

Review Article

Nicotine therapy in smoking cessation and its current trends

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Abstract

Smoking is a leading cause of premature death and disease. Tobacco is the leading cause of preventable death in the worldwide and is causally linked to several cancers. Cigarettes are a highly effective way of delivering the addictive drug nicotine. They do so by burning tobacco to create an aerosol of ultrafine particles that carries nicotine deep into the lungs, where it is rapidly absorbed, then travels through the left heart, reaching the brain in a few seconds. The combustion process also generates carcinogens, oxidizing agents, and other toxins. Nicotine addiction is a chronic brain disorder. Prolonged tobacco use results in physiologic dependence and a behavioral compulsion to use tobacco. A number of smoking cessation pharmacotherapies have led to increases in quitting and thus to significant benefits to public health. Nicotine replacement products (gums, transdermal patch, nasal spray, inhaler and lozenge), bupropion and varenicline used with counseling by physicians double the cessation rates at one year. Smoking cessation is the process of discontinuing tobacco smoking. Nicotine withdrawal often makes the process of quitting difficult. The choice of any pharmacotherapy for smoking cessation should be guided by an individual's preference, contraindications, and precautions for use. Simple advice to stop smoking results in an increased rate of quitting, and counseling increases abstinence rates as a function of time spent with the patient. The emerging trends for smoking cessation include the advancement of technology like smartphones, applications, etc. Nowadays smartphones, applications, E-cigarettes, and some new behavioral techniques and meditations, yoga are helping in the cessation of smoking in different aspects.

Introduction

Smoking cessation is associated with clear health benefits. Smoking is a real chronic disorder related to the intermittent and compulsive consumption of an exogenous substance, sustained by the development of an addiction status, which is mainly due to nicotine. Tobacco use increases the risk of many acute and chronic diseases, including cancers at many sites. Smoking harms nearly every organ in the body. One of the main reasons smokers keep smoking is nicotine. Nicotine, a drug found naturally in the tobacco plant, is highly addictive, as with such drugs as cocaine and heroin; activates the brain's reward circuits; and reinforces repeated nicotine exposure. Nicotine is a plant alkaloid, found in the tobacco plant, and addictive central nervous system (CNS) stimulant that causes either ganglionic stimulation in low doses or ganglionic blockage in high doses [1,2].

Formula: $C_{10}H_{14}N_2$

Molar mass: 162.23 g/mol

Boiling point: 247 °C

Melting point: -74 °C

Elimination half-life: 1-2 hours; 20 hours active metabolite

Addiction liability: High [3] (Figure 1).

Nicotine use as a tool for quitting smoking has a good safety history. The primary therapeutic use of nicotine is treating nicotine dependence to eliminate smoking and the damage it does to health. Controlled levels of nicotine are given to patients through gums, dermal patches, lozenges, inhalers, or nasal sprays to wean them off their dependence. It is known that smokers life expectancy is on average 10 years shorter than

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Keywords: Smoking cessation; Nicotine addiction; Therapy; E-Cigarettes; Emerging trends

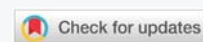




Figure 1: Structure of Nicotine.

non-smokers. Besides being involved in the pathophysiology of several types of malignant neoplasms, not only in the lungs, smoking represents the first cause of chronic respiratory diseases, such as chronic obstructive pulmonary disease. Cigarette smoking is also related to a higher susceptibility to pulmonary bacterial and viral infections, inducing structural changes in the respiratory tract and a decrease in immune response. The health harms of combusted tobacco use are now undeniable [3]. Strategies for helping smokers to quit include behavioral counselling to enhance motivation and to support attempts to quit and pharmacological intervention to reduce nicotine reinforcement and the withdrawal symptoms of cessation of tobacco use [4].

The bioavailability of nicotine by Nicotine Replacement Therapies (NRT) is much less than those of cigarette smoke. The patch provides a relatively stable, fixed dose of nicotine over a period of 16 to 24 hours. The other products have a more rapid onset and a shorter duration of action. Nortriptyline has been found effective in smoking cessation in two small studies that used 75 to 100 mg of the drug daily for three months, starting 10 to 28 days before the quitting date. Nicotine-replacement products can safely be combined with one another and with bupropion [4]. Smoking is one of the most difficult practices to get rid off.

Diversity of products

Cigarette: Tobacco rolled in paper for smoking. A typical cigarette weighs <1 g; regular length (70 mm long), king (84 mm), 100s (100 mm), and 120s (120 mm) Acidic, inhalable, pH 5.5–6. Average in rod, 13.5 mg (range: 11.9–14.5 mg); nicotine yield to the smoker: 1–1.5 mg/cigarette [5].

Cigar: Air-cured, fermented tobacco wrapped in material made at least, in part, of tobacco leaf Small filtered cigars (0.9–1.3 g tobacco), cigarillos (1.3–2.5 g tobacco), and large (premium) cigars pH 6.5–8.0 inhalable and/or buccal depending on product pH. Nicotine content ranges from 10 to 444 mg and dependent on weight of the cigar [5].

E-cigarette: Electric devices that produce an aerosol from a liquid that typically contains nicotine, propylene glycol, vegetable glycerin, and flavorings. Free base e-liquid: alkaline, pH 7–9; nicotine salts: acidic, inhalable, pH 3.5–6.8 E-liquid nicotine content from 0 to 100 mg/ml [5].

Waterpipe/Hookah: Charcoal-heated flavored tobacco passed through a water-filled chamber that cools the smoke. Water tobacco is a mixture of dried fruit, molasses and glycerin, and conventional tobacco leaf pH 3.8–5.8. Average of 1.13 mg/g and high of 3.30 mg/g for product containing nicotine; nicotine-free for herbal (nontobacco) varieties [5].

Nicotine addiction

Nicotine addiction is a chronic brain disorder and it always leads to death, whether early or late. Prolonged tobacco use results in physiologic dependence and a behavioral compulsion to use tobacco. Nicotine establishes and maintains tobacco addiction by complex actions that affect the neurochemistry of the brain [2]. Nicotine from cigarette smoke is rapidly absorbed in the lungs and then quickly passes into the brain. The rapidity of absorption is an important determinant of the addictiveness of a drug, and cigarette smoking is the most rapid method of nicotine delivery. Nicotine diffuses readily into brain tissue, where it binds to nicotinic acetylcholine receptors which are ligand-gated ion channels. Nicotine results in positive, though transient, psychological effects of pleasure, arousal, and mood modulation [1,2]. Smoking also facilitates nicotine addiction through sensorimotor factors associated with the act of smoking, e.g., the smell, taste, and feel of the cigarette smoke. Nicotine also stimulates dopamine in the midbrain. This release of dopamine is similar to that seen with drugs such as heroin and cocaine and is thought to bring about the satisfying sensations experienced by many smokers [1,2] (Figure 2).

Nicotine withdrawal

Withdrawal effects are largely mediated through nicotinic acetylcholine receptors. The drug nicotine can have a wide range of effects on the brain, such as:

- boosting mood and reducing appetite
- reducing depression and reducing irritability
- enhancing concentration and short-term memory
- producing a sense of well-being [6,7].

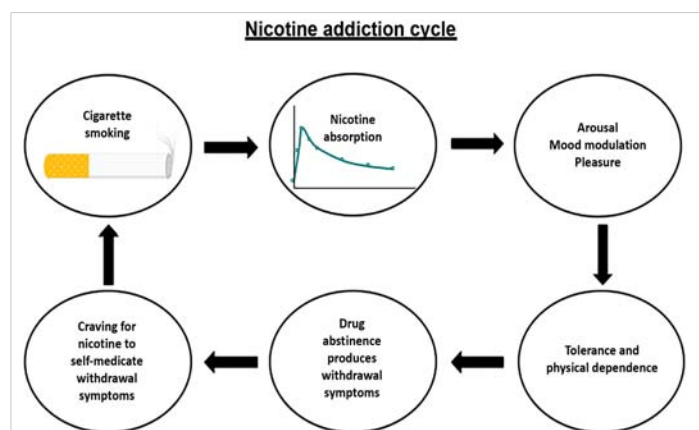


Figure 2: Nicotine Addiction Cycle.

Symptoms of nicotine withdrawal for smokers include:

- intense cravings for nicotine
- tingling in the hands and feet and sweating
- nausea and abdominal cramping
- constipation and gas
- headaches and coughing
- sore throat and insomnia
- difficulty concentrating
- anxiety and irritability [6,7]

Smoking cessation interventions

ASK: Identify and document tobacco use at every visit

ADVICE: In a clear, strong, and personalized manner, urge the patient to quit

ASSESS: Is the patient willing to make a quit attempt?

ASSIST: Use pharmacotherapy and/or behavioral counseling

ARRANGE: Schedule follow up contact [8,9].

Therapy for smoking cessation

There are several methods for smoking cessation. Mainly the two approaches have strong evidence of efficacy for smoking cessation are the counseling and pharmacotherapy. The two in combination achieve the top highest rates of smoking cessation. The Food and Drug Administration (FDA) has approved the following products for smoking cessation: nicotine replacement products (gum, transdermal patch, nasal spray, and inhaler), antidepressants, bupropion and varenicline [10,11]. The emerging trends for smoking cessation include the advancement of technology like smartphones, applications, etc. Nowadays smartphone apps, E-cigarettes, and some new behavioral techniques are helping in the cessation of smoking in different aspects.

Nicotine replacement therapy (NRT)

Nicotine replacement therapy is based on the controlled administration of nicotine and it is the most common method for the cessation. As well as the name states, it involves substituting one form of nicotine delivery for another (e.g. patches or gums for cigarettes) [10,11]. This, nicotine replacement therapy aims both the standing of, to stimulate nicotine receptors thus removing smoking craving and also the withdrawal symptoms. Controlled administration of nicotine reduces the positive effects induced by smoking to a lower dosage and slower pharmacokinetics. Nicotine is more slowly absorbed generating lower but prolonged blood peaks, compared to cigarettes, thus reducing rewarding effects and

withdrawal symptoms including irritability, anxiety, difficulty concentrating, dysphoria, increased appetite, weight gain, and sleep disorders [12].

Transdermal nicotine patches deliver nicotine at a relatively steady rate, so they are the most suitable routes of administration to reduce withdrawal symptoms. On the other hand, chewing gums, lozenges, inhalers and nasal sprays reduce symptoms faster than patches, but they provide worse basal coverage [10,11].

Nicotine gum

Nicotine polacrilex, better known as nicotine gum. It is available as 2 and 4 mg preparations. The patients are instructed to chew nicotine gum slowly until they feel mild tingling, indicates nicotine release. The patient should then place the gum between the cheek and gums of the teeth for seven minutes before chewing it again. This cycle will allow gradual buccal absorption, and should be continued for about 30 minutes per piece of gum.

DOSE: 2mg { $\leq$ 25 cig/day}, 4 mg { $\geq$ 25 cig/day} [13,14].

ADR: hiccups, sore throat, pruritus [13,14].

Nicotine patch

It is easy to use and delivers high doses of nicotine transdermally. A 16-24 hours patch is required to be applied for eight weeks. Patch sites should be rotated. 1% hydrocortisone is applied for skin reaction. A 16-hour patch is given to a patient who suffers from insomnia. Easy to use and provide steady nicotine levels.

DOSE: 7 mg/day, 14 mg/day, 21 mg/day [13,14].

ADR: erythema, shoulder/arm pain, pruritus [13,14].

Nicotine nasal spray

It requires patient counseling and education to ensure appropriate use. The medication should be sprayed against the lower nasal mucosa where it is absorbed. Therapy is usually discontinued by 12 weeks, but some patients may require longer use (up to 6 months).

DOSE: 10 mg/ml - 1spray-0.5 mg - 1 dose = 2 sprays [13,14].

ADR: sneezing, cough, nasal irritation, tearing, headache [13,14].

Nicotine inhaler

It consists of cotton impregnated with 10 mg of nicotine and enclosed in a small capsule, which the delivery device punctures on closure. When the user puffs on the device, vaporized nicotine is delivered to the mucosa of the mouth and posterior pharynx, where it is absorbed. Duration of therapy is six months with dose tapering in last three months.

DOSE: 4 mg [13,14].

ADR: Mouth/throat irritation, cough [13,14].

Nicotine lozenge

It is available in 2 mg and 4 mg preparations. It is used in the following dosage: weeks 1-6: 1 lozenge every 1-2 waking hours, weeks 7-9: 1 lozenge every 2-4 hours, weeks 10-12: 1 lozenge every 4-8 hours. Patients should not eat or drink 15 minutes before using the lozenge, and also should not use more than 20 lozenges per day. Easier to use in patients with denture, compared to chewing gum.

DOSE: 2 mg, 4 mg [13,14].

ADR: nausea, hiccups, mouth irritation, heartburn [13,14].

E-cigarettes

Electronic cigarettes are also known as e-cigarettes, e-cigs, vape pens, or vapor cigarettes. These devices may look like traditional cigarettes, pens, or USB flash drives. They can be battery operated or rechargeable. E-cigarettes do not burn tobacco, they have cartridges filled with a liquid that may contain flavorants, nicotine, tetrahydrocannabinol (THC), or cannabinoid (CBD) oils and other chemicals. The e-cigarette heats the liquid chemicals into a vapor or steam that a person inhales, which is why using these is often called "vaping." E-cigarettes have emerged as a potential smoking cessation tool [15] (Figure 3).

Notes: Carbon monoxide, nicotine, free radicals, carbonyls (including acrolein), and particulate matter are known components of tobacco-cigarette smoke that contribute to cardiovascular disease. Electronic cigarettes do not emit carbon monoxide, but still deliver nicotine, and often (but not

always) detectable levels of these other components, making their cardiovascular risk less clear.

One of the main differences between e-cigarettes and tobacco cigarettes are expected to largely determine the potential risk is the lack of combustion and tobacco. Propylene glycol and glycerol are mainly used in e-cigarettes as solvents and for the production of visible aerosol [15]. The chemistry profile of e-cigarette liquid and aerosol is less harmful compared to tobacco cigarettes for a variety of potentially toxic compounds such as tobacco-specific nitrosamines, phenols, nitrates, polycyclic aromatic hydrocarbons, aromatic amines and carbon monoxide [16-20]. Many of the toxins present in tobacco cigarette smoke are absent from e-cigarettes, while others are present in lower levels. E-cigarettes are one of the most controversial issues in public health today. There is little doubt that they are less harmful than smoking, but there is disagreement on the level of risk reduction and efficacy. It is widely used.

Bupropion

Bupropion is a betaphenylethylamine derivative. It is the first medication which does not contain nicotine and is useful for smoking cessation therapy. It is an aminoketone antidepressant. It has both noradrenergic and dopaminergic activity. Norepinephrine and dopamine play important roles in the development of nicotine dependence. Nicotine stimulates the release of these and other neurotransmitters. The recommended dosage of bupropion is 150 mg twice daily [21,22]. Bupropion was originally marketed and is still widely used as an antidepressant. Sustained release bupropion was

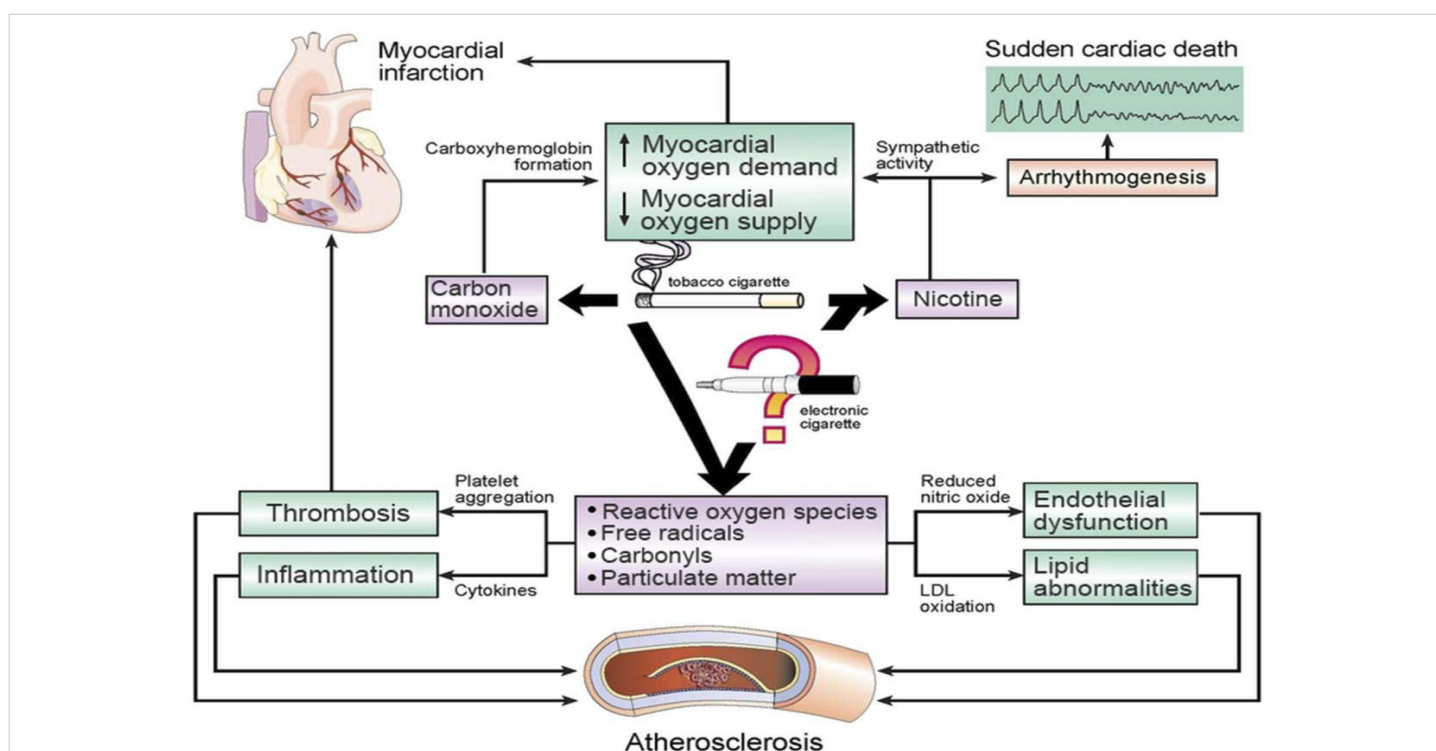


Figure 3: Effects of tobacco-cigarette smoke on cardiovascular disease.

found to aid smoking cessation independent of whether a smoker is depressed or not. Bupropion used for one year for relapse prevention was demonstrated to be safe and effective and significantly better at promoting cessation than placebo (Figure 4).

Molecular Formula: $C_{13}H_{18}ClNOHCl$

Dosage: 150 mg tab. taken daily for 3 days, increasing to 150 mg twice daily [23].

ADR: Trouble sleeping, Nightmares, Dry mouth, Agitation, Indigestion, Irritability [23].

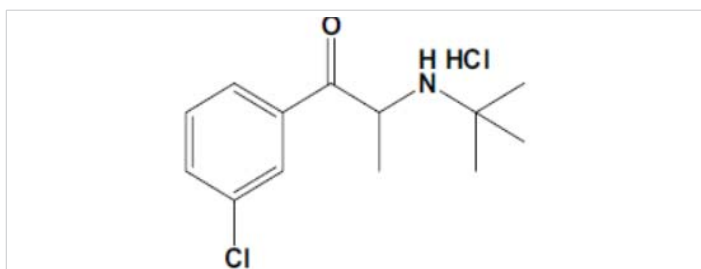


Figure 4: Structure.

Varenicline

Varenicline is a partial agonist of the $\alpha 4\beta 2$ receptor, which mediates dopamine release and is thought to be the major receptor involved in nicotine addiction [24]. The drug is given orally, 0.5 mg daily for first three days, 0.5 mg twice daily on days four to seven, and then the dose is increased to 1 mg twice daily for 12 weeks. An additional 12 weeks of treatment can be given to reduce the chance of relapse. Varenicline is superior to bupropion in both efficacy for achieving abstinence from smoking and in delaying smoking relapse [25]. The main side effect is nausea which can be reduced by taking it after food and with a glass of water. It is contraindicated in pregnancy and childhood. It decreases the urge to smoke and reduces withdrawal symptoms and is therefore considered a first-line medication for smoking cessation [25] (Figure 5).

Molecular Formula: $C_{13}H_{13}N_3C_4H_6O_6$

Dosage: 0.5 mg daily for 3 days, 0.5 mg twice daily for four days, 1 mg twice daily for remaining treatment duration [26].

ADR: Trouble sleeping, Nausea, Headache, Vomiting, Altered taste, Gas [26].

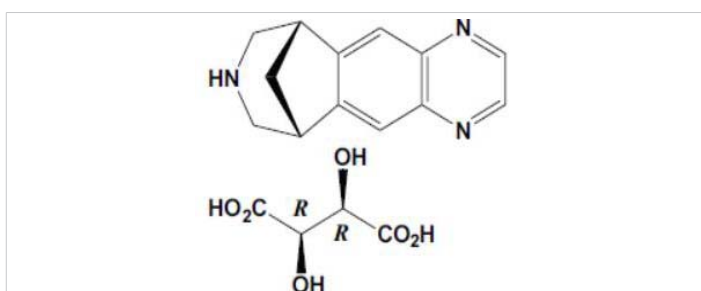


Figure 4: Structure.

Cytisine

A plant alkaloid with high affinity for the $\alpha 4\beta 2$ nicotinic acetylcholine receptor subtype, cytosine is derived from the plant *Cytisus laburnum*. The course of treatment starts at one tablet every 2 h (six total) on days 1–3, with a scheduled quit date at day 5, tapered to 1–2 tablets daily by days 21–25 [27]. It has been used medically to help with smoking cessation. Cytosine has a short half-life of 4.8 hours, and is rapidly eliminated from the body (Figure 6).

Molecular Formula: $C_{11}H_{14}N_2O$

Dosage: Oral, tab.; increasing dosages from every 2 hours to 1–2 tabs per day [28].

ADR: changes in both taste and appetite, dryness in the mouth, headache, irritability, nausea, constipation, tachycardia [28].

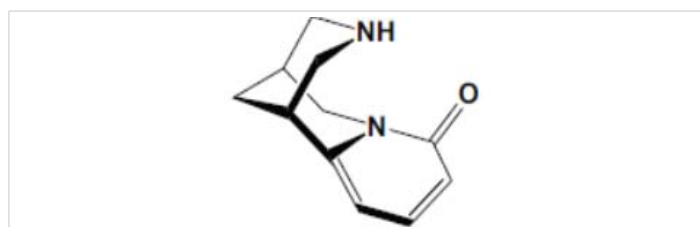


Figure 6: Structure.

Nortriptyline

The second generation tricyclic antidepressant, nortriptyline, is regarded as the most promising alternative to bupropion, with noradrenaline and serotonin transporters being their main inhibitory targets. Nortriptyline has been effective in smoking cessation. It affects chemicals in the brain that may be unbalanced in people with depression. Nortriptyline is thought to produce its effects via noradrenergic and dopaminergic mechanisms independently of its antidepressant actions. Although it is often used to treat depression, it is also used for pain and to improve sleep. It has been found to be safe and effective over many years of use. It is not recommended for use in children [6] (Figure 7).

Molecular Formula: $C_{19}H_{21}N$

Dosage: Oral, tab.; 25 to 100 mg per day or titrated dosages to serum levels recommended for depression [6].

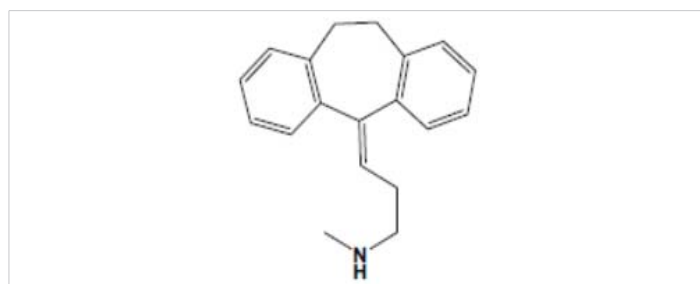


Figure 7: Structure.

ADR: sleep problems, Shakiness, dry mouth, blurry vision, and constipation [6].

Nicotine vaccine

Antibodies against nicotine inhibit its passage to brain, thus preventing its addiction-reinforcing activities. Three nicotine vaccines are under investigation at present. These vaccines offer promise in the management of relapse following cessation of smoking [29]. Nicotine vaccines induce the immune system to produce antibodies that bind to nicotine molecules in the bloodstream to form a molecule that is too large to cross the blood-brain barrier and produce its rewarding effects. NicVAX is an experimental conjugate vaccine intended to reduce or eliminate physical dependence to nicotine [29] (Figure 8).

Behavioral techniques

Behavioral Activation is a behavioral-based treatment that has been proposed as suitable for smoking cessation, as it simultaneously addresses reinforcement-related variables and also mood management. These behavioral approaches encourage change towards cessation by

encouraging are include the evaluation of the stimuli and consequences surrounding smoking, and by encouraging new responses. All health professionals have a role in delivering smoking cessation interventions to enable more people who smoke to quit and to remain smoke free. Quitting smoking is a complex process that involves psychological, physiological, and environmental variables. Behavioral interventions focus on the environment and the individual's thoughts and actions in relation to the environment. Behavioral approaches based on social learning theory stem from the observation that behavioral change is difficult. There is a dose-response relationship between the intensity and duration of behavioral smoking cessation interventions and their effectiveness.

Cognitive Behavioral Therapy is a promising psychological intervention for people who want to quit smoking because changing and restructuring thought processes, combined with new learning behaviors, is essential for people who want to effectively quit smoking and maintain cessation. Cognitive Behavioral Therapy alone does not usually have a significant effect on smoking cessation, but is very successful when combined with other quit strategies. What you think and

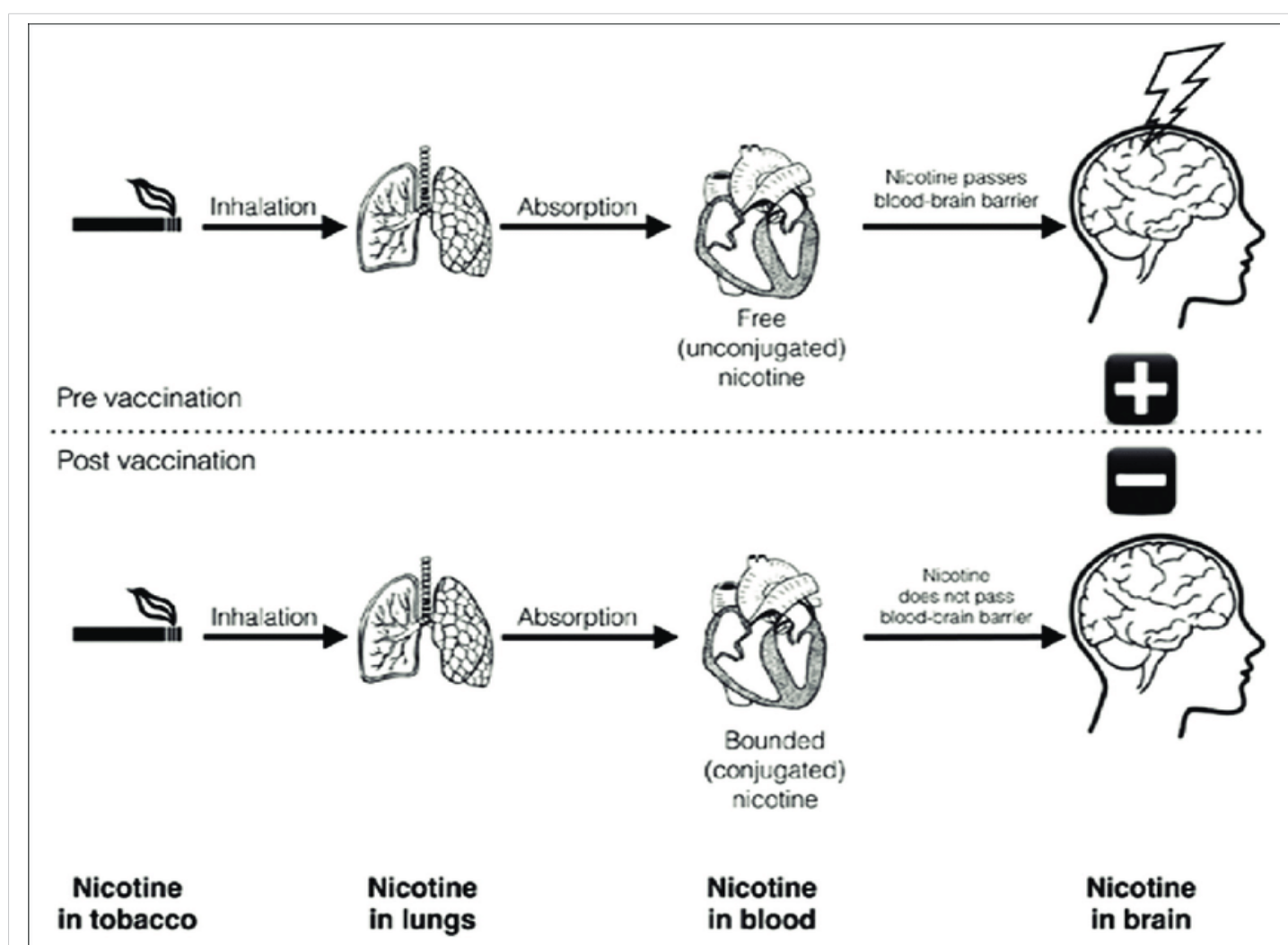


Figure 8: Mechanism of action of a vaccine against nicotine addiction In-the absence of vaccine.

feel about smoking has a large impact on your behavior. The behavior in this case is smoking and any action that encourages smoking. Individualized problem-solving strategies to help you cope with difficult environments and situations. Identifying social or environmental cues that trigger the urge for a cigarette.

Emerging trends

Technology is constant in our daily lives. We use it to connect with loved ones, to help find everything from a restaurant to a doctor, and to do our jobs, and it is a part of our day to day life. The apps developed for smoking cessation include (eg. Quitter's Circle app) can provide helpful tips on quitting smoking and send reminders for important dates, such as your Quit Date and your first healthcare provider visit. The app also helps you stay motivated by tracking your progress along your quit journey, tallying how many days you've stayed smoke free and how much money you've saved. Quitters and their Supporters to use social media to stay connected for a successful quit. While it's a relatively new area of study, research has shown that social media can indeed be helpful in quitting smoking.

Telemedicine or online pharmacy services are helping in various ways for the fastening and helping of our day to day life, and also the wearable technologies also available in the helping of smoking cessation. Mainly starting from simple rubber bracelets that count your daily steps to the most high-tech smart watches, consumers have a variety of options for digital accessories that help track their health and fitness. These types of several devices help to monitor your daily heart rate, seeing how your vitals improve over time, or use the diet and fitness trackers to help stay on target with your health goals. To improve the quality of life is the main deal for these gadgets and technologies.

Conclusion

Smoking is one of the most difficult practices to get rid of. All smokers trying to quit should receive support from doctors as well as family and friends. Smoking habit nearly kills the person and also the surrounding smoker. Smoking cessation pharmacotherapy such as nicotine replacement therapy, bupropion, and varenicline are moderately effective with side effects, but as well as not only these kind of therapy is not much effective, when we advise some extra activities also. However, a person interested in smoking cessation must have some strength and a peace of mind. Behavioral therapy is also important as well as the pharmacologic therapy, not only the drugs and side effects, the meditation and yoga also very good activity for a person to get good peace of mind and to get strength for to fight against the nicotine withdrawal syndromes. The emerging technologies around us are very much helpful to fully achieve the smoking cessation successfully. Wearable technology and smartphone apps should be helpful from the starting stage of smoking cessation. It helps the patient to

know the day to day activity, pulse rate and heart rate. As stated, a combined therapy including technology, counseling, pharmacotherapy, meditation, and extracurricular activities to forget about even the thinking of smoking helps the person to achieve the goal more conveniently and easily. A routine should help the patient more effectively with the help of applications and weekly once counseling and group discussions with other persons who are also trying to quit smoking. These interactions help the patient's mind and give high confidence. We must consider and take every aspect of help and activities for the smoking cessation and take support from family as well as friends and colleagues.

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