



Smoking Cessation: A Review

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Abstract

Smoking is a leading cause of preventable death worldwide. Smoking damages almost all organs and body systems and reduces the overall health of a person with the highest mortality, especially due to respiratory and cardiovascular disease. Evidence shows that the symptoms and prognosis of smoking-related diseases will improve after smoking cessation. Smoking cessation is one of the most important ways to improve the prognosis of patients with respiratory ailments. Counseling and treatment can increase the chances of smokers to successfully smoke cessation. Smoking cessation therapy must include pharmacological treatment (Nicotine Replacement Therapy (NRT), bupropion, varenicline or N-acetylcysteine) combined with nonpharmacological therapy.

Keywords: bupropion, N-acetylcysteine, NRT, smoking cessation, varenicline

INTRODUCTION

Smoking is the world's leading cause of preventable disease and death. Smoking harms almost every organ of the body. Smoking causes about 90% of all lung cancer deaths and about 80% of all deaths from Chronic Obstructive Pulmonary Disease (COPD). Passive smoking is also harmful to health, especially for children.^{1,2} The results of the Global Adult Tobacco Survey (GATS) 2021 saw an increase in the number of adult smokers by 8.8 million people, from 60.3 million in 2011 to 69.1 million smokers in 2021. Smoking in Indonesia has increased in the last ten years.^{3,4}

Almost all smokers are aware of the dangers of tobacco and most smokers want to quit. However, nicotine contained in tobacco products is highly addictive. Without support quitting attempts only 4% of smokers who try to quit on their own will succeed. Professional support and smoking cessation therapy have been shown to more than double a smoker's chances of successfully quitting.⁵⁻⁷

Smoking cessation recommended by the World Health Organization (WHO) and Food and Drug Administration (FDA) is the best option, but limitations in drug availability and side effects make us choose other alternatives in treating patients.

Treatment using Nicotine Replacement Therapy (NRT), non-NRT and currently using n-acetylcysteine is one of the options that can help in smoking cessation efforts.^{1,3,6} Of all smoking patients, few of them try to stop smoking but struggle with the negative feedback of smoking. Therefore, this study aims to review the current option for smoking cessation that is available until this day.

TOBACCO CIGARETTES

Cigarette smoke contains more than 4500 chemicals, 250 of which are known to be harmful and at least 70 of which cause cancer. Some of the chemicals contained in tobacco smoke are nicotine, tar, cyanide, benzene, cadmium, methanol, acetylene, ammonia, formaldehyde, hydrogen, arsenic and carbon monoxide.^{2,8,9}

E-CIGARETTE

E-cigarettes are also called Electronic Nicotine Delivery Systems (ENDS) and Electronic Non-Nicotine Delivery Systems (ENNDS), which are methods for delivering nicotine by vaporizing a solution through a device while still providing the sensation of hand-to-mouth movements resembling smoking. There are currently four generations of e-cigarettes. The use of e-cigarettes is not considered smoking but "vaping".⁸⁻¹⁰

Most e-cigarette refill solutions contain propylene glycol, glycerol, ethylene glycol and polyethylene glycol mixed with flavoring agents and some nicotine. Almost all e-cigarette refill solution products contain tobacco alkaloids

(such as nornicotine, anabasine and anatabine) or synthetic nicotine, they also contain formaldehyde and Tobacco Specific Nitrosamines (TSNAs) which are carcinogens such as N-nitrosonicotine (NNN), N-nitrosoanabasin (NAB), N-nitrosoanabatin (NAT) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). The nicotine label levels on cartridges from several brands were found to be inconsistent with the actual levels, even ENNDS, which from several examinations contained nicotine.¹¹⁻¹³

EPIDEMIOLOGY

Countries with amount smokers in 2020 are China, India, Indonesia, the United States, Russia, Bangladesh, Japan, Turkey, Vietnam and the Philippines. The top ten countries form around two-thirds of the population of world smokers, with 30% of smokers in China. Indonesia occupies order third the largest amount smokers in the world from the GATS results noted that 27.9% are smokers aged 15-24 years.^{3,10,14}

SMOKING AND RESPIRATORY DISEASES

The impact of smoking affects blood circulation, heart, lungs, stomach, skin, bones, brain, mouth and throat, reproduction and fertility. Smokers in Indonesia experience 45% stroke, 81% heart attack, and 85% lung cancer. Quitting smoking improves health, saves lives and reduces financial problems.¹⁵⁻¹⁷

Lung diseases caused and affected by cigarette smoke are airway cell and epithelial damage, chronic obstructive pulmonary disease (COPD), lung cancer,

aggravation of asthma and increased risk of developing pulmonary infections. Inhaled particles from cigarette smoke are deposited in the airway depending on their size, with larger airborne particles in the upper airway and smaller particles deposited in the alveoli. Cigarette smoke causes oxidative stress resulting in chronic inflammation and inflammatory cells to the airway with activation of epithelial cells, alveolar macrophages, neutrophils and T lymphocytes.¹⁸⁻²⁰

Smoke from cigarettes causes macrophages and epithelial cells to become active and release chemokines. C-X-C Chemokine Ligand 1 (CXCL1) and C-X-C Chemokine Ligand 1 (CXCL8) act on CCR2 to activate neutrophils and monocytes, respectively, whereas C-C Chemokine Ligand 2 (CCL2) acts on C-C Chemokine Receptor 2 (CCR2) to activate monocytes. Type 1 helper T cells and type 1 cytotoxic T cells are activated by C-X-C chemokine ligand 9 (CXCL9), C-X-C chemokine ligand 10 (CXCL10), and C-X-C chemokine ligand 11 (CXCL11), which act on C-X-C chemokine receptor 3 (CXCR3).¹⁹⁻²¹

Together, these cells secrete neutrophil elastase and matrix metalloproteinase-9 (MMP-9) protease, which damages the alveolar wall and causes elastin breakdown. Transforming Growth Factor Beta (TGF-) is also released by macrophages and epithelial cells, which causes the small airways to fibrosis.¹⁹⁻²¹

HEALTH BENEFITS OF QUITTING SMOKING

There are both short-term and long-term advantages to quitting smoking. Knowing the advantages of quitting might be a good motivator. Stopping smoking behavior will significantly lower the risk of death, from the initial 20 minutes of improved blood pressure, heart rate, and blood flow to the reduction of all causes of smoking-related mortality if it can be accomplished.^{1,6,22}

The greatest method to shield your loved ones from the risks of secondhand smoke is to stop smoking. The advantages of quitting smoking for the body over time are shown in Table 1.^{1,6,22}

Table 1. Benefits of Quitting Smoking¹

Smoking Quit Period	Benefit
20 minutes	Improve blood pressure, heart rate and blood flow.
12 hours	All the nicotine in the body has been metabolized and the CO level in the blood returns to normal
24-48 Hours	Nicotine will begin to be eliminated from the body, the function of taste and smell will improve, the cardiovascular system will improve
5 days	Most of the nicotine in the body is gone.
2-6 Weeks	Accelerate the healing of infectious wounds on the body and the function of the airway cilia and lung function improve.
1 year	The risk of coronary heart disease decreases by 50%.
5 years	The risk of stroke decreases at the same rate as a non-smoker
10 years	The risk of lung cancer is reduced by 50%.
15 years	All-cause mortality and the risk of coronary heart disease decreased to the same level as non-smokers.

Table 2. Nicotine Withdrawal Effects²³

Nicotine Withdrawal Effects	Time (After Quitting Smoking)
Anxiety	1-2 weeks
Easily offended, frustrated and angry	≤4 weeks
Sleep disorders/insomnia, impatience, difficulty concentrating and depression	≤4 weeks
Appetite increases, weight increases	≤10 weeks

NICOTINE DEPENDENCE

Nicotine is the substance responsible for a person's dependence on tobacco products. Nicotine is a class of alkaloids produced by tobacco that is very fat soluble so that it is easily absorbed in the oral mucosa, lungs, digestive mucosa and skin. Nicotine can cross the placenta and excreted through breast milk. Cigarettes generally contain 6-8 mg of nicotine. The main characteristics of drug dependence include the use of drugs that cause psychoactive effects and the reward pathway system that influences user behavior.^{24,25}

The potential for a drug to cause dependence is generally determined by the speed at which the drug penetrates the brain. The faster the drug penetrates the brain, the greater the potential for the drug to cause dependence. When smoking a cigarette, nicotine enters the bloodstream and reaches the brain faster than drugs given intravenously.²³⁻²⁵

Nicotine is a selective agonist compound of Nicotinic Acetylcholine Receptors (nAChR) which plays an important role in the cognitive function of the human body. The effect of nicotine dependence is an important role of the neurotransmitter dopamine in an area in the brain called the Ventral Tegmental Area

(ATV) which is where nAChR releases dopamine. Dopamine will stimulate a sense of happiness for smokers.²³⁻²⁵

The more a person smokes, the more they will be exposed to nicotine. The brain will adapt to certain levels of nicotine. As the adaptability increases, the number of nAChR units increases. ATV regions and neurons in the brain will be activated increasingly. In addition, nAChR is stimulated by nicotine resulting in the hoarding of dopamine in the brain reward system will reach peak levels followed by a decrease in nicotine levels. This decrease in nicotine levels will reach the point of withdrawal syndrome which can only be eliminated by smoking again.^{23,25,26}

EXAMINATION OF NICOTINE AND CARBON MONOXIDE LEVELS IN SMOKERS

Several biomarkers can be used to determine a person's smoking status, namely through examination of nicotine levels, cotinine levels (another form of nicotine) and thiocyanate levels in plasma, urine and saliva, blood carbon monoxide levels (COHb) and examination of expiratory air carbon monoxide (CO) levels using a portable CO meter (smokerlyzer). Examination to assess nicotine dependence can use the Fagerstorm Test.^{1,27}

Table 3. Methods for Smoking Cessation²⁸

Method	How to Stop Smoke
Stop instantly	Today patient still smoking, tomorrow patient completely stop. This method needs pharmacological therapy to reduce the effect of nicotine separation.
Delay	Postpone moment cigarette first, 2 hours each day from the day before. Amount smoked cigarettes not counted. Example: Day 1: 09.00; Day 2: 11.00; Day 3: 13.00; Day 4: 15.00; Day 5: 17.00; Day 6: 19.00; Day 7: 21.00-last
Subtraction	The amount smoked cigarettes every day was reduced in a manner gradually with the same amount up to 0 bars. For example, smoking an average of 28 cigarettes cigarette a day. Stop smoking planned in 7 days. Day 1: 24 sticks; Day 2: 20 sticks; Day 3: 16 sticks; Day 4: 12 sticks; Day 5: 8 sticks; Day 6: 4 sticks; Day 7: 0 sticks

Therapy

The World Health Organization (WHO) recommends 2 methods of approaches that can be taken to help individuals quit smoking, namely the 5A and 5R. The 5A approach is used in patients who are ready to quit smoking. This approach consists of 5 components Ask, Advice, Assess, Assist and Arrange which have been summarized to make it easier for clinicians to educate patients. The 5S approach is used for smokers who don't want to quit smoking which consists of Relevance, Risk, Rewards, Roadblocks and Repetition. The smoking cessation program that is usually implemented in Indonesia is the 4T approach, namely Ask, Study, Help and Follow up.^{1,8,18,29}

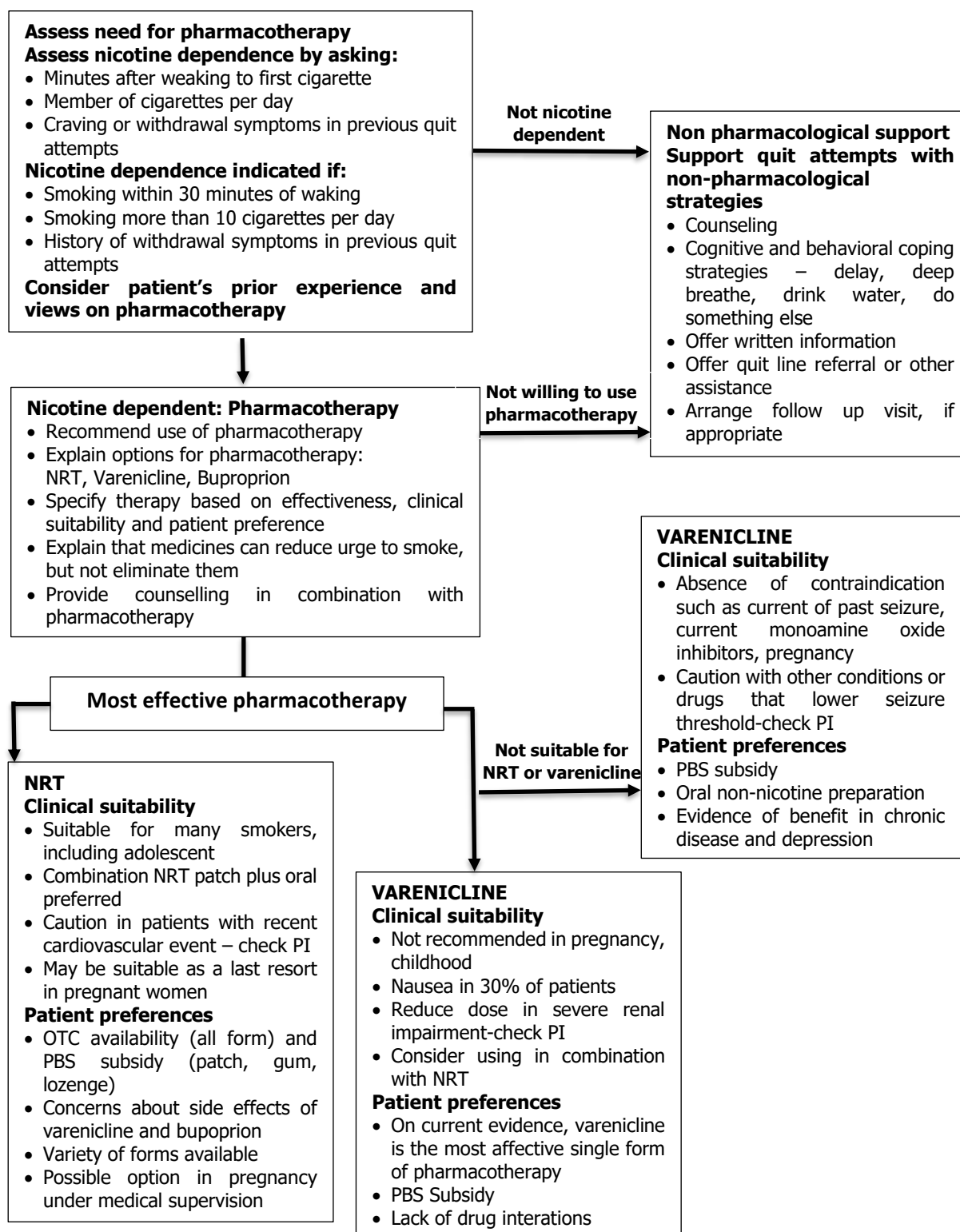
Worldwide guidelines for smoking cessation recommend immediate quitting and do not support gradual reduction and delays in quitting attempts. Hawley et al's study showed that 49% of the immediate cessation group successfully quit compared to 39.2% of the gradual cessation group. Participants who chose gradual cessation were significantly less likely to quit than those who chose immediate cessation.

These smoking cessation methods are described in Table 3.^{30,31}

Pharmacotherapy

Every smoker, whether they are ready to quit or not, should be given access to pharmacotherapeutic techniques since medication can encourage patients to cut back on smoking and raise the possibility that they will eventually try to quit. Nicotine Replacement Therapy (NRT) or Non-Nicotine Replacement Therapy, which includes bupropion hydrochloride and varenicline tartrate, are pharmacotherapies for quitting smoking that have been approved by the Food and Drug Administration (FDA).^{22,30,31}

The patient's comorbidities and adverse effects, as well as the drug's accessibility, should be taken into account while choosing pharmacologic therapy. Compared to smokers in general, patients with respiratory diseases have a stronger and more immediate need to stop smoking. Because of this, doctors must be proactive and persistent in encouraging their patients to stop smoking and offering them treatments to do so.^{22,27,30}

Figure 1. Smoking Cessation Algorithm²²

The use of large doses of N-acetylcysteine (NAC) is an option and has been studied because the availability of pharmaceutical therapy is limited in

Indonesia. In a 4-week study employing NAC, Harlivasari et al. from the University of Indonesia had a success rate of 37.7%.^{22,27,30}

Table 4 . Nicotine Replacement Therapy (NRT)²²

Drug	Dose	Giving	Side effects
Nicotine <i>patch</i>	Initial dose	Installing a new <i>patch</i> every morning	Skin irritation
21 mg	21 mg on ≥10 cigarettes/day	Location rotation to prevent skin irritation	Trouble sleeping
14 mg	14 mg on <10 cigarettes/day	If you have insomnia or sleep disturbances, don't use it when going to sleep	
7 mg	After 6 weeks, consider lowering the dose Use ≥3 months		
Nicotine <i>lozenges</i>	If the first cigarette ≤30 minutes after waking: 4 mg	Position it between the gums and cheek, let it dissolve slowly	Mouth irritation
4 mg	If the first cigarette >30 minutes after waking: 2 mg	1 fruit every 1-2 hours (max 20/day)	Notch
2 mg	Use ≥3 months		Chest pain Nausea
Nicotine <i>gum</i>	If the first cigarette ≤30 minutes after waking: 4 mg	Chew briefly until the mouth feels tingling, then position the gum in the cheek until the tingling is gone.	Mouth irritation
4 mg	If the first cigarette >30 minutes after waking: 2 mg	Discard gum after 30 minutes of use, 1 piece per hour (max 24/day)	Jaw cramps
2 mg	Use ≥3 months		Chest pain Notch Nausea
Nicotine inhaler 10mg/cartridge	10mg/ml Each cartridge has about 80 puffs Use ≥3 months	Puff to mouth/throat until the urge to smoke subsides Do not inhale into the lungs. Replace cartridge if the nicotine taste is gone. Use 1 cartridge every 1-2 hours (Max: 16/day)	Mouth and throat irritation Cough if inhaled deeply
Nicotine nasal spray 10mg/ml (10 ml per bottle)	10mg/ml 0.5 mg per spray Each bottle has 200 sprays Use ≥3 months	Spray 1 spray in each nostril Spray every 1-2 hours (max: 80/day)	Nose and throat irritation Rhinitis Sneeze Cough, watery eyes

Nicotine Replacement Therapy (NRT)

The first medicine for treating smoking cessation is called nicotine replacement therapy (NRT). The majority of the nicotine in cigarettes is temporarily replaced by NRT use, which lowers the desire to smoke and eases withdrawal symptoms. This makes it easier to stop smoking altogether once you start. NRT medications include lozenges, chewing gum, nasal and oral sprays, and skin

patches that deliver nicotine slowly but no faster than smoking to the brain.^{28,32}

When NRT is used, the urge to smoke lessens and nicotine is released right away. There is proof that all types of NRT increase the likelihood of quitting. The likelihood of giving up smoking rises by 50% to 60%. Other NRT formulations may be coupled with nicotine patches. The type of substance, skin irritation from using patches, and irritation of the oral mucosa from using gum and pills are all side effects

of using NRT. Heart palpitations and chest pain were the most severe side effects that studies have documented.^{28,32}

Non-Nicotine Replacement Therapy

Vareniklin is a nicotinic partial agonist. It was found that varenicline reduced the urge to smoke to a lesser extent than bupropion. Varenicline binds to the $\alpha 4\beta 2$ nAChR subtype with high affinity and selectivity which can reduce withdrawal symptoms. Varenicline was shown to be more effective than NRT and bupropion monotherapy. Combined use of varenicline and NRT has been shown to increase the success of smoking cessation attempts.^{22,28}

Table 5. Non-NRT²²

Drug	Dose	Side effects
Varenicline	The initial dose is 0.5 mg/day Maintenance dose 1 mg 2x a day For 3 months	Nausea, Headache, Insomnia
Bupropion	Initial dose of 150 mg/day Then increase to 150 mg twice daily for 3 months	Dry mouth, Insomnia, Headache, Nausea, Vomiting, Restlessness

Bupropion is the first licensed non-nicotinic pharmacological therapy for smoking cessation. Bupropion was first approved as an antidepressant in other countries. Bupropion works by blocking norepinephrine and dopamine. Bupropion has similar efficacy in NRT and is equally effective in smokers. Combination therapy between bupropion and NRT is more effective than bupropion alone or NRT

alone. Bupropion is contraindicated in smokers who have a current seizure disorder or previous history of seizures, bulimia, anorexia nervosa and who take monoamine oxidase inhibitors.^{33,34}

N-acetylcysteine (NAC)

N-acetylcysteine (NAC) is a widely available drug with mechanisms of increasing intracellular glutathione levels, antioxidant, modulating oxidative, immunoinflammatory, glutamatergic, and neurotrophic pathways. N-acetylcysteine can currently be used as a smoking cessation therapy and is easy to apply because it is readily available. Nicotine stimulates nACh in the central nervous system, which can increase the release of several neurotransmitters such as dopamine, glutamate and serotonin. The use of NAC can reduce nicotine-dependent behavior, which is modulated by glutamate. The pathway is by replacing glutamate levels by inhibiting GluR2/3 receptors which can reduce the return of nicotine craving.^{27,30}

Harlivasari et al's study used a randomized placebo-controlled trial in smokers conducted from January to December 2018 from the University of Indonesia. A total of 90 smokers received treatment divided into two groups, namely NAC 2x1200 mg and placebo for 4 weeks. In the NAC group, it was 37.7% while the placebo group was 6.7%. There were statistically significant improvements in Fagestorm score and exhaled CO values at the end of the study. N-acetylcysteine proved to be safe and well tolerated in

patients for smoking cessation. N-acetylcysteine had no significant side effects, only pruritus, nausea, headache and high blood pressure, so NAC can be applied to people in Indonesia.^{27,30,35}

CONCLUSION

Smoking is the leading cause of preventable death worldwide. Counseling/non-pharmacological approaches and pharmacotherapeutic interventions can improve smoking cessation success. World Health Organization suggests 2 models of approaches that can be taken to assist individuals in quitting smoking, namely 5A and 5R. Nicotine Replacement Therapy or Non-Nicotine Replacement Therapy pharmacotherapy options are bupropion and varenicline. The use of N-acetylcysteine can be used as a pharmacological therapy option in smoking cessation efforts.

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