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REVIEW

NEW TRENDS IN THE TREATMENT OF NICOTINE ADDICTION

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Abstract: The aim of this study was to discuss the therapeutic substances used to treat nicotine addiction, not registered in Poland. This paper presents the results of the latest clinical trials and the possibility of their use in the treatment of nicotine addiction. The first two discussed drugs – clonidine and nortriptyline are recommended by clinical practice guidelines AHRQ (Agency for Healthcare Research and Quality) as the substance of the second line in the fight against addiction. Nortriptyline belongs to tricyclic antidepressants. Its mechanism of action is the inhibition of the reuptake of norepinephrine. It is suggested as the antagonist of activity of nicotinic receptors. The results confirm its efficacy in the treatment of nicotine addiction, but many side effects limit its use. Clonidine acts presumably by inhibition of sympathetic hyperactivity characteristic of symptoms associated with nicotine rehab. The remaining compounds under discussion, such as: venlafaxine, fluoxetine, moclobemide and rimonabant, are not registered in any country with an indication to use in the treatment of nicotine addiction, however, due to the mechanism in which they act, the possibility of their use in the treatment of this disease is considered. The possibility of using anxiolytics such as: buspirone, diazepam, meprobamate and β-blockers: metoprolol and oxprenolol is also considered in order to treat the anxiety appearing as one of the symptoms of abstinence. An interesting proposal to combat nicotine addiction are vaccines – NicVAX, CYT002-NicQb and TA-NIC. Currently, they are in clinical phase I and II of their development. Their operation would be based on the induction of specific antibodies that bind nicotine in the plasma, thus prevent it reaching the nicotinic receptors. Preliminary results confirm the possible positive effects in the prevention and treatment of nicotine addiction.

Keywords: nicotine addiction, nortriptyline, clonidine, bupropion, cannabinoid receptor antagonists, anxiolytic drugs, inhibitors of cytochrome CYP2A6, nicotine vaccines

According to the World Health Organization studies, in Poland, percentage of daily smoking women over 20 years old is 26%, and percentage of men in the same age is 43%. Epidemiological calculations showed, that in the year 2000 smoking was the reason of ca. 69 thousands of deaths in Poland (including: 57 thousands of men and 12 thousands of women) (1).

It has been proven, that smoking tobacco is the best known factor of many diseases. To the health consequences connected with tobacco smoking belong: diseases of circulation system, chronic obstructive pulmonary disease, hypertension, atherosclerosis and tumors. The big problem is also passive smoking, result of which is predominantly increased risk of lung cancer and ischemic heart disease (2–4). Epidemiological studies, referred to the effects of smoking on human health, which were conducted, confirm rightness of tobacco dependence fighting.

In Poland, one of the most frequently used questionnaire, which helps to discern tobacco addiction is Fagerstöm test (2, 5). It's used to measurement of pharmacogenic component of nicotine addiction. Maximal number of points, which can be obtained from this test is 10. Result equal or higher than 7 indicates probable pharmacological addiction. In this case, physician should consider introduction of pharmacological treatment (4, 6).

Currently, it its believed that doctor – patient conversation and motivating the patient by doctor to stop smoking, and stay in abstinence as long as pos-

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sible has a great importance. But besides „conversation" , pharmacological treatment is also used, as a help for patient in smoking quitting process, especially to relieve withdrawal symptoms.

In Poland, first choice drugs, which are used in nicotine addiction are nicotinic replacement therapies and bupropion SR (3, 4). Quite popular drugs also used in fighting the addiction are varenicline and cytisine. The choice of drug is usually a result of doctors experience in use of certain product, occurrence of indications and preferences and individual patient characteristics (3).

Second line drugs in America, but not registered for nicotinism treatment in Poland, are clonidine and nortriptyline. Despite the demonstrated effectiveness of treatment nicotine addiction, the use of them is limited, mainly due to side effects, which are occurring more often than for the first-line drugs). This drugs are not approved by FDA (Food and Drug Administration) as drugs used for nicotinism treatment, but are recommended by AHRQ (Agency for Healthcare Research and Quality) in some cases: when using of first-line drugs (individually or in the therapy complexes) is not bringing effects or they are contraindicated (4, 7–10).

Nortriptyline

It is a drug belonging to the tricyclic antidepressants. Its effect in the treatment of nicotine addiction results from inhibition of the reuptake of norepinephrine. It has a relatively high affinity for both the serotonin receptors and serotonin conveyors, as well as dopamine transporters. There is evidence that nortriptyline acts as a weak antagonist of nicotinic receptors, suggesting a potential mechanism of action in the fight against nicotine addiction (10–12).

The effectiveness of nortriptyline as a medicament that helps to stop smoking were evaluated in two double-blind placebo-controlled studies. In each of these studies were involved approximately two hundred people. From these studies were excluded those, who suffered from depression after their inclusion in the study, in order to eliminate the effects of non-action of the antidepressant nortriptyline. It was found that the use of nortriptyline statistically increases the number of people who stopped smoking in comparison to the number of people who stopped smoking using placebo. There was two-fold increase in the smoking cessation one year after the start of therapy, resulting from the use of nortriptyline *versus* placebo. In subsequent studies, a fivefold increase was found. These studies involving 413 test persons, suggest that nortriptyline may be helpful in quitting smoking (13). Other studies have shown that nortriptyline combined with transdermal nicotine system increases the frequency of stop smoking over the average observed when using only nicotine transdermal patches (14). In the treatment of nicotine dependence by nortriptyline, dosages applied were between 25 mg and 100 mg per day (15).

Nortriptyline, an antidepressant medication from the group of tricyclics, may increase the risk of suicide (4). Other side effects in the use of tricyclic antidepressants may be a block of: muscarinic receptors, (which results in: dry mouth, dim vision, constipation, urinary retention), histamine H1 reepors (which results in: sedation, sleepiness, weight gain), and α1-adrenergic receptors (which results in orthostatic hypotension) (4, 16, 17). Although nortriptyline may have any of the these side effects mentioned above, it is considered as one of the least sedative tricyclic antidepressants, as well as is rarely associated with orthostatic hypotension (17).

Clonidine

Clonidine is the second of the drugs recommended in the treatment of second-line treatment of nicotine addiction by AHRQ clinical practice guidelines. Furthermore, a drug is used to treat withdrawal symptoms occuring during treatment of opioid and alcohol addiction. Its effects are probably related to the reduction of sympathetic overactivity, characteristic for withdrawal symptoms (11). Clonidine is an agonist of α2-adrenergic receptors and is usually used as a medicine against hypertension. In connection with the possibility of the emergence of withdrawal reactions, characterized by a sudden increase in blood pressure, which can lead to hypertensive crisis, the elimination of clonidine treatment has to be done slowly (11).

Clonidine activity was evaluated in three meta-analyses, which rated the results of research on the impact of clonidine on smoking cessation. One of the meta-analyses based on the conclusions of nine randomized controlled trials, double-blind, showed that clonidine is helpful in increasing the percentage of people's stop smoking (OR 2.36, 95% CI: 1.69–32.8) (18). The second meta-analysis has led to a similar conclusion: OR 2.0 (95% CI: 1.3–3.0) (19). Third among the meta-analyzes serving as a basis for AHRQ recommendations also showed that clonidine increases the percentage of people who stop smoking to a much greater degree than placebo (OR 2.1, 95% CI: 1.4–3.2) (16). On the basis of these meta-analyzes it was concluded that clonidine is an effective drug to help quit the habit in some

populations. So far it is not clear which patients most effectively react to treatment with clonidine. Studies suggest that clonidine is effective in women and ineffective in men, while other studies have shown similar effects of clonidine in both genders (20).

The use of clonidine is contraindicated in pregnant women, and among people inclined to risky behavior. The most common side effects of clonidine include: dry mouth, drowsiness, dizziness, sedation, above average fatigue or tendency to constipation (4, 11). During treatment, however, may be disclosed much heavier symptoms that clinicians and patients should be aware of, such as: allergic reactions, slow heartbeat and sometimes an increase or decrease in blood pressure (11).

In spite of this extensive research, the role of clonidine as smoking cessation aid is still unclear. In view of these uncertainties, the occurrence of side effects and the possibility of withdrawal reactions, clonidine is considered as a second-line help in quit smoking.

Antidepressants different than bupropion and nortriptyline

Recent studies suggest that smoking results from desire of self-compensation of mood disorders through administration of substance, which stimulates dopamine release and neurons connected with reward system. There are ongoing researches on possibility of using substances such as: venlafaxine, fluoxetine and moclobemide in treatment of addiction (11, 15). Results of current studies confirm that effectiveness of this drugs is comparable with placebo and nicotine replacement therapy (15).

The mechanism of pharmacological action, which is a condition for effectiveness of individual antidepressants is unclear. For example, nortiptyline has high affinity to norepinephrine and serotonin transporters, but bupropion has relatively low affinity. On the other hand, paroxetine, for which effectiveness as a drug which may be used in therapy of addiction wasn't demonstrated, has similar to bupropion and higher than nortriptyline affinity to dopamine transporters. According to what stays above, antidepressants action can not be explained only by analyzing of interaction with monoaminergic receptors (11).

Cannabinoid receptor antagonists

Endocannabinoids and their receptors CB1 and CB2, which are located on surface of neurons, are forming endocannabinoid system. This structure is responsible for regulation of synthesis and release of γ-aminobutyric acid, which controls synthesis of dopamine (reward system). It has been shown that for addicted persons that system is deregulated and that receptors CB1 are hyperactive. These receptors play a role in cerebral system of reward, control of food intake, substance abuse and habitual behavior (11). Rimonabant is a selective antagonist of cannabinoid receptor CB1 (which is located in brain, adipose tissue, skeletal muscles and liver (11)). In preclinical studies, drug intake resulted in reducing the amount of ingested nicotine. The efficacy of drug was assessed in Cochranes systematic review, based on reliable, randomized two clinical trials of third phase. Higher possibility of stop smoking and maintenance of abstinence after one year was observed in group of patients to which rimonabant was given in the dose of 20 mg/day, compared with placebo (OR: 1.46, 95% CI: 1.16–1.85) (21).

In clinical trials, clear evidence about rimonabant effectivenes was not observed. Usage of rimonabant probably contribute to significant reduction of weight gaining, after quit from smoking. The most common side effects of rimonabant are diarrhea and upper respiratory tract infection. The impact of rimonabant on the cardiovascular system was not noticed so far. According to that, this drug seems to be safe and may be used in nicotine addictional treatment, with using it's preventing weight gain property, which is disruptive side effect in the process of quitting smoking for many addicted. However, the introduction of rimonabant as a drug used in nicotine dependence should require more studies (11).

Anxiolytic drugs

Suggestions about usage of these drugs in the treatment of nicotine dependence are due to the fact that nicotine has properties to reduce anxiety and tension. Anxiety may also be one of the symptoms that arise from abstinence. The use of anti-anxiety medication would be designed to reduce withdrawal symptoms. Suggested anxiolytics include: buspirone, diazepam, meprobamate, ondansetron and β-blockers (metoprolol and oxprenolol) (22, 23).

Inhibitors of cytochrome CYP2A6

In human body, ca. 70–80% of nicotine is metabolized to cotinine and this transformation is catalyzed by CYP2A6 enzymes. It was shown that polymorphic differences in formation of these enzymes are important in pharmacokinetics of nicotine and formation of dependence. Considering these data, we can conclude that inhibitors (specific

block) of CYP2A6 may be used in nicotine addiction treatment. There are suggestions about possibility of using them together with nicotine replacement therapy (NRT), which may increase the level of nicotine without changes in its dose (11, 24). It was observed that using strong inhibitors of CYP2A6 – methoxsalen and tranylcypromine together with nicotine chewing gum, a significant increase of levels of nicotine in plasma and reduction of the urge to smoke (25, 26) occurred.

Opioid receptor antagonists

Nicotine exposition is connected with activation of cholinergic nicotine receptors, resulting in a release of neurotransmitters (including endorphins). Their presence is associated with a reduction in anxiety and tension and the feeling of pleasure and relaxation. There are opinions that using of antagonists of opioid receptors, can reduce rewarding of nicotine action. In one study conducted on rats, it was demonstrated that opioid receptor antagonists, such as naloxone or naltrexone, reduce the number of cigarettes smoked, lower satisfaction with smoking and increase the likelihood of quitting smoking (27). This study suggests that opioid receptors can modulate the reinforcing effects of nicotine (28).

GABAergic drugs

Theoretically, GABA neurotransmission affecting drugs can reduce reinforcing effects of nicotine that can be helpful in fight against tobacco addiction (29). Proposed for this kind of action drugs are: vigabatrin, baclofen, gabapentin and tiagabine. Results of studies of these drugs show that there are neurobiological mechanisms through which GABA neurotransmission affecting drugs can be helpful in treatment of tobacco dependence. Unfortunately, until now, relatively few studies considering these drugs have been conducted. However, considering results of laboratory and preclinical studies, it may be possible that in the future, these drugs may be used in such treatment (11).

Mecamylamine and lobeline

Drugs contained in this group previously have already been assessed earlier in terms of their usefulness in the treatment of tobacco addiction. Both drugs are characterized by a low efficiency, and low side effect profile (11). Mecamylamine is a noncompetitive antagonist of nicotinic cholinergic receptors. In theory, an antagonist should block the physiological effects of nicotine, including its reinforcing effect. Consequently, the use of mecamylamine should lead to a reduction in the desire to smoke a cigarette (30). It was found in some cases that mecamylamine given smokers instead of decreasing, increases nicotine craving and may even tempt to reach for another cigarette (30, 31). There is evidence that mecamylamine is useful in treating nicotine dependence in certain "resistant" smokers. A limitation to its use are side effects such as: hypotension, dizziness and constipation (31).

Lobeline, along with nicotine, was one of the first drugs used in the treatment of nicotine dependence (32). Lobeline is the alkaloid and nicotine receptor agonist, obtained from the leaves of the bloated lobelli ((*Lobelia inflata*). Starting from the thirties of the twentieth century, it was often used in the form of different preparations. A recent study on the effectiveness of lobeline in long-term treatment of addiction provides evidence proving that lobeline may be helpful in stopping smoking. Side effects of lobeline include: nausea, dizziness and vomiting. Tablets and pills containing lobeline can cause irritation of the throat (32).

Nicotine vaccine

Studies on the development of nicotine vaccines are now in progress (phase I and II clinical trials). The principle of operation is based on the fact that nicotine vaccines induce the production of antibodies, which can bind the particles in the plasma nicotine, preventing it to reach the call characteristic of receptors and the effect of smoking. In one of the study, rats were given the active vaccine or placebo, and 30 min later they were given nicotine at a dose of 0.03 mg/kg intravenously, corresponding to acceptance by smokers nicotine contained in two cigarettes (33). Compared with the control, the vaccine reduced the concentration of nicotine in the brain in dose dependent manner (65% decrease in the concentration at the highest doses). The use of vaccine prior to the administration of five doses of nicotine (corresponding to 10 cigarettes burn) over the period of 80 min also changed the distribution of nicotine to the brain (11). Potential mechanisms and clinical usefulness of vaccines is intriguing. On the one hand, thanks to anti-smoking vaccine smoking ceases to give pleasure, and it helps to break the addiction, but on the other hand, as a result of significant reduction or elimination of nicotine reaching the brain, some smokers will increase the dose of nicotine taken in order to provide commonly used (before treatment) doses.

The results of the studies so far have indicated the use of such vaccines in preventing relapse of addiction. They may also be used among adolescents as a preventative treatment for preventing

smoking. Undoubtedly, further studies are evaluating the potential benefits and ethical implications of such an intervention (34).

There are several companies conducting clinical trials of anti-nicotine vaccines. Among them are: Nabi (NicVAX [Nicotine Conjugate Vaccine]), Cytos (CYT002-NicQb), and Celtic Pharma (TA-NIC) (35). NicVAX vaccine consists of a hapten 3'-aminomethylnicotine, which was connected to protein A obtained from the *Pseudomonas aeruginosa* (11). Preclinical studies have shown that vaccination with NicVAX prevents nicotine to reach the brain and blocks the effects of nicotine, including effects that can lead to addiction. Clinical studies have shown that vaccination with NicVAX of smoking people who sincerely want to quit smoking in conjunction with the patient's motivation to quit smoking and abstinence as long as possible by a physician, has significant beneficial effects for quitting smoking. In the second phase of clinical trials, 68 smokers not interested in quitting are given three different doses of the vaccine or placebo (36, 37). The vaccination took place on the following days of the therapy: 0, 28, 56 and 182. The subjects were monitored for a period of 38 weeks. The results showed that the vaccine is safe to use and well tolerated. In addition, although there was no attempt on its effectiveness, it has been observed that the ratio of 30-day abstinence was significantly different among the doses, and the highest rate was characterized by the highest dose of vaccine administration. There was no increase in the number of test persons of cigarettes smoked in order to compensate for the nicotine neutralization effect was observed among the patients. In November 2011, the results of phase III of clinical trials with NicVAX® in which the treatment not meet the primary endpoint were published. Further studies of phase II of the trials with NicVAX in combination with varenicline also fail to meet the primary endpoint. Currently, the clinical trials concerning the NicVAX vaccine have been discontinued (38).

The vaccine CYT002–NicQb is based on a virus-like particle obtained by a recombination of the bacteriophage Qb mantle protein. In the first phase of clinical trials, two intramuscular injections or a placebo were given to a group of 40 healthy and non-smoking volunteers in four-week intervals (39). Specific IgM antibodies began to appear after 7 days and IgG after 14 days. The level of antibodies has been increased after the second injection. It has been shown that the vaccine is safe and well tolerated. In phase II of the clinical trials (double-blind sample), 340 people addicted to cigarette smoking were vaccinated using the said vaccine 5 times in one-month intervals (40). Among the subjects showed a negligible abstinence, lasting 2–6 months, slightly higher compared to the abstinence people used a placebo. A significant effect was found among a group of people who have demonstrated high levels of antibodies. Moreover, it was not observed that people who re-started smoking compensated for the nicotine's neutralization effect by increasing the number of cigarettes smoked (40).

Immunotherapeutic vaccine TA-NIC has been evaluated in two phase study conducted in the UK, studying 120 smokers. During the study there were no adverse side effects. The vaccine's effectiveness is comparable to the placebo's effect (41, 42).

In summary, it can be stated that the nicotine vaccines may be effective in the treatment of tobacco addiction, however, the approval of these products probably will take several years.

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