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An integrated approach to pharmacotherapy in smoking cessation: the role of varenicline, bupropion, cytisine, and nicotine replacement therapy

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An integrated approach to pharmacotherapy in smoking cessation: the role of varenicline, bupropion, cytisine, and nicotine replacement therapy.

Abstract

Introduction: Smoking tobacco is a significant global health issue, contributing to various diseases, including heart disease, cancer, and respiratory disorders. Quitting smoking is not only a beneficial decision for an individual's health but also for society as a whole. Pharmacological therapy plays a crucial role in the smoking cessation process by supporting and increasing the chances of success.

Aim of study: To compare four medications used in smoking cessation: varenicline, bupropion, cytisine, and nicotine replacement therapy, in terms of their characteristics, mechanism of action, efficacy, and adverse effects.

Materials and Methods: A review of available data in the PubMed database regarding medications registered in Poland for the treatment of nicotine addiction.

Research Results: The efficacy of all four medications in smoking cessation was demonstrated. Individuals using varenicline, bupropion, cytisine, or nicotine replacement therapy had higher chances of quitting smoking compared to placebo groups. Specifically, varenicline showed the highest efficacy among all the medications studied. Despite a high level of safety profile, each therapy can cause various adverse effects, with the most serious being the risk of seizures associated with bupropion.

Conclusions: Varenicline, bupropion, cytisine, and nicotine replacement therapy are valuable tools in the process of smoking cessation and increase the chances of successfully quitting the addiction. The choice of a specific medication may depend on individual patient preferences

and clinical factors. These findings should be taken into consideration when making therapeutic decisions in the field of smoking cessation.

Keywords: smoking cessation, varenicline, cytisine, bupropion, nicotine replacement therapy

Introduction

Cigarette smoking is a major cause of premature mortality and morbidity worldwide and represents a significant economic burden. [1] In 2012, the global amount of health care expenditures due to smoking-related diseases was $422 billion, while the global total economic cost of smoking (including health expenditures and lost productivity) was $1,436 billion [2]. In high-income countries, the leading causes of smoking-related deaths are lung cancer, emphysema, heart attack, stroke, upper respiratory tract cancer and bladder cancer. In addition, smoking contributes to eye disease, periodontal disease, cardiovascular disease, chronic obstructive pulmonary disease, stroke, diabetes, rheumatoid arthritis or immune system dysfunction. Moreover, smoking during pregnancy can increase the risk of adverse reproductive outcomes, such as ectopic pregnancy, low birth weight and premature birth. Exposure of children to secondhand smoke has been linked to sudden infant death syndrome, impaired lung function and respiratory disease, as well as cognitive and behavioral disorders. [3] Large studies in the United Kingdom, the United States, Japan and India have examined the ultimate impact on mortality in male and female populations, many of whom started smoking in early adulthood and did not quit. All of these studies showed that in middle age (about 30 to 69 years), mortality among cigarette smokers was two to three times higher than among similar individuals who never smoked, leading to a reduction in life expectancy of about 10 years on average. Those who smoked cigarettes from early adulthood but stopped at age 30, 40 or 50 gained about 10, 9 and 6 years of life expectancy, respectively, compared with those who continued smoking. While mortality associated with tobacco use increases slowly after starting to smoke, the effects of quitting occur much more quickly. People who started smoking in early adulthood but quit before the age of 40 avoid more than 90% of excess risk in the following decades of life compared to those who continue smoking. Even those who quit smoking at age 50 avoid more than half of the excess risk, although there are significant risks. [1]

The eighth report on the global tobacco epidemic, published by the World Health Organization on July 27, 2021, found that in 2019, the global smoking rate among people over the age of 15 was 17.51%, with 847 million adult men and 153 million adult women

smoking by July 2021. A report by the World Health Organization highlights that about 10% of global deaths are smoking-related, and 7 million people die from smoking each year. If this pattern of tobacco consumption continues, by 2030. 8 million people will die from tobacco-related diseases each year. Therefore, when trying to control tobacco use to improve public health, an important step is to find effective ways in quitting smoking. [4] It is also worth highlighting the fact that 70% of tobacco users want to quit. However, those who try to quit smoking make an average of about six attempts before achieving long-term abstinence. [5]

The Involvement of the α4β2 receptor in the mechanism of addiction.

The most important addictive component of tobacco is nicotine, which acts by binding to cholinergic nicotinic receptors (nAchRs) in the central and peripheral nervous systems. In the brain, nAchRs are pentameric structures composed of α and β subunits in varying proportions. The most common subtypes are α4β2 and α7. About one-third of the α4β2 nicotinic receptors are located on dopaminergic cells in the ventral tegmental area, the nucleus accumbens and the prefrontal cortex. Nicotine binding to the α4β2 receptor in the ventral tegmental area stimulates the release of dopamine into the paraventricular nucleus accumbens, which is thought to be the underlying reward and reinforcing effect of nicotine in addiction. [6,7] There is evidence from both human and animal studies that indicate the involvement of the α4β2 receptor in nicotine addiction. For example, a human study using positron emission tomography (PET) suggests that α4β2 receptors are almost completely occupied by nicotine after smoking an entire cigarette [8]. In rats, blocking α4β2 receptors, for example, with mecamylamine, prevents self-administration of nicotine [9].

In addition, genetic deletion of the α4 or β2 subunit in mice eliminates intravenous self-administration of nicotine [10]. However, selective restoration of α4 or β2 subunits in the ventral capsular region using lentiviral vectors restores intravenous nicotine self-supply in mice [10].

In conclusion, the above observations strongly suggest the involvement of neuronal AchR α4β2 receptors in nicotine addiction. They also suggest that the α4β2 receptor may represent a promising therapeutic target for the treatment of smoking disorders.

Varenicline (Champix)

Varenicline tartrate was originally developed by Pfizer in 1997 as a smoking cessation agent based on the molecular structure of cytisine. [6] The discovery of varenicline was based on the premise that the acetylcholinergic nicotinic receptor (nAChR) α4β2 is responsible for nicotine's addictive properties, and that varenicline's dual partial agonist and antagonist effects could improve abstinence rates over nicotine replacement therapy, which exhibits full agonism to this receptor. [11] It has been hypothesized that during the period of attempted smoking cessation, the partial agonist activity will replace nicotine to some extent (reduce nicotine craving and abstinence symptoms). In contrast, during relapse, antagonistic activity will reduce nicotine reinforcement by competing with inhaled nicotine for the same nAchR α4β2 binding sites (in other words, it reduces smoking pleasure). [12] In 2006. Varenicline was approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of tobacco dependence.

Mechanism of action: Varenicline binds with high affinity and selectively to neuronal nicotinic α4β2 cholinergic receptors, on which it acts as a partial agonist, and in the presence of nicotine as an antagonist. It is worth noting that varenicline has a higher affinity for this receptor than nicotine, but at the same time has a lower intrinsic efficacy than nicotine. Thus, varenicline can block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopaminergic system, which is the neuronal mechanism responsible for the reinforcement and reward phenomenon that occurs as a result of smoking. [6]

The standard treatment time is 12 weeks. A 1 mg tablet is taken twice daily. In patients who have managed to stop smoking, an extended treatment period of another 12 weeks may be considered. At the beginning of treatment, the patient can smoke cigarettes, but must set a quit date during the first or second week of therapy. The most common side effects include nausea (which is highly dose-dependent), occurring in 30% of patients in the first week of therapy taking 2mg of varenicline daily and in 16% of patients taking 1mg daily. In most cases, their severity is low to moderate and does not lead to treatment discontinuation. In second place is insomnia, which occurs in 14-37.2% of patients, is most common in the first month of treatment and its severity decreases with the duration of therapy. Headaches, unusual daydreaming, dry mouth, constipation or weight gain may also occur, but these are less common, temporary effects of mild/moderate severity. [6, 13, 14]

Bupropion (Zyban)

Bupropion was originally developed as an antidepressant drug. Its genesis dates back to 1974, when it was patented by Burroughs Wellcome (now GlaxoSmithKline) and approved by the FDA in 1985. In 1997 it was approved for marketing in the US as the first non-nicotine smoking cessation drug. In addition to its proven antidepressant and anti-smoking effects, bupropion has other uses. One of its side effects is weight loss, [15] which may be a desirable feature in the context of smoking cessation (when giving up tobacco, patients often gain weight).

Mechanism of action: bupropion is an amino ketone antidepressant that inhibits the reuptake of dopamine and, to a lesser extent, norepinephrine into the synaptic vesicles of neurons; it has no effect on the serotonin system. [16, 17] It also acts as a nicotinic receptor antagonist [18]. Although it was developed as an antidepressant, it is not more effective in depressed patients compared to non-depressed patients. Therefore, it exerts its effect on smoking cessation in ways other than alleviating the symptoms of depression. At the same time, it should be mentioned that the mechanism of action of the drug in the context of smoking cessation is not fully explained. [16]

The minimum duration of therapy is 7 weeks. It is taken 2 tablets per day of 150 mg with a min. 8-hour interval. The maximum daily dose is 300mg. It is recommended to start bupropion treatment while still smoking.

Bupropion is metabolized by cytochrome P450 2D6 (acts as an inhibitor) and interacts with drugs metabolized by this enzyme, i.e. SSRIs, tricyclic antidepressants, propafenone, risperidone [16]. Nearly half of patients experience side effects. They occur in about half of those treated during the first two weeks, and then symptoms decrease and occur in a few percent of people by the end of treatment. The most common are insomnia and dry mouth. Nicotine withdrawal also causes symptoms that are similar to the side effects reported during bupropion therapy. [16] In addition, in the past, Bupropion has had a U.S. warning related to suicidal thoughts and behavior in children, adolescents and young adults. However, in December 2016, researchers published a safety review which concluded that the threatening effects of bupropion on mood and behavior were less than previously represented. As a result, the warning changed. However, the report noted that the reactions remain a concern, especially in patients with severe mood disorders or schizophrenia. This report issued by the FDA was clearly related to the use of bupropion in the context of smoking cessation, not the treatment of depression. [19] The most significant contraindication is a history of epilepsy.

Clinicians and researchers first noticed the occurrence of epileptic seizures in the 1980s, and bupropion was withdrawn from the market between 1986 and 1989. However, this was related to the use of too high a dose of the drug, and today a daily dose of up to 300mg is considered safe. When prescribed to people with no history of seizures or risk factors for seizures, the risk has been calculated to be about 1 in 6,000 for first-time users of bupropion. [16] Other contraindications include bipolar disorder, eating disorders, and the use of other drugs that lower the seizure threshold, i.e. antidepressants, antipsychotics, systemic corticosteroids, tramadol. Also, patients who abuse alcohol, discontinuing sedatives, or patients who have suffered head trauma are also at risk for a bupropion-induced seizure. [16, 19]

Cytisine (Tabex, Recigar, Desmoxan)

Cytisine is the main alkaloid of Common Goldenseal /Cytisus Laburnum/, commonly known as , "false tobacco". It is found in central and southern Europe, among other places. Cytisine was first discovered in 1818 and isolated in 1865. During World War II, it was used by German and Russian soldiers as an accessible and inexpensive substitute for tobacco. [20] As a drug, it was introduced in 1964 (under the trade name Tabex, produced in Bulgaria) in eastern and central Europe, while there were still no approved measures in smoking cessation in western countries. [21] In Poland, it has been available since the 1970s, but the preparation was very rarely used. It was only after Poland's accession to the European Union that cytisine began to gain more popularity in Poland (and internationally), thanks in part to research led by Prof. Witold Zatonski. Despite this, it remains unavailable in many countries to this day, including the United States, or countries in Western Europe.

Mechanism of action: Cytisine is a partial agonist of nicotinic receptors, mainly the alpha4beta2 subtype. It competes with nicotine for the same receptors, and because of its stronger binding, it gradually displaces nicotine from them. At the same time, it has a weaker ability than nicotine to stimulate these receptors. Weaker than nicotine, it passes into the central nervous system. In the central nervous system, cytisine is believed to act on the mechanism that causes nicotine dependence and affects the release of neurotransmitters. It prevents nicotine-dependent full activation of the mesolimbic dopaminergic system and moderately increases dopamine concentrations in the brain, thereby alleviating central nicotine withdrawal symptoms. In the peripheral nervous system, cytisine stimulates and then paralyzes the vegetative ganglia of the nervous system , causing reflex stimulation of respiration and secretion of catecholamines from the medullary part of the adrenal glands,

raises blood pressure and counteracts peripheral nicotine withdrawal symptoms. This makes it possible to achieve a gradual reduction in the body's dependence on nicotine and weaning from smoking with fewer withdrawal symptoms [22].

The duration of treatment is 25 days. With the duration of therapy, the number of pills taken decreases. You should definitely quit smoking no later than the 5th day after starting treatment.

The most common and main side effect is gastrointestinal disorders, which occur with higher frequency for cytisine than in the placebo group (12% vs. 7.2%). In contrast, there were no significant differences between cytisine vs placebo for headache, insomnia, nausea. No differences were found in the total incidence of all adverse effects. [23]

NRT - Nicotine replacement therapy (Nicorette, NiQuitin)

Nicotine replacement therapy was approved in 1984 in the United States. It is the most widespread and best-studied treatment for tobacco dependence syndrome. Treatment consists of replacing tobacco smoke with pure nicotine, which has little biological harm and suppresses the symptoms of nicotine craving when smoking is stopped.

Mechanism of action: nicotine works by stimulating neuronal nicotinic acetylcholine receptors (nAchR) in the ventral tegmental area of the brain, resulting in the release of dopamine in the nucleus accumbens. It thus leads to a reduction in nicotine withdrawal symptoms in regular smokers who abstain from smoking. [24] It does not completely eliminate withdrawal symptoms, as none of the available nicotine delivery systems reproduce the rapid and high nicotine levels achieved when inhaling cigarette smoke. All available therapeutic nicotine products rely on systemic venous absorption and therefore do not achieve such rapid systemic arterial delivery. High doses of nicotine reach the brain from the cigarette within seconds. Therapeutic products reach lower levels within minutes (e.g., for lozenges) and hours (for transdermal patches). [24] NRT products come in various forms: gums, transdermal patches, nasal spray, oral inhaler, tablets. The transdermal patch is a slow release form of nicotine delivery. Different dosages are available which, on the one hand, allows for better adjustment depending on the degree of addiction, and on the other hand, allows the body to gradually adjust to lower nicotine levels and eventually to a nicotine-free state. Other products than transdermal patches, on the other hand, are acute dosage forms of nicotine - thanks to their immediate release, they provide rapid relief of cravings. Treatment time usually lasts 10 weeks. Those with intolerable withdrawal symptoms can be treated with

combination therapy. The most common combination is a 7, 14 or 21 mg transdermal patch and any form of acute form (gum, lozenges, nasal spray, etc.). [25]
The most common side effects include pruritus (22%), vivid dreams (16.6%), insomnia (14.5%), nausea (8.3%), headache (6.2%), vomiting (2.5%) and dizziness (7.5%). [25, 26]

Efficacy evaluation

The EAGLES study, a randomized, double-blind clinical trial involving 8144 smokers, directly compared the efficacy and safety of varenicline, bupropion, nicotine patch and placebo showed a significantly higher 6-month quit rate with varenicline (21.8%) than with bupropion (16.2%) and nicotine patch (15.7%). Each therapy was more effective than placebo (9.4%). Combining nicotine patches with other NRT products is more effective than using a single NRT product. Combining drugs with different mechanisms of action in some studies increased smoking cessation rates compared to using a single product. [27] E.g., one network meta-analysis showed that, compared to placebo, the combination of varenicline with bupropion had the best effect of all combination therapies (odds ratio (OR) = 6.08, 95% confidence interval (CI) [3.47, 10.66]). In addition, the combination of varenicline with bupropion was superior to varenicline with nicotine replacement therapy (OR = 1.66, 95% CI [1.07, 2.59]). [19] Although the aforementioned therapies have well-documented efficacy in smoking cessation vs placebo, the results of combination therapies in different studies may vary. E.g., the combination of varenicline with NRT shows higher efficacy in various studies, while others show no additional benefit from the combined intervention. [28, 29]
In the case of cytisine, evaluating the efficacy of this drug is more difficult. Most meta-analyses compare results for varenicline, bupropion, NRT and placebo. Due to the lack of cytisine in these studies, only separate papers mainly comparing cytisine vs placebo (and not yet for varenicline, bupropion, or NRT) can be cited. In one such meta-analysis covering various papers from 1968 to 2011, cytisine was more than one and a half times more effective than placebo (RR=1.59; 95% CI 1.43 to 1.75). In contrast, another meta-analysis including 2 studies from 2008 and 2011 providing follow-up for 6 months showed more than 3-fold efficacy in smoking cessation vs placebo (RR=3.29; 95% CI 1.84 to 5.90). [23] While the experience over cytisine is consistent regarding the drug's efficacy itself, there is a small body of research relative to varenicline, bupropion or NRT.
In summary, varenicline is the most effective drug in monotherapy. Bupropion, NRT and cytisine show lower efficacy and have a different mechanism of action. Therefore, they can be

interchangeably chosen in subsequent attempts to quit smoking, depending on the individual patient's needs. Combination therapies are more effective than monotherapies, with varenicline + bupropion being the best documented combination. Also, nicotine replacement therapy is more effective with a transdermal patch + lozenge, for example, than a single nicotine replacement product.

Cost analysis

The cheapest form of therapy is cytisine. 1 pack of 100 tablets is sufficient for the full treatment time, i.e. 25 days, and costs about 60 zlotys. On the other hand, the most expensive is varenicline, which is used for 12 weeks and you have to pay PLN 960 - 1260 for the treatment. For nicotine replacement therapy, the price depends on the duration of treatment. For example, 7 transdermal patches (enough for 7 days) cost about 70 zlotys, and for 10 weeks (which is the maximum duration of use) - 700 zlotys. In the case of gums, 8-12 units per day are usually used, for several weeks, resulting in a similar cost to the patch.
Bupropion is used for 7-8 weeks. For the original drug (Zyban) you have to pay about 900 zloty. Generic drugs, on the other hand, cost about 250 zlotys, but have no registration for treating nicotine addiction.

Conclusion:

Analysis of available data indicates that varenicline, bupropion, cytisine and nicotine replacement therapy are valuable tools in the smoking cessation process. Each of these agents has shown some effectiveness in reducing nicotine cravings and facilitating quitting. The choice of a particular drug can be tailored to the patient's individual preferences, clinical factors and other determining factors. In the therapies described, drugs can be used alone or in combination. Of these, varenicline was designed from the outset as an anti-smoking drug and has shown the highest efficacy. However, it should be noted that this therapy is expensive and can cause side effects in the first month of treatment. Cytisine, on the other hand, is the cheapest drug and is not inferior in effectiveness to bupropion and nicotine replacement therapy. It also has few side effects and is safe. However, it is important to note that its effectiveness is not as well documented as that of other therapies, mainly due to its lower popularity in Western countries. In the case of nicotine replacement therapy, the benefits include a simple mechanism of action (delivery of pure nicotine without harmful substances

from tobacco smoke), the ability to choose different forms of nicotine delivery depending on patient preference (patches, lozenges, aerosols, etc.) and easy availability. Bupropion, on the other hand, has additional benefits that the other three drugs do not, such as better weight control when trying to quit smoking, and treatment of depression. However, caution should be exercised due to the existence of serious contraindications and the numerous interactions that bupropion has with other drugs, which may pose some risks. In conclusion, the drugs in question can significantly help in the fight against tobacco addiction. Given that 70% of addicts want to quit smoking and on average make 6 attempts before achieving long-term abstinence, a properly integrated approach to pharmacotherapy can make it much easier to permanently break the smoking habit.

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