

Review Paper

A Narrative Review on Smoking Cessation Pharmacotherapy



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ABSTRACT

Nicotine addiction and smoking are chronic conditions that increase the risk of various diseases, including cardiovascular diseases and cancer. Hence, it is highly recommended for all nicotine addicts to quit smoking. Pharmacotherapy along with psychotherapy is important in helping people quit smoking. Several medications, such as nicotine replacement therapy, varenicline, and bupropion are used for this purpose. Different delivery systems for nicotine replacement therapy are available, such as transdermal patches, gums, lozenges, and sublingual tablets. Bupropion and varenicline are widely used as therapeutic options in smoking cessation pharmacotherapy. In this paper, we have reviewed the clinical use of pharmacotherapeutic options available to aid smoking cessation in patients.

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Introduction

The prevalence of smoking worldwide is reported at 32.6% in males and 6.5% in females and about 7 million deaths annually are because of smoking [1]. Smoking cessation is the act of stopping smoking and overcoming nicotine addiction. It is a crucial step toward enhancing the overall health status and reducing the risk of assorted smoking-related diseases. However, ceasing smoking can be challenging due to the addictive nature of nicotine. Smoking cessation pharmacotherapy refers to the use of medications to help in the process of quitting smoking [2].

A recent review of workplace smoking cessation programs discovered that individual counseling, group therapy, pharmacotherapy, and multiple intervention programs were all associated with more elevated cessation rates than minimal or no treatment [3, 4]. According to Cochrane reviews, nicotine replacement therapy and non-nicotine pharmacotherapies, such as bupropion and varenicline can help individuals stop smoking [5]. Therefore, pharmacotherapy may be helpful in these patients [2].

The most effective approach for physicians to manage patients seeking smoking cessation involves counseling and pharmacotherapy. This combinatory method is more successful than each method alone [3, 4]. Increasing the knowledge of healthcare providers on the specifications of different therapeutic options as part of smoking cessation plans is necessary. This review provides a summary of the studies and clinical data on specific pharmacotherapy options used to treat nicotine dependence as well as other medical treatments.

Understanding Pharmacotherapy in Smoking Cessation

There are several types of medication available for smoking cessation. Nicotine replacement therapy is a common form of pharmacotherapy that involves delivering a controlled dose of nicotine to reduce withdrawal symptoms and cravings [2]. Bupropion is an antidepressant that can be an alternative medication for reducing nicotine cravings and withdrawal symptoms. Combining pharmacotherapy with behavioral interventions, such as counseling or group therapy, is more effective than using either intervention alone [3]. Smoking cessation pharmacotherapy and medication, in combination with behavioral interventions, offer a highly effective approach for individuals looking to quit smoking [6]. This

approach tackles both the physical and psychological aspects of nicotine addiction, thereby increasing the chances of successful smoking cessation. One of the studies mentioned in the literature maintained that combining nicotine replacement therapy with continuous counseling resulted in successful smoking cessation among participants [7].

Types of Smoking Cessation Medication

There are several types of medication available for smoking cessation. Nicotine replacement therapy is a commonly used pharmacotherapy that supplies a controlled dose of nicotine to decrease cravings and withdrawal symptoms. Nicotine replacement therapy can come in assorted forms, including patches, gum, inhalers, and nasal sprays. These products deliver nicotine without the contaminated chemicals found in cigarettes. Varenicline, a pharmacotherapy marketed under the brand names Champix® and Chantix®, represents a non-nicotine therapeutic option that mitigates nicotine cravings by blocking the effects of nicotine in the brain [8]. Bupropion is another option to treat nicotine cravings in patients trying to quit smoking. Both bupropion and varenicline are superior to placebo in increasing the odds of quitting smoking with significant odds ratios.

Nicotine replacement therapy

Providing nicotine can minimize nicotine and tobacco withdrawal symptoms [9]. Several clinical recommendations suggest nicotine replacement therapy (NRT) as the first treatment option for smokers seeking pharmacological assistance. The goal of NRT is to relieve nicotine withdrawal symptoms by providing nicotine without the use of tobacco while the individual breaks the behavior of cigarette smoking [9]. Depending on the country, NRT is either marketed as a transdermal patch or as a buccal absorption device (gum, lozenge, nasal spray, inhaler, or sublingual pill) [10]. All forms of NRT are comparable in effectiveness as individual products [11].

Nicotine transdermal patch (long-act)

In the nicotine transdermal patch formulation, nicotine is released from the skin patch. This patch has a slow-onset, long-acting nicotine delivery pattern that provides fairly consistent relief over 24 h but requires several h to reach the peak levels [9, 12], which is the most potent adhesive in smokers with a higher level of dependence. The nicotine patch provides the first nicotine delivery of all NRT products and is the simplest form of NRT [13].

With the help of doses, users can reduce their nicotine consumption over several weeks or more, allowing their bodies to adapt to the decreasing doses of nicotine and eventually reach a nicotine-free state [9]. This particular feature of adaptation makes nicotine patches essential to acute NRT formulations. In this formulation, instead of using the medicine during the day, the patient only needs to apply the patch on their skin in the morning. The length of treatment with the nicotine patch is longer (more than 8-10 weeks) than other NRT methods. The patch may be continued for longer, even indefinitely if needed, because NRT is safer than continuing to smoke [14]. In a randomized trial of 568 smokers that compared eight weeks of nicotine patch therapy with 24 weeks of nicotine patch therapy, the more prolonged treatment had a higher rate than seven days per week at week 24 [15]. The patches are usually marketed with recommendations for dose reduction over 12 weeks. Dose reduction does not improve smoking cessation [16].

Nicotine gum

Nicotine gum is a common short-acting NRT. Based on the literature, nicotine consumption is helpful in NRT; however, it does not mean that consumption and its effects are always constant. Contrastingly, the consumption and impact are always consistent. Nicotine gum could be based on the argument that different people consume different amounts of nicotine gum, depending on their daily consumption limit, in addition to other variables, such as age, body mass index, gene expression, peak concentration, and age [12, 17].

Nicotine gum includes 2 and 4 mg doses [9]. Studies recommend that patients consume at least one nicotine gum when they wake up and whenever they feel the urge to smoke. Meanwhile, patients gradually reduce consumption over the following six weeks for a minimum treatment period of three months [10]. The act of chewing this particular gum results in the release of nicotine, which is then absorbed through the oral mucosa. In addition, if the gum is chewed too quickly, irritation of the stomach and esophagus may occur. The nicotine absorbed from the gastrointestinal tract is primarily metabolized by the liver [18]. Furthermore, too rapid chewing may result in too much nicotine release which may bother the patient. The method of chew and park is the most accepted method of using nicotine gums and results in stable concentrations of nicotine based on the patients' receptors [17].

Nicotine lozenges

Nicotine lozenges are a common short-acting NRT product that can be used instead of nicotine for patients who need intermittent doses and periods of nicotine but are unable to chew gum for several disruptive individuals, such as individuals with maxillofacial gum disorders and teeth [12, 16, 19].

Nicotine lozenges are available in doses of 1, 2, and 4 mg [10]. There is a significant reduction in tobacco use compared to the amount used in the first two weeks of use. Smokeless tobacco users tolerate and approve nicotine lozenges [20].

The nicotine lozenge is administered by placing it in the mouth and allowing it to dissolve for 30 min without chewing. The dosage is similar to that of nicotine gum and should be gradually reduced over six weeks until the desired number of tablets per day is achieved. This formulation has side effects, including mouth burning and nicotine-related side effects, such as abdominal pain, nausea, vomiting, diarrhea, headache, and palpitations [16].

Nicotine nasal spray

Nicotine nasal spray is the fastest delivery method to the patient because this formulation delivers nicotine aqueous solution to the nasal mucosa. The increase in nicotine levels caused by the use of nicotine nasal spray is much higher than other NRT methods (the maximum nicotine level in the body is reached within 10 min of use) and is more accurate than the changes in nicotine consumed during smoking [10, 12, 17]. Studies show that nicotine patches and nasal sprays reduce fetal exposures compared to smoking [21].

The use of this product typically lasts for approximately three months but may have various side effects, such as nose and throat irritation, rhinitis, sneezing, and tearing. Nasal irritation is a common issue that affects 94% of patients within the first two days of use and persists in 81% of patients after three weeks of treatment [22].

Oral inhaler of nicotine

A nicotine inhaler consists of a mouthpiece and a plastic cartridge containing 10 mg of nicotine [9, 16]. It can be sprayed in the mouth (should not be inhaled or swallowed for some time). This method can be used in patients who have cravings for smoking. The speed of absorption through an inhaler is similar to that of nicotine gum [23].

Its use can lead to common side effects, including hiccups, throat movement, and nausea. Conducted studies to determine whether the use of oral nicotine inhalers could lead to reductions in substance use concluded that nicotine inhalants effectively and safely reduced smoking over 24 months [15, 24].

Sublingual tablet

Sublingual tablets are taken sublingually with no need to chew. They usually take 30 min to dissolve. Patients who are highly addicted to nicotine can use two sublingual tablets (a total of 4 mg) per dose. This formulation's side effects include sore mouth or throat and dry or burning mouth [10, 12, 25].

Varenicline

Varenicline is a partial $\alpha_4\beta_2$ nicotinic acetylcholine receptor agonist [26]. Dopamine (the main neurotransmitter associated with nicotine use) can be released through this receptor, and this mechanism can reduce withdrawal [8, 16]. Varenicline may be used continuously for up to six months of abstinence if well tolerated [27, 28]; however, a longer preload period of up to five weeks before the quit date is also recommended to achieve abstinence therapy [27].

Varenicline can cause common side effects, such as nausea, insomnia, strange nightmares, headache, nasopharyngitis, and dry mouth [29]. Varenicline dose reduction can minimize adverse effects, especially nausea. Patients who have previously experienced significant skin reactions and hypersensitive responses to varenicline should not use it. Considering the importance of chronic obstructive pulmonary disease (COPD) disease in patients addicted to smoking, clinical studies show that varenicline is safe for tobacco users with COPD [30].

Despite earlier concerns, subsequent data suggest that varenicline does not cause as many neuropsychiatric side effects as compared to nicotine replacement or bupropion. Additionally, clinical trials indicate that varenicline does not raise the risk of suicide or suicide ideation, depression, aggression, or death compared to the drug [31].

The potential risk of disease from varenicline is less than the risk of continuing to smoke and it does not appear to increase the risk of heart disease in patients with cardiovascular disease (CVD) [32]. A randomized trial of 714 smokers with stable CVD showed no difference in mortality or major cardiovascular events at week 52 in those assigned to 12 weeks of varenicline [33].

A review of varenicline vs drug efficacy showed that varenicline (as monotherapy and in combination with other drug therapies, especially bupropion) was superior to counseling or placebo in achieving smoking cessation [34]. Also, compared to other therapeutic drugs, varenicline is superior to bupropion, e-cigarettes, single-agent NRT, cytisine, and values with combined NRT [35-37].

Bupropion

Bupropion is a drug that helps stop smoking in depressed or non-depressed smokers. Bupropion's mechanism of action for smoking cessation is unknown; however, bupropion works by increasing noradrenergic and dopaminergic activity in the central nervous system [9, 38, 39].

In the context of smoking cessation assistance, sustained-release bupropion requires five to seven days for blood levels to achieve a steady state. Research studies have suggested that a treatment course spanning at least 12 weeks can significantly decrease the probability of relapse. Therefore, it is strongly recommended that individuals consider a longer period of treatment to improve their chances of success [16, 38, 39].

The most common side effects of bupropion are insomnia, restlessness, dry mouth, nausea and vomiting, and headache. Considering that COPD and CVD diseases are more prevalent in smokers, a review of studies shows that bupropion is safe and stable for use in people with CVD and COPD for smoking cessation.

The review of studies for the efficacy of bupropion against drugs showed that smoking cessation was more effective in a six-month follow-up with bupropion monotherapy than placebo or no psychiatric treatment [12, 40]. Also, the effectiveness of bupropion is equivalent to a single NRT; however, it has lower effectiveness than varenicline and combined NRT [41, 42].

Time to Consider Pharmacotherapy in Smoking Cessation

Smoking cessation can reduce the risk of premature death and improve the quality of life for smokers. People who smoke and quit smoking by the age of 40 have a longer life expectancy [6]. Meanwhile, individuals who quit smoking after age 70 or after developing tobacco-related diseases can still benefit from reduced mortality. For people who smoke, it is never too late to achieve the benefits of smoking cessation; accordingly, group smoking cessation interventions double quit rates at a 6-month follow-up [43]. Implementation of group-based smoking

cessation programs, which include multiple behavioral interventions, is recommended for effective smoking cessation care [12, 44].

Future Trends in Smoking Cessation Pharmacotherapy

Studies in personalized medicine centers and genetic studies show that systemic glycochens, including hyporetin, endogenous opioids, and GABA, play a role in the effects of nicotine changes. These findings have led to the development of compounds that effectively regulate nicotine-related behaviors, such as using methods related to mGluR2/5 and GABAB receptors, which show better properties and fewer side effects compared to agonists and antagonists. Also, they are now beginning to be evaluated for efficacy in clinical trials. Therefore, these recent advances in our knowledge of the neural mechanisms involved in nicotine will hopefully translate into new drugs and smoking cessation [45, 46]. In addition, new pharmacologic agents to aid smoking cessation are in the early stages of clinical trials. In particular, acetylcholinesterase inhibitors and N-acetylcysteine have a positive effect on smoking cessation compared to placebo control groups and groups receiving usual smoking cessation treatments in clinical trials [44].

Conclusions and Recommendations for Smoking Cessation

Cigarette smoking addiction remains a critical worldwide health issue, supported by robust evidence linking smoking to malignant cell growth in several body organs, including but not limited to the oral cavity, pharynx, larynx, and lungs. It is appropriate for all healthcare providers to know the smoking status of all individuals and to provide relevant and helpful smoking advice to all patients. One of the most important steps for smoking cessation is pharmacotherapy. Over the years, the effectiveness of various smoking cessation interventions has been investigated worldwide. Pharmacological interventions including NRT, bupropion, and varenicline, as well as new pharmacotherapies, such as personalized medicine and the use of immunological drugs in smoking cessation, have shown beneficial evidence. It is recommended to design clinical studies to evaluate the effectiveness of different combinations of medication classes in smoking cessation. Also, we recommend evaluating the long-term effect of smoking cessation pharmacotherapy on the healthcare of the patients.

Ethical Considerations

Compliance with ethical guidelines

This article is a review with no human or animal sample.

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Authors' contributions

Conceptualization and study design: Mohammad Fathalipour, Sara Asadi, Omid Moradi; Drafting the manuscript: Sara Asadi, Maryam Babaei, Omid Moradi; Critical revision of the manuscript for important intellectual content: Omid Moradi and Sara Asadi; Administrative, technical, scientific support and supervision: Mohammad Fathalipour and Sara Asadi.

Conflict of interest

The authors declared no conflict interests.

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