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Review Article

Nicotine Withdrawal Syndrome

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Abstract

Smoking remains a global health problem that contributes significantly to morbidity and mortality. Although most smokers are aware of the harmful effects of smoking, many struggle to quit due to nicotine dependence and the development of nicotine withdrawal syndrome (NWS). This literature review aims to examine the mechanisms, clinical manifestations, and management approaches for NWS. Nicotine contained in tobacco products binds to nicotinic acetylcholine receptors (nAChRs) in the central nervous system and triggers the release of various neurotransmitters that play a role in the addiction process. Cessation or reduction of nicotine consumption after chronic use causes neurobiological changes such as upregulation and desensitization of nAChRs, disruption of the dopaminergic system, and involvement of the habenular complex, hippocampus, and amygdala, which underlie the onset of nicotine withdrawal symptoms. NWS symptoms typically appear within 4–24 hours after nicotine cessation, peak on the third day, and can last for several weeks. Clinical manifestations include affective symptoms such as anxiety, irritability, depression, and anhedonia; somatic symptoms such as increased appetite, gastrointestinal disturbances, and tremors; and cognitive symptoms such as impaired concentration and memory. The level of nicotine dependence can be assessed using the Fagerström Nicotine Dependence Test. Treatment includes behavioral interventions and pharmacotherapy, such as nicotine replacement therapy, bupropion, and varenicline. The combination of behavioral and pharmacological therapy has been shown to increase smoking cessation success compared to either intervention alone. A better understanding of the mechanisms and management of NWS is expected to increase the success of smoking cessation programs and reduce the burden of tobacco-related diseases.

Keywords: Nicotine Withdrawal Syndrome, Nicotine, Nicotine Dependence, Quit Smoking, Nicotine Replacement Therapy

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Introduction

Smoking is the second-largest contributor to disability-adjusted life-years (DALYs) globally, contributing to 148 million DALYs annually. The World Health Organization (WHO) estimates that smoking contributes to 12% of deaths in men and 6% of deaths in women worldwide.[1] The 2021 Global Adult Tobacco Survey (GATS) showed an increase in the number of adult smokers by 8.8 million, from 60.3 million in 2011 to 69.1 million in 2021.[2] Cigarettes and tobacco account for the second-largest consumption value (12%) of household consumption in Indonesia after food and beverages.[3] Smoking contributes to increased morbidity and mortality in Indonesia.[1]

Most smokers are aware of the dangers of smoking but are still unable to quit. One reason is the nicotine in cigarettes, which creates a stronger desire to smoke compared to concerns about the negative impacts of smoking and the determination to quit. Several studies have reported the prevalence of nicotine withdrawal syndrome in smokers. Of 554 adult smokers in the United States, 87% reported quitting after one week. Of 2,862 male smokers in Japan, 67% reported symptoms of nicotine withdrawal syndrome.[4] In Indonesia, only 15.7% of smokers reported successfully quitting, lower than the same proportion in Korea (41.2%) and Australia (22.4%).[5] Various strategies have been developed in many countries in an effort to reduce the prevalence of smoking, but smoking remains a major cause of morbidity and premature death worldwide.[6]

Despite the high awareness of smoking hazards, cessation remains a significant challenge because of the neurobiological basis of nicotine dependence. The objective of this literature review is to examine the underlying neurobiological mechanisms of nicotine withdrawal syndrome (NWS), identify its varied clinical manifestations, and evaluate current management strategies, including behavioral and pharmacological interventions, to enhance the success rates of smoking cessation programs.

Smoking and Nicotine Withdrawal Syndrome

Cigarettes contain numerous chemicals that are harmful to smokers and those around them. Of the more than 7,000 chemicals found in cigarettes, at least 250 are known to be harmful to health. Among the various hazardous chemicals found in cigarettes, 69 can cause cancer.[7] Smoking can also lead to addiction, and nicotine is the most influential substance in making someone dependent on tobacco products, including cigarettes.[8]

Dependence on cigarettes and other tobacco products caused by nicotine is similar to dependence on drugs such as heroin and cocaine. Nicotine is a substance naturally found in the tobacco plant. The amount of nicotine entering the body is influenced by how a person inhales the tobacco product and its nicotine content. Nicotine is absorbed into the bloodstream through the lining of the mouth and lungs, then reaches the brain within seconds. Inhaling tobacco cigarettes more frequently and deeply increases the amount of nicotine absorbed by the body.[8]

Nicotine: Properties and Metabolism

Nicotine is an organic chemical compound belonging to the alkaloid family, naturally produced by various plants, such as those belonging to the Solanaceae family: tomatoes, potatoes, and tobacco. Nicotine acts as an agonist at most nicotinic acetylcholine receptors (nAChRs) in the body. Nicotinic acetylcholine receptors mediate rapid neurotransmission in the central and peripheral nervous systems. The fundamental pharmacological effect of nicotine is its action on nAChRs. Activation of nAChRs in the central nervous system can produce cognitive enhancement and increased control over arousal and negative emotions.[9]

Nicotine has acute neurophysiological effects, including antinociceptive effects. Nicotine is an exogenous ligand of nAChRs and affects various functions in the central nervous system by triggering the release of endogenous opioids (such as endorphins, enkephalins, and dynorphins) in the supraspinal cord and inducing the release of methionine-enkephalin in the spinal cord, as well as by activating the hypothalamic-pituitary-adrenal (HPA) axis. Nicotine has substantial physical dependence liability. The opioid receptor antagonist naloxone elicits nicotine withdrawal after repeated nicotine administration, and naloxone-induced nicotine withdrawal is inhibited by the concurrent administration of an opioid receptor antagonist. Overall, this suggests that nicotine-induced antinociception and the development of physical dependence are mediated by the endogenous opioid system via α7 nAChRs.[10]

Nicotine is metabolized through three major pathways: P450-catalyzed 5′-oxidation, UGT-catalyzed N-glucuronidation, and flavin monooxygenase (FMO)-catalyzed N′-oxidation. The iminium ion product of nicotine oxidation is metabolized to cotinine. Three minor pathways, namely methylation of the pyridine nitrogen to the nicotine isomethonium ion, 2′-oxidation, and N-oxidative demethylation, also contribute to nicotine metabolism. Cotinine is metabolized by three major pathways: 3′-oxidation to trans-3′-hydroxycotinine, cotinine N-glucuronidation, and cotinine N-oxidation. Unlike nicotine, N-oxidation of cotinine occurs at the pyrrolidine nitrogen, and this reaction is catalyzed by P450 enzymes. 3′-Hydroxycotinine is further metabolized to its O-glucuronide conjugate. Minor metabolites of cotinine include 5′-hydroxycotinine and norcotinine.[11]

In addition to cotinine, 12 nicotine metabolites excreted in the urine have been identified. Nornicotine and norcotinine have been found in the urine of smokers, but norcotinine has not been detected in the urine of individuals administered cotinine. Norcotinine is the primary product of cotinine metabolism catalyzed by P450 2A6 in vitro. Norcotinine has been found in the urine of dogs administered nornicotine. Nornicotine is also present in tobacco smoke, and some of the nornicotine in smokers is derived from that exposure. The concentration of the isomethonium ion of nicotine can be measured in the urine of smokers. The most recently identified nicotine metabolite, 3′-hydroxycotinine, may be a product of norcotinine oxidation.[11]

Definition of Nicotine Withdrawal Syndrome

Nicotine withdrawal syndrome is a group of symptoms that appear in the first few weeks after stopping or reducing nicotine use. Nicotine withdrawal refers to the effects experienced by individuals, depending on the amount of nicotine they consume after stopping or reducing nicotine use. Nicotine is the most common addictive substance found in tobacco and tobacco products, including cigarettes, cigars, chewing tobacco, e-cigarette liquids, and nicotine medications such as nicotine gum.[12]

Molecular Mechanisms in Nicotine Withdrawal Syndrome

Upregulation of Nicotinic Acetylcholine Receptors (nAChRs)

Long-term nicotine exposure leads to an upregulation of nicotine binding in the central nervous system of individuals experiencing repeated nicotine exposure. This increased pool of nAChRs contributes to the development of symptoms associated with nicotine withdrawal syndrome. Studies using radioligands with specificity for β2-containing nAChRs in single-photon emission computed tomography (SPECT) have

found that smokers have more cortical, striatal, and cerebellar β2 nAChRs than non-smokers.[13]

The number of β2 nAChRs in the anterior cingulate and frontal cortex is significantly correlated with the number of days after smoking cessation. This translates into a progressive increase in the number of β2 nAChRs proportional to the number of consecutive days of abstinence. Furthermore, a significant negative correlation was observed between the availability of β2 nAChRs in the post-central gyrus or somatosensory cortex and the desire to relieve symptoms by smoking.[13]

Desensitization of nAChRs

Some combinations of nAChR subunits make the receptor complex more susceptible to upregulation mechanisms. Desensitization is a mechanism that contributes to upregulation. The half-life of nicotine in humans is 2 hours or more, and then nicotine accumulates steadily to reach a stable plasma concentration, with a range of nicotine plasma concentrations between 10 and 50 ng/mL. Long-lasting nicotine concentrations indicate that nAChRs repeatedly exhibit high affinity for nicotine. Therefore, receptors undergo transitions between different conformations in response to ligand binding and dissociation, and agonists tend to stabilize them. Desensitized conformations of nAChRs have a higher affinity for agonists, so nAChRs increasingly adopt a desensitized conformation in response to chronic nicotine exposure.[13]

Receptor desensitization is the primary effect of the upregulation observed with chronic use of nicotine-containing products. Regular cigarette use results in persistent circulating nicotine levels throughout the day, and nAChR desensitization occurs in response to the continued activation of nAChRs in the central nervous system. After 2 days of smoking cessation, cravings diminish only after nAChRs return to saturation levels. However, the degree of desensitization is not always equal across all nAChR subunit combinations.[13]

When nicotine levels begin to decrease or even disappear, nAChRs recover from desensitization by potentially activating cholinergic signaling. This process is a key factor in the neurobiology of nicotine withdrawal. Considering these dynamics, Gould et al. have proposed pharmacological strategies to repair the nAChR system with compounds that maintain receptor desensitization or reduce cholinergic signaling and prevent upregulation and activation, thus mitigating the negative effects of nicotine withdrawal.[13]

Structure and Anatomical Pathways of Nicotine Withdrawal Syndrome

Different anatomical structures in the central nervous system can express different nAChRs. Variation in nAChRs, combined with specificity determined by afferent or efferent projections, results in distinct neurochemical and signaling pathways that underlie withdrawal syndrome. Evaluating behavioral changes that occur after deletion of specific nAChR subunits is crucial for characterizing each subunit's contribution to withdrawal syndrome.[13]

When withdrawal symptoms exhibited by wild-type mice are absent in mice lacking functional expression of specific nAChR subunits in specific central nervous system structures, that subunit appears to be crucial for the withdrawal symptoms. Such experiments further characterize the neural circuits contributing to withdrawal syndrome and allow for the development of more specific and personalized therapies.[13]

Dopaminergic System

The mesocorticolimbic dopamine system is identified as important in the development of addictive behavior, and dopamine signaling is involved in reward-based reinforcement. The dopaminergic ventral tegmental area (VTA) is widely involved in the rewarding aspects of addictive drugs. The lack of expected effects from dopaminergic deficits in the mesolimbic pathway is one of the neurochemical mechanisms underlying nicotine withdrawal symptoms. Deficiencies in dopaminergic transmission contribute to anhedonic or dysphoric states. In addition, the decrease in basal dopamine levels persisted for at least 5 days in experimental mouse models after 12 weeks of chronic nicotine administration. These changes in dopamine activity during withdrawal then correlate with a decrease in the modulatory influence of β2 nAChRs on dopamine release.[13]

The circumstances that cause the hypodopaminergic withdrawal-related effects are still unclear. However, increased inhibition of the VTA is a potential mechanism, as gamma-aminobutyric acid (GABA) input is sufficient to suppress action potential firing. In addition, GABAergic afferents reach the VTA from the substantia nigra pars reticulata, nucleus accumbens, ventral pallidum/globus pallidus, laterodorsal tegmentum, pedunculopontine nuclei, diagonal band of Broca, bed nucleus of the stria terminalis, and the caudal end of the VTA, called the rostromedial tegmental nucleus (RMTg). Activity in the RMTg increases after exposure to aversive stimuli and decreases after exposure to rewarding stimuli, indicating an inversely correlated signaling pattern.[13]

Habenular Complex and Interpeduncular Nucleus

The habenular complex, consisting of the lateral (LHb) and medial (MHb) nuclei, is a diencephalic epithalamic structure located ventrally along the dorsal third ventricle. The habenular complex provides signaling underlying fear, anxiety, depression, and stress. The lateral nuclei send excitatory projections to the RMTg and are a key component of the circuitry underlying negative reward.[14] In addition, cholinoceptive cellular populations in the MHb are associated with the aversive effects of nicotine. Through these projections, the MHb releases acetylcholine (ACh), substance P (SP), and glutamate into the interpeduncular nucleus (IPN).[15]

Hippocampus

The hippocampus is a crucial structure for the manifestation of cognitive deficits during nicotine withdrawal. Administering nicotine to rats undergoing withdrawal can improve cognitive deficits. This effect is not solely due to a reduction in the response threshold inherent to nicotine. Similar deficits are observed when an nAChR antagonist (dihydro-β-erythroidine) is administered to the hippocampus of rats receiving long-term nicotine. This mechanism also implicates β2 nAChRs in the manifestation of memory-related deficits during nicotine withdrawal. Furthermore, chronic nicotine use upregulates various nAChRs in the hippocampus, and the duration of upregulation of β2 subunits relative to other nAChR subunits is closely related to the duration of memory-related withdrawal symptoms.[13]

Extended Amygdala

The bed nucleus of the stria terminalis (BNST), the central nucleus of the amygdala (CeA), and the nucleus accumbens shell (NAc-Sh) form the extended amygdala and constitute an anatomically and neurochemically interconnected system. This system is involved in the stress-related components of drug withdrawal and is the site of interaction between corticotropin-releasing factor (CRF) and norepinephrine transmission. Nicotine withdrawal causes an increase in CRF in the central nucleus of the amygdala, and blockade of CRF1 receptors reduces anxiety-like behavior induced by nicotine withdrawal. CRF/CRF1 receptor signaling in the CeA also results in nicotine withdrawal-induced increases in nociceptive sensitivity in nicotine-dependent rats.[16]

Genetic Influence

Nicotine dependence is also influenced by genetic and environmental factors. Heritability accounts for 50–75% of the risk of dependence. Risk factors for nicotine dependence can be identified using genetic methods such as linkage analysis and candidate gene studies, as well as genome-wide association studies (GWAS). Linkage analysis assesses the presence of phenotypes in families with a high predisposition to identify disease-causing loci in relation to genetic markers. Candidate gene analysis assesses the association between alleles of specific genes potentially involved. Genome-wide association studies, unlike the candidate gene approach, do not limit the analysis to the association between specific genes and phenotypes.[13]

Symptom severity is largely influenced by nicotine consumption. Furthermore, behavioral models in transgenic mice have revealed that specific nAChR subunits, cellular components, and neural circuits are critical for the expression of withdrawal symptoms. Consequently, further mapping the neuronal circuits and nAChR subpopulations underlying nicotine withdrawal syndrome will enable personalized therapies, making them more effective in treating nicotine dependence.[13]

Signs and symptoms

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), there are seven main symptoms associated with nicotine withdrawal syndrome: irritability, anxiety, mood disturbances, difficulty concentrating, increased appetite, insomnia, and restlessness. Symptoms may also include constipation, dizziness, nightmares, nausea, and a sore throat. In practice, nicotine withdrawal symptoms can be classified as affective, somatic, and cognitive.[13]

Affective symptoms include anxiety, anhedonia, depression, dysphoria, hyperalgesia, and irritability. Somatic symptoms include tremors, bradycardia, gastrointestinal disturbances, and increased appetite. Cognitive symptoms include difficulty concentrating and memory impairment. Symptoms manifest within 4–24 hours after discontinuing chronic use of nicotine-containing products. Symptoms peak around day 3 and gradually decrease over the next 3–4 weeks. Although these symptoms cause discomfort to individuals who discontinue nicotine use, they do not result in harmful consequences.[13]

Identifying and Management Strategies for NWS

Prochaska describes patient readiness to quit smoking in five stages. In the precontemplation stage, the patient is not ready to make a change, but the doctor can motivate the patient to quit. In the contemplation stage, the patient acknowledges that tobacco use is a problem and will consider quitting. In the preparation stage, the patient and doctor develop a plan by setting a quit date, evaluating the use of pharmacotherapy, and determining available social support.[17]

Table 1. Fagerström Nicotine Dependence Test[9]

Patient-focused questions	Points for answers
How soon after you wake up do you smoke your first cigarette?	• Within 5 minutes (3) • 6–30 minutes (2) • 31–60 minutes (1) • After 60 minutes (0)
Do you find it difficult to refrain from smoking in places you shouldn't, like movie theaters?	• Yes (1) • No (0)
Which cigarettes don't you want to give up?	• First in the morning (1) • Others (0)
How many cigarettes do you smoke in a day?	• 31 or more (3) • 21–30 (2) • 11–20 (1) • 10 or fewer (0)
Do you smoke more in the morning?	• Yes (1) • No (0)
Would you still smoke if you were so sick that you were in bed?	• Yes (1) • No (0)

* A score of 7 or more indicates high dependence

The action stage is when the patient attempts to quit. The patient should contact the healthcare team frequently for support and solutions to address triggers for returning to

smoking. The patient enters the maintenance stage when the smoking cessation process is maintained. The doctor should assess the level of nicotine dependence when designing a cessation plan. This is done to guide the selection of pharmacotherapy for patients attempting to quit. The Fagerström Nicotine Dependence Test (Table 1) can be used in daily practice. The doctor should inquire about tobacco use at each visit using one of two methods: the 5A method or the Ask, Advise, Refer method. Resources to assist with the smoking cessation process should be available and should be deliverable by a member of the healthcare team. Once a patient who uses tobacco is identified, intervention should begin immediately.[17]

5A Model

The first step is "Ask," which begins with questions about tobacco use at each visit with the goal of increasing screening and cessation rates. The questions are aimed at identifying whether the patient is a current smoker, a former smoker, or has never smoked. The second step is "Advise," which provides a clear, strong, personalized message that focuses on the benefits of quitting. Physicians can use influential social factors (such as children, grandchildren, or financial benefits) to help patients determine the benefits of quitting.[17]

The third step is "Assess," which is conducted at each visit by reviewing the patient's motivation and readiness to quit and identifying barriers to quitting. The fourth step is "Assist," which helps patients navigate challenges and difficulties in quitting. The fifth step is "Arrange," which is the second recommended follow-up within the first month. If the patient is using pharmacological therapy, compliance, side effects, and the patient's perception of the usefulness of nicotine replacement medication should be reassessed.[17]

Ask, Advise, Refer (AAR) Approach

The "AAR" model is a more concise and simplified approach to the 5A model, which may be useful for busy clinicians who are unable to complete all five steps of the 5A model. The first step is "Ask," which involves asking the patient about their tobacco use. The second step is "Advise," which provides advice and suggestions to the patient on how to quit smoking. The third step is "Refer," which refers the patient to more qualified resources, including quitlines and support groups.[17]

5R Model

The first step is "Relevance," which encourages patients to demonstrate how to quit smoking in a relevant way. Patient motivation has the greatest effect when it is relevant to the patient's disease status (e.g., COPD), family or social situation (such as children or grandchildren at home), health problems, age, and gender. The second step is "Risks," which encourages patients to identify the negative impacts of tobacco products. Commonly recognized risks include cardiovascular disease, lung cancer, and COPD.[17]

The third step is "Rewards," which asks patients to identify relevant benefits of quitting tobacco use. Benefits of quitting include an improved sense of smell, financial savings, reduced tobacco odor, a healthier mouth, and improved personal and family health. The fourth step is "Roadblocks," which asks patients to identify barriers to quitting and then provides options and solutions to overcome these barriers. The fifth step is "Repetition," which repeats the assessment of the patient's readiness to quit. If the patient is still not ready to quit, repeat the intervention at a later date. Ongoing counseling and motivational strategies play a key role in helping patients quit tobacco use.[17]

Pharmacotherapy

Nicotine Replacement Therapy

Pharmacotherapeutic interventions for the treatment of tobacco dependence in adults include bupropion SR, varenicline, and nicotine replacement therapy (NRT), such as the use of nicotine patches. Nicotine acts on the reward pathway, as do all addictive substances. The goal of nicotine replacement therapy is to eliminate the urge to use tobacco products and reduce the effects of nicotine withdrawal syndrome.[18]

Smoking cessation rates can increase from 10% in control groups to 17% in people using any form of NRT. Using two types of NRT has been shown to be more effective than using one type alone. There is evidence that combining a nicotine patch (slow-release nicotine) with a short-acting NRT (e.g., gum, lozenges, nasal spray, and inhaler) is more effective than using NRT alone. The nicotine patch is worn for 16 hours daily for 8–10 weeks, available in doses ranging from 5 to 25 mg.[18]

Bupropion SR

The success rate of smoking cessation attempts increased from 11% in the control group to as much as 19% in the group using bupropion. Bupropion was originally developed as an antidepressant, but has proven effective as a smoking cessation therapy. Several studies have shown that NRT combined with bupropion SR is more effective than bupropion alone. The initial dose of bupropion is 150 mg per day for 3 days, followed by a maintenance dose of 150 mg twice daily.[18]

Varenicline

Varenicline is a selective α4β2 nicotinic receptor partial agonist that reduces cravings and withdrawal symptoms by blocking nicotine binding. Smoking cessation rates have been shown to increase from 12% in the control group to 28% in the varenicline group. In 2009, the US Food and Drug Administration (FDA) implemented a black-box warning for varenicline due to safety reports linking the drug to psychiatric adverse events, including mood disturbances, agitation, and suicidal tendencies. The risk of these events was found to be lower than previously thought. Therefore, the FDA removed the black-box warning for serious mental health adverse

events in 2016. The starting dose of varenicline is 0.5 mg once daily for 3 days, then 0.5 mg twice daily from days 4 to 7, then 1 mg twice daily until week 12.[18]

Combination of Behavioral Interventions and Pharmacotherapy

Combining behavioral interventions with pharmacotherapy can increase smoking cessation success rates from 8% to 14% compared with minimal behavioral interventions such as brief quit advice. Combination interventions include behavioral components delivered by a smoking cessation counselor combined with NRT. Adding behavioral interventions to pharmacotherapy also increases cessation success rates in patients using a combination of pharmacotherapy and behavioral interventions.[19]

Pharmacotherapy addresses the physiological determinants of withdrawal, such as receptor upregulation and desensitization, while behavioral therapy addresses psychological triggers and barriers to quitting. Behavioral counseling helps patients identify roadblocks and develop rewards for staying smoke-free, while nicotine patches reduce the somatic symptoms, such as tremors and bradycardia, that often lead to relapse. Support during the action stage also ensures that patients have solutions for immediate triggers while their nAChRs are still recovering from chronic desensitization.[19]

Choosing the Optimal Therapy

The use of two nicotine replacement agents is recommended to increase the likelihood of success in quitting. Nicotine patches provide a slow but prolonged release of nicotine to minimize the likelihood of withdrawal symptoms, and nicotine gum or lozenges can be used for immediate symptom relief. Gum and lozenges can also be used to manage nicotine cravings in patients taking varenicline or bupropion. Most therapies are recommended for 3 to 6 months. However, for most patients, the risks of continuing tobacco use far outweigh the risks of continuing nicotine replacement therapy to support smoking cessation.[17]

There is significant variation in the success rate of smoking cessation. Without intervention, patients have a success rate of up to 11%, and adding behavioral therapy can increase the success rate to 21%. Despite the variation in success rates in the literature, all nicotine replacement therapy products are considered equally effective. Nicotine replacement therapy can increase the cessation success rate by up to 70% compared to unassisted quitting.[17]

Conclusion

Smoking is a factor that increases morbidity and mortality in Indonesia. Dependence on cigarettes is caused by nicotine in tobacco entering the bloodstream, then binding to nicotinic acetylcholine receptors (nAChRs) and affecting the central nervous system through the release of endogenous opioids. One of the challenges in quitting smoking is the emergence of nicotine withdrawal syndrome, a group of symptoms that occur in the first few weeks due to stopping or reducing the amount of nicotine after chronic nicotine use. Nicotine withdrawal symptoms are classified into affective, somatic, and cognitive symptoms. Therefore, combining behavioral therapy with pharmacotherapy can increase the success rate of smoking cessation efforts.

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