoking ≥ 20 years and higher intensity of smoking ≥ 20 cigarettes/day were significant factors associated with the presence of NCD.⁶

The risk of death due to medical reasons increases with smoking as well as daily smoking of even a minute quantity of tobacco consumption. Approximately, 1 in 20 deaths of women and 1 in 5 deaths of men between the age group of 30-69 years can be directly attributed to casual smoking.⁷

Is Nicotine the only culprit?

Nicotine although addictive, is not directly responsible for all the health hazards of tobacco consumption. Cigarette smoke has more than 7000 compounds that are harmful and lethal.⁸ Various compounds present in tobacco smoke such as carcinogens, toxicants, particulate matter and carbon monoxide are also responsible for the increased health risks related to tobacco smoking.¹

Nicotine is not a confirmed carcinogen. Epidemiological studies on humans have failed to support the notion that Nicotine promotes cancer pathway activation. The extent to which Nicotine can be directly held responsible for development of cancer requires more research. Tobacco smoke rather than Nicotine is a larger contributor to progression of cardiovascular disease (CVD).⁹

Tobacco smoking exposes the smoker to oxidative stress which is major factor for development of chronic obstructive pulmonary disease.³ Nicotine's harmful effects on fetal development, when

consumed during pregnancy is proven by scientific evidence. Even in vulnerable populations like those CVS disease or pregnant women or those with immune suppression tobacco smoking is the

bigger hazard than nicotine itself. In the absence of additives and flavorings present in tobacco, Nicotine can be safely used according to FDA approved Nicotine replacement therapy.⁹

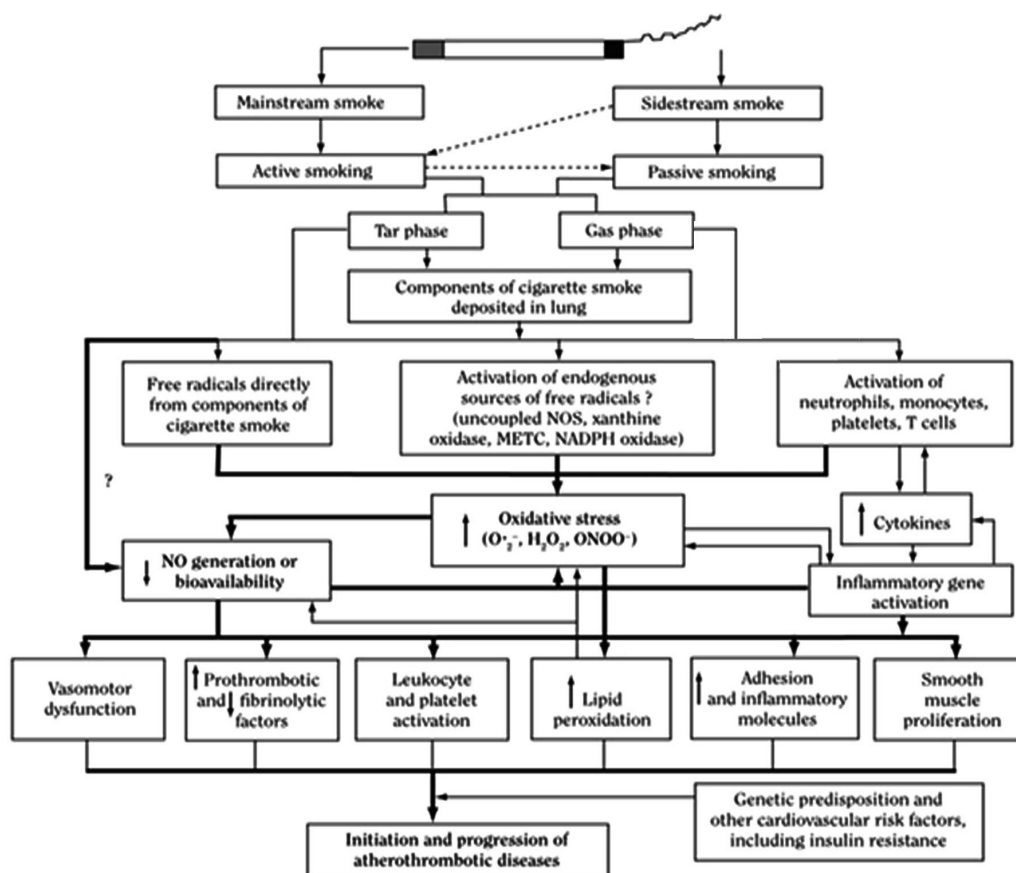


Fig. 2: Components of cigarette smoke leading to cardiovascular dysfunction.^{3,8}

Nicotine may have some health benefits include protection against illnesses and diseases like:

- Alzheimer's disease (AD)^{10,11,12}
- Parkinson's disease (PD)^{13,14,15}
- Improve memory and learning in otherwise healthy individuals^{16,17}
- Beneficial positive association between nicotine and ulcerative colitis¹⁸

Tobacco Harm reduction theory

Tobacco harm reduction (THR) is a public health strategy to lower the health risks to individuals and wider society associated with using tobacco products.¹⁹ Tobacco harm reduction has been defined as “minimizing harms and decreasing total mortality and morbidity, without completely eliminating tobacco and Nicotine use”. Tobacco

abstinence or tobacco cessation is the ideal outcome, which not being practical in the real world that has led to acceptance of alternative ways to reduce harm among tobacco users. Harm reduction is a complementary strategy to tobacco prevention and cessation, not it's substitute.²⁰ The goal of tobacco harm reduction is to lessen the total level of harm of tobacco use at individual as well as population levels.

The availability of Nicotine replacement therapy (NRT), novel Nicotine and tobacco products (NNTPs), such as e-cigarettes and heated tobacco products (HTPs) or heat-not-burn (HnB) products have provided impetus to the application of tobacco harm reduction strategies on a large scale. The use of alternatives to cigarette smoking that have been developed, may be seen as a way to reduce risk in smokers who opt for them completely and if sufficient number of smokers make that switch, it

reduces the average rates of health issues in society caused by smoking.²¹

Rationale for adoption of tobacco harm reduction

As a consensus was reached regarding elements in tobacco other than Nicotine contributing majorly to increased morbidity and mortality among smokers; the notion of offering smokers who are unwilling or unable to quit, less harmful tobacco products seemed feasible for its benefits to individual as well as public health.¹⁰

Practical application of THR can be summarized in the form of a mathematical equation factoring two variables: (i) the relative degree of risk that

these alternatives present versus conventional combustible cigarettes (ii) the rate of acceptance of alternatives among smokers as a substitute for conventional cigarettes, thus determining the number of smokers making a complete change in favor of alternatives and its ultimate impact on public health.²²

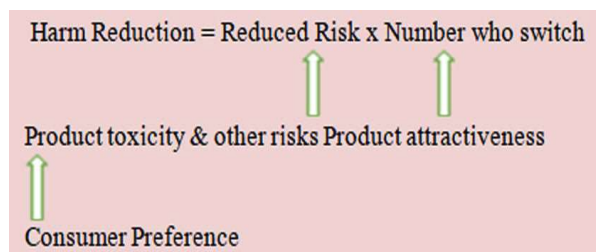


Fig. 3: The Tobacco Harm Reduction Equation.²²

THE HARM CONTINUUM

The harm minimization continuum postulates that all products that contain Nicotine are not equally harmful rather they cover a range from

extremely low harm (e.g., Nicotine replacement therapy) to extremely high harm (e.g., cigarettes, cigars, and hookah). Smokeless tobacco lies much lower on the risk scale than combustible products but its risk varies when compared to similar products.^{18,21,23}

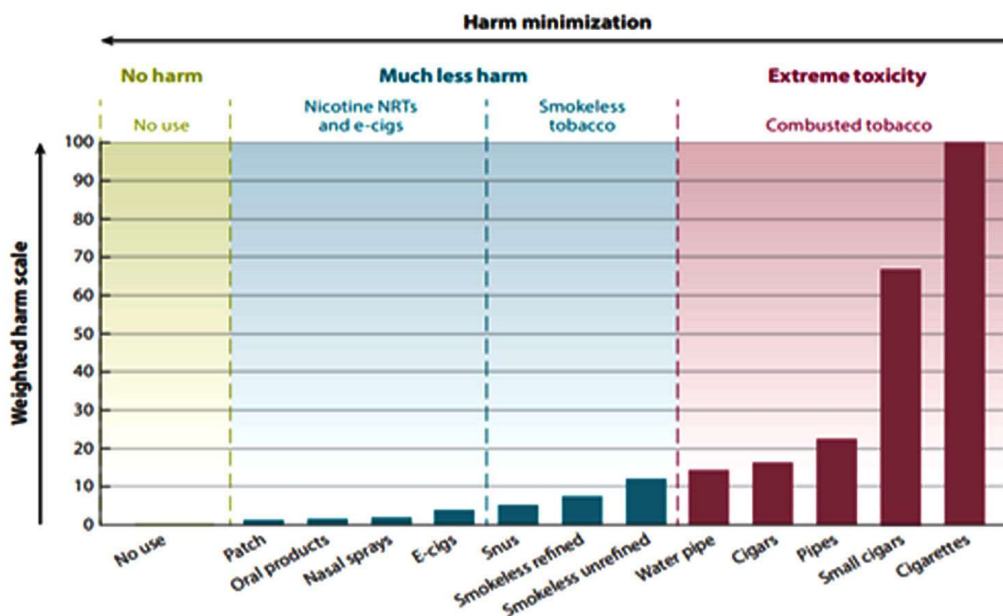


Fig. 4: The figure depicts four panels representing classes of Nicotine containing products.²¹

Products containing tobacco are depicted as combustible or smoked (panel 1, right) and non-combustible or smokeless (panel 2, right middle). Smokeless products are much less hazardous than smoked tobacco, but varies in safety within the smokeless tobacco category; e.g. snus is relatively less harmful than unrefined tobacco. Heat-not-burn tobacco products would fall into this panel. Panel 3 (left middle) displays

group of nicotine delivery products that do not contain tobacco. Panel 4 (left) depicts no use and thus no exposure.²¹

All nicotine containing products are not equally harmful, rather can be graded on a scale ranging from least harmful to most harmful with 'no use' at one extreme and cigarettes at the other extreme to be the most harmful to health.

The emphasis of harm continuum is: Although, NRT and NNTPs are not completely safe, but are much safer when compared to cigarette smoking. A meta-analysis found Nicotine replacement therapy to be an effective method to accomplish sustained smoking cessation for smokers unwilling or unable to quit.²⁴ Compared to cigarettes, Nicotine consumed through NRT is considerably safer, as the patient is not exposed to the harmful products released on tobacco combustion.

No serious health hazards have been linked to long-term, through consistent NRT use. Safety concerns over use of NRT in vulnerable groups such as in pregnant women, those suffering from

cardiovascular disease or in adolescents must be weighed against the harmful effects of its likely alternative i.e., cigarette smoking.²⁵

3-D Model for Harm Minimization

This 3-D model for harm minimization encapsulates Nicotine and tobacco products, according to these three features: (a) harmfulness, (b) appeal, and (c) satisfaction including dependence. The figure below can be used as a guide to predict the acceptance and utilization of Nicotine alternatives among the public, as a replacement for smoking on a scale large enough to make an impact on the public health.^{18,21}

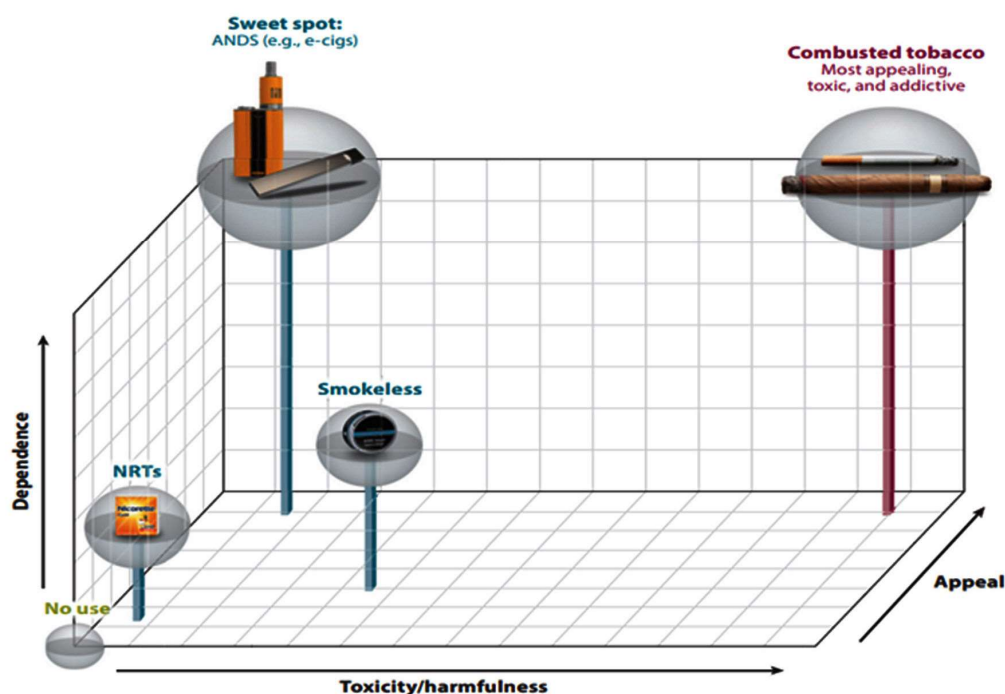


Fig. 5: Multidimensional framework for Nicotine-containing products^{18,21}

Nicotine delivering products and tobacco products can be denoted within a 3-D framework: harmfulness lies on the X-axis, appeal or popularity lies on the Z-axis and satisfaction, including addiction/dependence lies on the Y-axis. The most popular, highly satisfying and most harmful nicotine containing product can be placed at the topmost corner on right, furthest away, whereas abstinence lies at zero on all the three axes.

According to this configuration, combustible products/cigarettes can be graded as the most appealing, satisfying, and toxic. The space indicates Nicotine delivering products which are safer but also less popular or utilized due to its lower potential to satisfy cravings on the left, front and bottom-most area of the model. Such products are

not preferred among the smoking population and not consumed enough to replace cigarettes.

The two important factors playing a role here are minimal risk along with preference towards the product, encouraging its use on a scale large enough to create a positive change away from cigarette smoking for a huge population and eventually on the national as well as global level. A successful application of this concept can be seen in Sweden where cigarettes were replaced by snus, which lies within the area where high appeal, satisfaction and lower toxicity overlap.^{18,21}

Dependence can be understood in terms of satisfaction the user derives from the product as well as its addiction capacity. The three-dimensional

space is a visual imagery of the standing of different nicotine delivery products on the basis of their dependence, appeal and risks. Locating different Nicotine delivery products within this space, can help compare the different products and choose an appropriate one which is adequately performing on the above mentioned three factors.^{18,21}

Nicotine Replacement Therapy (NRT)

MECHANISM OF ACTION

Rapid rise in nicotine levels obtained through cigarette smoking block the Nicotinic acetylcholine receptors, whereas dip in the Nicotine levels activate these receptors kicking off withdrawal symptoms and craving for more Nicotine. In such a scenario, use of an NRT promising slow paced release is helpful due to two reasons, (i) due to slower delivery of Nicotine to the receptors, they do not undergo instant activation and blockage; the process becomes much slower, (ii) the amount of Nicotine inhaled for on-the-spot satisfaction is not under direct control of the consumer. Absence of additional elements, otherwise present in cigarettes like menthol and acetaldehyde

condensation products reduce the addiction factor.²⁶

Although NRT may not be successful in complete resolution of withdrawal symptoms, it offers a compensatory approach to smokers willing to quit or decrease their consumption of cigarettes. The essential reason why NRT may not be as satisfactory for a smoker is that it cannot reproduce the instantaneous spike in Nicotine levels in blood similar to cigarette smoking.²⁵

The slow and steady delivery of Nicotine stabilizes its levels in blood, thus distinguishing it from cigarette as well as tapering of both positive and negative triggers associated with cigarette smoking.²⁶

Nasal sprays, inhalers, gums and lozenges release Nicotine into the systemic circulation through oral or nasal mucosa with the Nicotine levels peaking within a matter of minutes. In case of transdermal patches, Nicotine levels peak after few hours of application. Bioavailability of Nicotine swallowed in the form of pills/tablets is extremely low (30%–40%) as most of it is deactivated in the acidic environment of the stomach, while the remaining is transported to the liver where it undergoes first-pass hepatic metabolism.²⁶

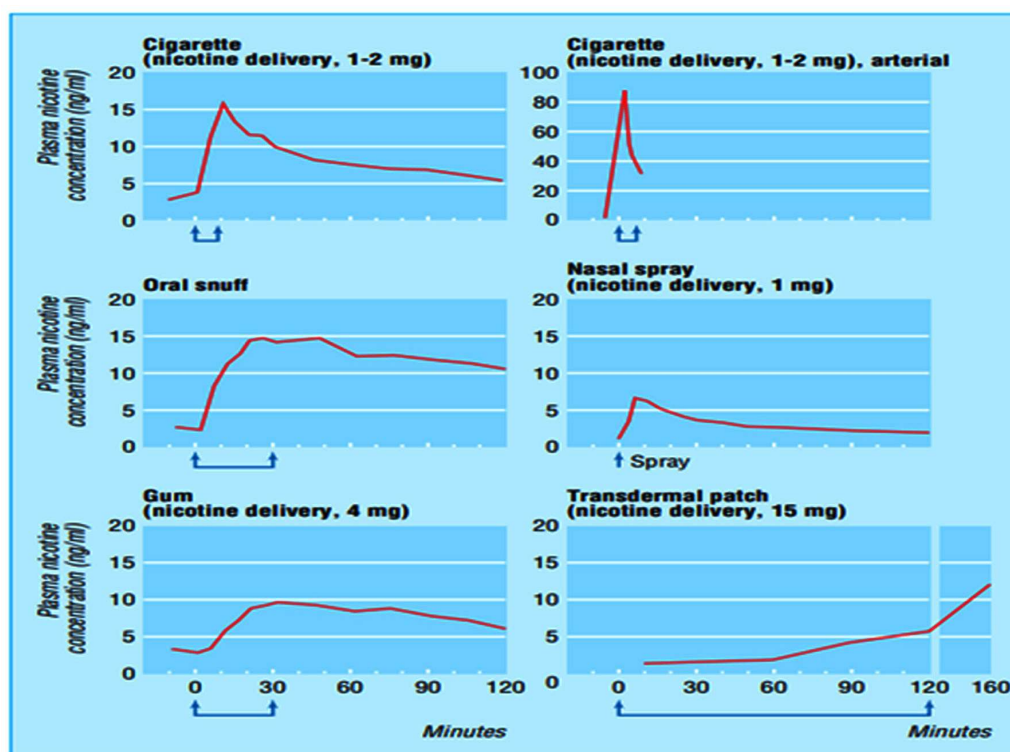
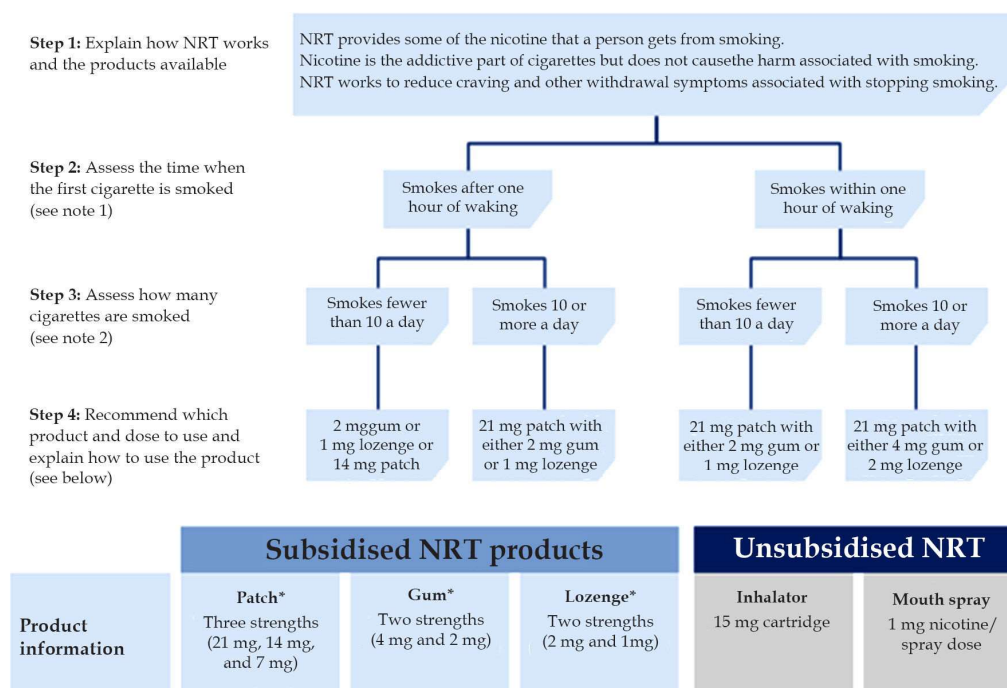


Fig. 6: Graph comparing rise in blood Nicotine concentrations after smoking a cigarette and after using different NRT products. Values are for venous blood except where indicated.²⁵

Table 1: Various Nicotine Delivering Solutions²⁷

Nicotine products	Available doses	Cautions/Warnings	Uses	Adverse events
Transdermal patches	Doses of 5 mg, 10 mg, 15 mg applied over 16 hours. Doses of 7 mg, 14 mg, 21 mg applied over 24 hours.	Remove patches before sleeping for smokers with insomnia and other sleep related adverse events.	Apply a single patch daily on clean, unbroken skin which should be removed before bed (16 h patch) or next morning (24 h). New patch should be applied on fresh skin.	Local skin reaction Insomnia
Chewing gum	2 mg and 4 mg doses	In case of TMJ disease or using dentures. Avoid food or drink 15 min prior to or while using.	Chew on the gum until it tastes strong, keep the gum between gum and cheek; chew again until taste fades. Avoid excessive swallowing.	Hiccups Jaw ache Mouth soreness Dyspepsia
Sublingual tablet	2 mg dose	Insomnia and Nicotine dependence	Place under tongue until dissolves.	Mouth soreness
Lozenge	1 mg, 2 mg and 4 mg doses	Consume only one lozenge at a time. Total limit consumed 20 lozenges in 24 hours. Avoid food or drink 15 min prior to or while using.	Let it sit in mouth and dissolve slowly (around 20–30 minutes/lozenge), rolling it around the mouth. Do not swallow excessively or whole. Do not chew on the lozenge	Nausea Heartburn
Nicotine inhalation cartridge plus mouthpiece	Cartridge containing 10 mg	Initially, irritation of mouth and throat may occur.	Inhale shallow puffs at every 2 seconds or four puffs every minute. Continue for up to 30 minutes.	Nasal irritation
Electronic cigarette (EC)	-	Might be addictive	Drawn the vapor from E-Cigarette into the mouth very slowly. After holding for a second or two, it may be inhaled. Expel vapor through the mouth or nose.	Irritation of mouth and airways Chest pain Palpitation
High dose nicotine patches	≥42 mg daily	Irritation at the site where patch is applied. Disturbed sleep	Apply a single patch daily on clean, unbroken skin which is to be removed before sleeping.	CVS adverse events Headache Asthenia Dyspepsia Vomiting Myalgia
Combination of patch and acute forms (nicotine gum, spray, lozenge, & inhaler)	7, 14, and 21 mg doses of transdermal nicotine along with dosage of any one acute form.	Insomnia Nicotine addiction	Simultaneous utilization of both patch and acute nicotine forms.	Irritation of mouth and airways Nausea and vomiting

TMJ- Temporomandibular joint, EC- Electronic cigarette, CVS- Cardiovascular

Fig. 7: Algorithm for NRT Prescription.²⁸

Alternate Methods

Alternate methods for smoking cessation which are backed by inconclusive evidence include:

aromatherapy, acupuncture, hypnosis, herbal supplements/formulations and psychedelic mushrooms.²⁹

Table 2: Psychological intervention for smoking cessation³⁰

Intervention	Application
Cognitive behavioral therapy (CBT)	CBT equips a smoker with problem-solving and coping skills, to prevent relapse. It also provides cognitive restructuring for smoking addiction mindset. Combining CBT and NRT is highly effective for smoking cessation. CBT sessions are group-based or individual of long duration ranging from 50 min to 2 hours.
Contingency management (CM)	CM includes doling out financial incentives for smoking cessation. Its efficacy increases on combining it with CBT for smoking cessation.
Mindfulness Based Interventions (MBIs)	MBIs strive to increase self-awareness among the smoker regarding his/her environment, thoughts, emotions, and physical sensations related to cigarette craving, helping the smoker develop and practice the ability to "sit with" cravings or triggers.
Smartphone/Computer based applications and technologies	Studies have proven the success of smoking cessation help delivered via technology such as phone application, SMS etc. Delivering MBI and CBT sessions or even anti-smoking reminders via mobile apps, video calls, websites, text-messages and WhatAapp updates can increase the accessibility and reach of smoking-cessation assistance.

CBT- Cognitive behavioral therapy NRT- Nicotine Replacement Therapy, MBI- Mindfulness-Based Interventions, CM- Contingency management

Advances in Nicotine delivery systems

Electronic Nicotine Delivery Systems (ENDS) or Electronic Cigarettes

E-cigarettes are battery operated devices with an electronic vaporization system and a liquid containing reservoir, which on heating releases

an aerosol to be inhaled by the user. The liquid is composed of glycerol, propylene glycol, water, nicotine and flavorings that the user can choose. E-cigarettes delivers Nicotine without combustion. They are also known as e-vaporizers, e-hookahs, hookah pens, vapers, vape pens, and mods.^{27, 31}

Although, e-cigarette consumption is safer than tobacco smoking, but it is accompanied with various health hazards. E-cigarettes, due to their unique flavors attract even non-smokers. E-cigarettes are banned by the government in Brazil, Uruguay and India due to various health concerns while in United Kingdom, it is a legal and acceptable device to quit smoking.³²

Heat-Not-Burn Tobacco Products (HTP)

Heat-not-burn device heat tobacco to a temperature high enough to release vapor, without combustion or producing smoke. These products heat tobacco leaf/sheet rather than a liquid, thereby distinguishing them from e-cigarettes. The rationale behind this product is that combustion of tobacco releases harmful chemicals, so only heating it would prevent the release of those chemicals, making it safer for users.³³

The change in cumulative exposure (CCE) of the compounds emitted by HTPs and cigarettes and compared the two to conclude that the CCE was estimated to be 10 to 25 times lower when using HTPs instead of cigarettes.³⁴ It can be stated with moderate certainty that heat-not-burn devices are safer than cigarette smoking.²⁴

Nicotine Preloading

Nicotine preloading, pre-cessation or pre-quitting is known as using NRT for weeks before quitting smoking. This method helps unlearn the learned association between smoking and pleasure through decreased desire to smoke as well as lesser satisfaction from smoking due to already saturated nicotine receptors.²⁷

True Pulmonary Inhaler

A true pulmonary inhaler is hypothesized to rapidly deliver Nicotine directly into the lungs similar to cigarette smoking and provide instant satisfaction to cravings while also resolving the withdrawal symptoms. With the use of this type of inhaler the smoker could eventually reduce his Nicotine intake and decrease his dependency. Practically, designing such a device has its own set of challenges, hence it is still being researched.²⁷

Nicotine Vaccines

Administration of Nicotine based vaccines are hypothesized to trigger the immune system to recognize it as foreign and to mount an immune

response against the drug. Thus, vaccines may help reduce the amounts of Nicotine penetrating the brain, although it is still being researched.²⁷

Preferred Smoking cessation methods

According to a systematic review, the best scoring smoking cessation strategies include: NRT, combination therapy, CBT, self-help material and counselling via telephone/mobile app/internet.³⁵ The most preferred smoking cessation methods among users were mobile apps for quitting, NRT and internet websites.³⁶ There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain.³⁷ The U.S. Food and Drug Administration authorized the marketing of science backed Tobacco Heating System as modified risk tobacco products (MRTPs) in 2020.³⁸

DISCUSSION

Experts including the US Surgeon General and the UK Royal College of Physicians concur that nicotine although addictive, is not the primary contributor to lung cancer, cardiovascular disease, and emphysema. Instead, these are caused by inhaling the harmful compounds formed when tobacco is burned. In-fact, the UK Royal College of Physicians is on record, saying, "Nicotine is not, however, a highly hazardous drug, it is inherently unlikely that nicotine inhalation itself contributes significantly to the mortality or morbidity caused by smoking. The main culprit is smoke, and if nicotine could be delivered effectively and acceptably to smokers without smoke, most if not all the harm of smoking could probably be minimized."

Regulators in several countries particularly those that are well geared to challenge anomalies, notably in the US, in UK, in Germany as well as in Japan have taken an enlightened view to allow and not prohibit the use of such alternatives that reduce the harmful impact of smoking. There is consensus view that such products can in-fact help the process of de-addiction through a gradual weaning-off process.

CONCLUSION

The concept of harm minimization is the foundation for smoking cessation. Smoking cessation strategies should be tailored to the

smoker's motivation to quit, and degree of tobacco dependence/ addiction. Smokers who are unwilling or unable to quit, require an anti-smoking strategy which satisfies their needs as well as reduces the harms. Availability of NRT, NNTPs and psychological interventions have been somewhat successful in filling the gap. A simultaneous or combined use of any of these techniques have been more effective in achieving smoking cessation, rather than deploying a single strategy one at a time. A mutual and coordinated effort by government bodies, health agencies, medical workers and smokers themselves to encourage use of alternatives to cigarettes will help create a positive and tangible impact in terms of public health.

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Conflict of Interest: Nil

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