REVIEW ARTICLES

Update on the Treatment of Smoking Dependence

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Introduction

Nicotine is the main alkaloid of tobacco smoke and the principal modulator of the psychopharmacological effects associated with the behavior of smokers.[1] The way nicotine modulates smoking behavior is by stimulating the release of dopamine in the nucleus accumbens of the mesolimbic system,[2] a function common to all substances with psychoactive properties.[3] When stimulated, the nicotine receptors located in the mesostriatal dopaminergic neurons promote the release of dopamine in these areas. This is how nicotine produces behavioral stimuli and sensations of pleasure.[4]

The increase in dopamine secretion in the nucleus accumbens caused by repeated administration of nicotine is subject to a phenomenon of behavioral sensitization,[5] which promotes the association between the ability of nicotine to produce pleasure or euphoria and the environmental cues or stimuli that predict the release of dopamine,[6] and it is this mechanism that modulates the smoking reflex.

Another important factor in this process is that smokers inhale nicotine in the form of tobacco smoke. Once inhaled, the smoke is distributed throughout the bronchial tree, from whence it is transported to the central nervous system so quickly that it is estimated that a nicotine bolus is delivered to the cerebral tissue 10 seconds after the smoke is inhaled. Moreover, tobacco smoke is rich in other compounds that can enhance the addictive effect of nicotine. Consequently, cigarette smoking is an almost ideal delivery system for an addictive drug since it increases the potential of the substance for causing dependence. This explains why tobacco is one of the most difficult addictions to break.[7]

However, well directed interventions aimed at promoting tobacco cessation are essential if we are to prevent tobacco-related morbidity and mortality, making this one of the chief missions of doctors specialized in respiratory diseases. In this context, various scientific societies have published guidelines summarizing the most important findings and clinical practice recommendations related to tobacco cessation.[8,9]

The treatment of nicotine dependence, like that of any other chronic disease, takes various forms, and pharmacotherapy is a crucial element in a multidisciplinary strategy. Various effective tobacco cessation treatments are currently available. Unless contraindicated, these treatments should be administered to all patients who are willing to quit smoking, and physicians should bear in mind that the overwhelming majority of patients who seek medical help are in a preparatory phase.[10]

The guidelines drawn up by the American College of Chest Physicians[9] and the National Institute for Clinical Excellence[11] recommend only 5 first-line drugs for tobacco cessation: bupropion, nicotine patch, nicotine gum, nicotine inhaler, and nicotine nasal spray. All of these therapies have been shown to significantly increase smoking cessation rates in various clinical trials, and have been approved by the US Food and Drug Administration and the European Drug Agency as effective products suitable for consumption. However, as has been indicated in an earlier article,[12] other treatments exist, which, while not marketed specifically as tobacco cessation therapies, have been used for this purpose with diverse results.[13-15]

Nonpharmacological Tobacco Cessation Therapy

Behavioral Therapy

Nicotine addiction involves psychological or psychobehavioral dependence, in addition to physical dependence. For this reason, various psychological techniques have been developed, which are aimed at enhancing the efficacy of tobacco cessation therapies. These treatments can be divided into 2 broad classes, individual therapy and group therapy.

In individual therapy the patient is followed up for 1 to 2 years. A patient-therapist relationship is established in which the former explains all of his or her apprehensions about tobacco use and fears of relapse. Furthermore, the therapist and patient discuss the possible appearance of withdrawal symptoms, how to deal with high risk situations, as well as the suitability of different pharmacotherapies and how these work. The structure and number of sessions and the interval

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between them is established on an individual basis according to the needs of the patient. Lancaster and Stead,[16] whose objective was to determine the efficacy of individual counseling as a aid to tobacco cessation, identified 11 published trials. Ten of these compared individual counseling to a minimal intervention, 2 compared different intensities of counseling, and 1 compared individual counseling to group therapy. The main result found was that individual counseling was more effective than the control therapy. The odds ratio for successful tobacco cessation was 1.55. There was no evidence that more intensive counseling was more effective than brief counseling, and neither was a significant difference in effect found between individual counseling and group therapy.

Group therapy is based on the commitments the individual members of the group—all of whom suffer from the same problem—make to each other, and on the mutual support they give each other. Such programs also offer participants the opportunity to learn behavioral techniques that will help them in their quit attempt. In group therapy sessions, smokers talk about their experiences, and particular attention is paid to the problem of relapse; participants are given advice on how to prevent relapse. Exhaled carbon monoxide is monitored at every session. The number of participants in each group should be between 5 and 15. The presence of 2 therapists is considered necessary. These professionals mix among the group in order to make sure that the director does not adopt the role of group leader.

A meta-analysis[17] evaluated the efficacy of group therapy by analyzing 13 studies that compared group therapy with self-help programs. The conclusions were that more people quit smoking with the assistance of group therapy (an odds ratio of 2.10), and that such programs were more effective than non-intervention or brief interventions (an odds ratio of 1.91). In 2 trials it was not demonstrated that group therapy was more effective than individual counseling when the intensity of both therapies was similar. It is interesting to note that there was evidence that group therapy generates extra benefits when associated with other smoking cessation aids, such as the various forms of nicotine replacement therapy (NRT).

Pharmacological Tobacco Cessation Therapy

Bupropion

Bupropion is currently the only pharmacological therapy not based on nicotine that has proven effective as an aid to smoking cessation. This fact has been recognized by numerous guidelines.[8,18]

The exact mechanism of action of bupropion is unknown. It has, however, been postulated that the action of inhibiting the neural reuptake of noradrenaline, serotonin, and dopamine could be responsible for the therapeutic effect of this drug. It is possible that bupropion reduces the smoker's need for nicotine without causing the symptoms of tobacco withdrawal by increasing the concentration of these monoamines in the neuronal synapsis of the nucleus accumbens and locus ceruleus.[19] Moreover, its effects of increasing the flow of dopamine, noradrenaline and, indirectly, of serotonin in the central nervous system could contribute to the reduction of other symptoms associated with tobacco withdrawal syndrome.[20]

The efficacy of bupropion has essentially been demonstrated by the work of Hurt et al[21] and Jorenby et al.[22] In 1997, Hurt et al published the results of a multicenter, randomized, double-blind, placebo-controlled study. The smoking cessation rate 6 weeks after completion of treatment was 19% in the placebo group and 44.2% in the group that received bupropion 300 mg (P<.001). Results for the same groups at 1 year reveal that the cessation rate had dropped to 12.4% in the placebo group and 23.1% in the bupropion group (P<.01).

The multicenter trial carried out by Jorenby et al,[22] published in 1999, compared the efficacy of bupropion and nicotine patches administered alone or in combination, and placebo. Analysis of the results at 4 weeks revealed an abstinence rate of 33.8% in the placebo group as compared to a significantly higher rate in the 3 other groups (48% in the group treated with nicotine patches [P=.05], 60.2% in the group receiving bupropion [P<.001], and 66.5% in the group treated with nicotine patches and bupropion [P<.001]). Analysis of the continuous abstinence rate on follow up at 1 year showed that the rates remained significantly higher (P<.001) in the 3 active-treatment groups than in the placebo group, although the percentages fell to 5.6% in the placebo group, 9.8% in the nicotine-patch group, 18.4% in the bupropion group, and 22.5% in the group treated with both nicotine patches and bupropion.

The efficacy of bupropion measured by the number of patients who quit smoking, is variable, ranging from 21% reported recently by one author[23] to 58.6% continuous abstinence at 12 months reported for another study[24] in which the patients received combined treatment of bupropion plus nicotine patches.

In their evaluation of the safety of the drug, Hurt et al[21] reported the occurrence of various adverse events during the cessation period; headache, rhinitis, and anxiety were as prevalent in the control group as in the treatment group, which led the authors to attribute these events to abstinence from tobacco rather than to the pharmacological treatment. There were significant differences between the groups with respect to dry mouth, which occurred in 13% of the patients treated with bupropion. Another side effect reported was insomnia, which affected 34.6% of the patients treated with bupropion 300 mg. Jorenby et al[22] also reported insomnia (42.4% in the bupropion group and 47.5% in the group treated with bupropion and nicotine patches). Other, rarer, side effects were reported by Tripathi and Greenberger,[25] who described a serum sickness-like reaction characterized by dyspnea, angioedema, and

petechiae. Finally, Patten et al[26] described the appearance of 5 cases of increased depression among patients included in the 2 clinical trials mentioned above. The patients affected had a prior history of depression, and the frequency of this side effect was between 0.25% and 2.7%.

With respect to the optimum length for bupropion treatment, in most of the trials drug was administered for a period of no more than 8 weeks. However, some authors advocate a longer treatment period (45 weeks) in order to achieve greater control of craving.[27]

Another interesting fact reported in the literature is that not all smokers manage to quit smoking after starting treatment with bupropion. For this reason, various predictive models have been drawn up with the object of identifying the profile of the smoker ideally suited to this kind of treatment. Dale et al[28] carried out a multicenter trial enrolling over 600 patients treated for 7 weeks with bupropion. Logistic regression was used to identify predictors of smoking abstinence. Unifactorial analysis identified the following predictors: the dose of bupropion used, older age, lower number of cigarettes smoked per day, lower physical dependence on nicotine (measured using the Fagerström test), the longest time abstinent during a prior quit attempt less than 24 h, longest period of abstinence during a prior quit attempt more than 4 weeks, absence of other smokers in the household, and a greater number of prior quit attempts. Subsequently, on multivariate analysis using as candidates only those variables with a *P* value less than .01, the authors concluded by stating that bupropion was effective in treating cigarette smokers, and that the variables "lower smoking rate," "male sex," and "brief periods (ie, <24 hours) or long periods (ie, >4 weeks) of abstinence in prior quit attempts" were predictive of better outcomes regardless of the dose of bupropion used. In the same work the authors also explained that complete abstinence after the first two weeks of bupropion treatment was the most important predictor of patients who achieved long term abstinence. Other authors[29] have reported that patients with a higher anxiety level in their personality traits respond better to treatment with bupropion, and that this response is maintained at 3 and 6 months after starting treatment with this drug. Conversely, depression on starting treatment was shown to be a predictor of failure.

Nicotine Replacement Therapy

Nicotine is a highly addictive psychoactive substance comparable in this respect to amphetamines, cocaine and narcotics.[30] The effects of nicotine on the central nervous system depend on both blood levels and the occupation of the nicotine receptors in the brain,[31] so that when the smoker does not get sufficient nicotine he or she not only experiences the loss of the euphoric effects of the substance but also develops a withdrawal syndrome characterized by a series of symptoms, such as dysphoria, insomnia, irritability, anxiety, lack of concentration, decrease in heart rate, increased appetite, and weight gain.[32]

NRT is defined as the administration of nicotine by a means of delivery other than the inhalation of tobacco smoke, in quantities sufficient to alleviate withdrawal symptoms but not large enough to cause dependence. The withdrawal symptoms associated with tobacco cessation can be controlled by any of the forms of NRT as long as blood nicotine levels greater than 5 ng/mL are obtained. Furthermore, none of the NRTs produce such high blood nicotine peaks or deliver nicotine so quickly as the inhalation of tobacco smoke, making it rare for individuals to become addicted to any of the various therapeutic forms of nicotine administration.

NRT is indicated for the treatment of all smokers of more than 10 cigarettes per day who express a desire to give up the habit.[33] NRT is a safe treatment, even in patients with cardiovascular disease[34-37] despite the chronotropic effects of nicotine. Joseph et al[34] studied 584 smokers with cardiovascular disease. These patients were divided into 2 treatment groups: one group received NRT for 14 weeks, and the other received placebo for the same period. The authors found no any significant differences between the groups with respect to mortality, myocardial infarction, or hospital admission.

Very few studies have been carried out on pregnant women treated with NRT. However, the studies that have been published on the use of nicotine patches and gum in this population have not reported any increase in adverse effects on the fetus over those produced by smoking cigarettes, and therefore they do not indicate that this treatment is inadvisable in pregnant women. What is clear is that patients who wish to use NRT should be advised to start treatment before the fourth or fifth week of pregnancy, which is the point at which the nicotine receptors in the fetal brain first appear.[38,39]

The combined use of different forms of NRT has been considered as an effective alternative for smokers who are unwilling to stop smoking, but who do want to reduce the number of cigarettes smoked per day, or for smokers who have failed in multiple prior quit attempts. The objective of such combined therapy would be to prevent the appearance of withdrawal symptoms and in this way help the patient to reduce daily consumption, and also, as a result of the initial success achieved, to increase the smoker's motivation to give up the habit altogether.[40]

High dosage NRT is a new treatment regimen that has recently been investigated. The usual NRT dose generally produces plasma nicotine concentrations of between 35% and 60% of those obtained by the inhalation of tobacco smoke. This fact has been used as an argument to justify the use of larger doses than those conventionally used in order to achieve a higher percentage of successful attempts. Dale et al[41] demonstrated that high doses of NRT, which achieve between 90% and 100% of the values usually obtained by smoking tobacco, could be effective in the treatment of highly dependent smokers. The use of high-dose

NRT would be restricted to highly dependent smokers in whom tobacco cessation therapy has failed on numerous previous attempts. It should only be used under the supervision of specialized smoking dependence units.

Various forms of NRT are available in the Spanish market: gum, tablets, transdermal patches, inhalers, and nasal sprays. None of the many forms of NRT has been shown to be more effective than any other as an aid to tobacco cessation. They are, therefore, all equally effective, whether used alone or in different therapeutic combinations.[42-45]

One of the differences worth noting is that the forms of NRT that release nicotine slowly (patches) guarantee constant blood nicotine levels, making them ideal for the control of symptoms. The preparations that release nicotine more quickly deliver very high peak concentrations and can be used as a rescue medication when the patient is suffering from cravings or withdrawal symptoms.[46]

Gum. Nicotine gum is available in 2 mg and 4 mg formulations. The nicotine in the gum is bound to an ion exchange resin and is released gradually when the gum is chewed. Oral absorption is, therefore, conditioned by the chewing technique used. The gum should be chewed slowly until a strong flavor is noticeable; this indicates that the nicotine is being released. At this point, the user should stop chewing and park the wad under the tongue or between the cheek and gum until the strong flavor has disappeared, at which time the gum should be chewed again. When used correctly, the gum can produce nicotine plasma concentrations of 5 ng/mL to 10 ng/mL at 30 minutes.[47,48] Patients should be aware that acidic drinks and coffee consumed at the same time as the nicotine gum is used may impair nicotine absorption.

The adverse events most commonly reported are gastric and oropharyngeal disorders and pain in the temporomandibular joint.

The dose administered will depend on the degree of the patient's nicotine dependence; thus a dose of 2 mg should be administered to smokers with low dependence and 4 mg to those whose dependence is moderate to high.[49] The recommended duration of treatment is between 3 and 6 months. Although no differences in quit rate have been observed between nicotine gum taken ad libitum and according to a fixed dosage regimen, most recommendations specify a fixed regular dosage (1 piece of gum every hour) with a minimum of 10 pieces of gum per day during the first few weeks, after which the dose is tapered gradually over the subsequent weeks. Hughes and Hatsukami[50] propose the gradual reduction of the nicotine dose administered by way of gum only after the third month of treatment because abrupt suspension of treatment might give rise to withdrawal symptoms. Using nicotine gum in conjunction with a behavioral support program doubles the abstinence rate obtained with treatment with placebo or psychological therapy without any pharmacological support. The strength of evidence rating for this statement is the best (level A), meaning it has been demonstrated by a comprehensive meta-analysis of 50 double-blind, randomized trials.[49]

Two factors appear to be fundamental in achieving success with nicotine gum treatment: the degree of the patient´s dependence and the treatment setting. In patients with low or moderate dependence on nicotine there are no differences between the results obtained with 2 mg and 4 mg gum. However, when highly dependent patients are treated with 4 mg gum as compared to 2 mg gum, the cessation rate increases significantly. This has been shown by 3 studies.[51-53] Another factor that influences the success of treatment with nicotine gum appears to be the site where such treatment is administered. Cessation rates are higher when the patient is treated in a specialized smoking unit than when he or she attends a primary health care facility; this result can probably be explained by the need for specialized education in the use of the gum.[54]

Nicotine tablets. Nicotine tablets for the treatment of smoking dependence have only recently become available on the Spanish market. These are sublingual tablets containing 1 mg of nicotine. The 1 mg dose is equivalent to the 2 mg nicotine gum, and the tablets are, therefore, only recommended for use by smokers with low to moderate dependency. Dosage and length of treatment are identical to those of nicotine gum.[55] Patients should be instructed never to chew the tablets, which are designed to be held under the tongue until they dissolve, because the nicotine should be absorbed through the oral mucosa, and absorption in the digestive tract should be avoided.

Sublingual nicotine tablets cause only a few mild side effects, which basically take the form of throat irritation, increased salivation and digestive disorders.

The nicotine tables have been shown to be effective in randomized, double-blind trials enrolling 1818 smokers, in which the smoking cessation rate in the treatment group (15%) was double that achieved in the placebo group (6%).[56]

Transdermal patches. The transdermal nicotine patch is made up of 3 quite separate layers: a bottom layer that adheres to the skin; a middle layer containing the nicotine, and a third, protective top layer. The size of the patch conditions the quantity of nicotine administered. Patches measuring 30, 20, and 10 cm^2 contain 21, 14, and 7 mg of nicotine respectively, which is released over a 24-hour period. The patches that release the active ingredient over a 16-hour period contain 15, 10, and 5 mg of nicotine.[57] With this form of administration, maximum concentrations in the blood are achieved after 5 to 10 hours of wearing the adhesive patch on the skin. The plasma nicotine levels produced are usually half those obtained by inhalation of tobacco smoke, if we consider smokers of less than one packet

per day. These low plasma nicotine values could provide an explanation for the fact that withdrawal symptoms are not uncommon in patients receiving this type of therapy.

The transdermal patch should be adhered to clean, dry, hairless skin and changed every 24 hours.[58] The most frequent side effect is mild erythema and pruritus at the site of the patch so that the site should be varied.

Other side effects are caused by the absorption of nicotine into the system during the night when using the 24-hour patches, which can cause insomnia. However, this type of patch has the positive effect of providing early morning plasma nicotine levels and therefore controlling withdrawal symptoms on waking. Patients using 16-hour patches may experience withdrawal symptoms on waking.

The ease of use of this product and the minimal presence of side effects makes this a first-line therapy. Transdermal nicotine patches are indicated for smokers with slight to moderate dependency. In highly dependent smokers patches used alone do not increase the cessation rate.[59] Combination therapy with patches plus another form of NRT taken ad libitum increases the cessation rate in patients who are unable to quit using only one form of NRT.[60]

A treatment period of at least 6 to 8 weeks and not more than 12 weeks is recommended.[57] Extending treatment beyond 12 weeks does not increase the cessation rate (evidence = A). No difference in efficacy has been found between abrupt and gradual withdrawal of treatment (evidence = A).[61,62] No difference in efficacy has been found between the 24-hour and the 16-hour patches, although the 24-hour formulation is considered preferable in patients who suffer from early morning craving, and the 16-hour formulation is recommended for patients who suffer from insomnia or nightmares.[63] The recommended dosage is a maximum dose during an initial period of 4 to 6 weeks, followed by a gradual reduction in dose for the remaining weeks. The recommended regimen is a dose of 21 mg/24 hour for 4 weeks, 14 mg/24 hours for 2-4 weeks and 7 mg/24 hours for another 2 to 4 weeks.

This type of NRT achieves a quit rate double that observed with placebo. This has been demonstrated by a recent meta-analysis of 33 clinical trials, which reported a mean odds ratio for abstinence with patches compared to placebo of 1.76.[49] Richmond et al[64] monitored 305 smokers who were treated with nicotine patches for 10 weeks. The trial included a control group of patients who received a placebo treatment for the same period. On follow up at 3 years, the cessation rate for the group treated with NRT was 13.8%, compared to 5.2% for the control group. In a multicenter trial, Daughton et al[65] demonstrated the greater efficacy of 21 mg patches when compared with the other doses. This greater efficacy was sustained in the short (6 months) and long term. In that study, after 4 to 5 years of follow up, the rate of sustained abstinence was still 20.2% in the group treated with 21 mg patches, 10.4% in the group treated with 14 mg patches, 12.8% for the patients using 7 mg patches, and 7.4% for the placebo group.

A recent meta-analysis[49] analyzed 6 clinical trials that compared transdermal nicotine patch therapy at high doses to patches at standard doses. In 3 of these trials, 24-hour patches were used, and high doses (42/44 mg) were compared with the standard doses of 21/22 mg,[66-68] while in the other 3 studies, 16-hour patches were used, and high doses of 25 mg were compared with the standard 15 mg dose.[69-71] When the overall results of these 6 studies were evaluated, a small benefit was found in favor of the group of patients treated with high dose patches, with an odds ratio of 1.21 (95% confidence interval, 1.03-1.42). The use of patches at a dose higher than the standard dose can be considered for smokers of more than 36 cigarettes per day and those who present symptoms of craving or other withdrawal symptoms when treated with standard dose nicotine patches.

Nicotine nasal spray. This device delivers an aqueous solution containing nicotine at a concentration of 10 mg/mL to the nasal lining. Each single spray (0.05 mL) delivers 0.5 mg of nicotine, and a dose consists of 1 spray into each nostril (1 mg total). In contrast to the 3 forms of NRT discussed above, the nasal spray produces plasma nicotine concentrations rapidly with a maximum peak 5 to 10 minutes after administration.[72] The appearance of side effects, such as nasal irritation, itching, sneezing, and watering eyes, is common during the first few days, but these symptoms tend to disappear after the first few weeks of treatment. Nicotine nasal sprays are contraindicated in patients who suffer from chronic nasal diseases or serious bronchial hyperreactivity.[73]

Stapleton et al[74] studied 227 smokers, of whom 116 were given a nicotine nasal spray and 111 were treated with placebo. At 1 year, the abstinence rate was 28.4% for the group treated with the nasal spray and 12.6% for the placebo group. After 3.5 years of monitoring, only 15.4% of patients treated with the nicotine nasal spray and 6.1% of the placebo group remained abstinent. In an open multicenter study of 57 smokers, Jiménez-Ruiz et al[75] evaluated the efficacy of psychological support in combination with nicotine nasal spray at a dosage of 1 mg to 2 mg per hour for 3 months. The abstinence rate was 39% at 3 months and 35% at 6 months.

A meta-analysis of several trials involving nicotine nasal spray revealed a mean abstinence odds ratio of 2.27 (95% confidence interval, 1.61-3.20).[49] The abstinence rates at 1 year achieved using this device were similar to those obtained with other nicotine delivery systems, such as gum (18%), nicotine patches (14%), oral inhaler (17%), and sublingual tablets (20%).[49]

Ad libitum administration is recommended for 6 to 8 weeks, without exceeding a dose of 5 mg per hour (10 instillations) or a total of 40 mg per day (80

instillations). After this initial period, the dose should be tapered gradually until treatment is completed at 3 to 6 months.

Nicotine inhaler. Nicotine inhalers, still unavailable in Spain, consist of a plastic cylinder fitted with a mouthpiece enclosing a porous capsule containing 10 mg of nicotine and 1 mg of menthol. Each inhalation delivers approximately 16 µg of nicotine, which is absorbed through the oral mucosa. It would take 80 deep inhalations within 20 minutes to achieve blood nicotine levels similar to those produced by smoking one cigarette. The plasma nicotine concentrations achieved with the inhaler are in the vicinity of 33% of those usually found in smokers of 1 pack per day. The most common side effects are irritation of the oropharyngeal mucosa and coughing, and the inhaler is not recommended for smokers with bronchial hyperreactivity.

In 1991, Rose and Levin[76] reported that tobacco dependency is conditioned by stimulation of the sensory receptors located in the pharynx and larynx. This type of NRT offers 2 types of benefits: firstly, it reduces withdrawal symptoms because it directly stimulates the sensory receptors of the pharynx; and secondly, it modifies behavioral tobacco dependence.

The recommended dosage regimen is at least 6 capsules per day for 3 to 6 weeks, followed by ad libitum treatment for 6 to 12 weeks. After this, treatment should be tapered over the following 3 months.[72] Controlled, double-blind studies reveal a sustained abstinence rate at 3 weeks of 29% compared with 14% for the placebo group, and 24% and 10% respectively at 3 months.[77,78]

Other Treatments

Although the therapeutic arsenal for the treatment of smoking dependence is not extensive, studies carried out with the aim of finding drugs with an anti-tobacco action do keep appearing in the literature. These include vaccines, the promising inhibitors of the hepatic cytochrome P-450 2A6 enzyme (CYP2A6), and various drugs that stimulate the central nervous system or the nicotine receptors. These are discussed in this section.

Nicotine vaccine. In the context of drug addiction, the aim of a therapeutic vaccine is to stimulate the production of specific antibodies that will fix the target drug and alter its pharmacokinetic properties. The principal objective is to reduce the quantity of the substance available or its distribution to the brain.

The speed with which nicotine is delivered to the brain and the concentrations achieved are determining factors in the processes of both smoking initiation and habit maintenance.[7] We now know that high doses of nicotine produce reward stimuli much greater than those produced by low doses, and that rapid delivery to the brain stimulates a much greater reward response than slow delivery. For example, a cigarette produces a much greater reward response than a nicotine patch. The nicotine vaccine stimulates the production of nicotine-specific antibodies that can bind nicotine with a high affinity and fix it in plasma. Because of their high molecular weight, these antibodies are too large to cross the blood-brain barrier so that the nicotine fixed by the antibody is thus blocked from entering the brain. In this way vaccination can modify the amount of nicotine that reaches the central nervous system.

Pentel et al[79] describe a vaccine composed of nicotine bound to an exogenous protein carrier by way of a short link. These authors demonstrated that rats which received a series of 2 to 4 vaccine injections produced high titers of antibodies highly specific to nicotine at 4 to 8 weeks. The same authors subsequently injected the vaccinated rats with nicotine and found that the distribution of nicotine to the brain was reduced by 60%.

De Villiers et al[80] demonstrated that vaccination in rats reduces the release of dopamine in the nucleus accumbens. This is the key biochemical effect that modulates nicotine dependence. These authors also showed that passive immunization of rats (by perfusion of nicotine specific antibodies) reduces the effects on blood pressure and motor activity produced by a single dose of nicotine. These findings demonstrate the principal that nicotine-specific antibodies can reduce some of the effects produced by nicotine and allow us to contemplate the possible use of such a vaccine for the prevention of relapse. Quitting smokers who suffer from withdrawal symptoms relapse because the only thing that alleviates their discomfort is smoking. If the vaccine blocked the sensation of relief produced by smoking again, the smokers would have less reason to continue smoking. In a similar study, Lindblom et al[81] demonstrated that, after immunization with high titers of nicotine antibodies, rats trained to administer themselves nicotine did not reinstate nicotine self-administration behavior when they were again exposed to this drug. These results indicate that active immunization against nicotine may effectively abolish the reinforcing action of nicotine on the brain, an effect that is critical to relapse in nicotine dependence.

Although these results seem promising, their importance in relation to the development of a treatment aimed at modulating smoking behavior in humans is not yet entirely clear. Models of nicotine dependence in rats clearly differ from those of cigarette smoking in humans, both in the way the drug is administered (intravenous or intraperitoneal in rats and inhaled in humans) and the nicotine dose (the doses required are generally higher in rats because of their accelerated metabolism of nicotine), and in the behavior that accompanies the habit of smoking, such as conditioned reflexes and social context. A study of a broader variety of animal models could be useful, but in any case clinical studies of smokers will be necessary to determine whether the vaccine can be useful in humans. A key question with respect to the use of the vaccine in

humans is whether smokers would try to compensate for the reduction in the nicotine effect by smoking more. Since the efficacy of the vaccine depends on both the plasma concentration of nicotine-specific antibodies and the dose of nicotine administered, clinical studies are needed to assess the importance of the role of the reward system and whether it could compromise the vaccine's efficacy.

New treatments based on the inhibition of the hepatic cytochrome P-450 2A6 *enzyme.* Blood and brain nicotine levels obtained through smoking are the result of the balance between the number of cigarettes smoked and the speed at which nicotine is metabolized. Around 80% of nicotine is metabolized to the inactive metabolite cotinine by way of C-oxidation, and CYP2A6 is responsible for 90% of this process.[82] Variations in the activity of this enzyme account for individual differences in the rate of nicotine metabolism and therefore influence various aspects of smoking behavior, such as the ability to start smoking and become addicted to tobacco, as well as the maintenance of higher or lower levels of tobacco use.[83]

Smokers who metabolize nicotine slowly maintain higher blood nicotine levels and suffer more side effects during initial tobacco use, that is, when they first start smoking. Once they become dependent, these smokers require a lower intake of nicotine from cigarette smoking to maintain the same blood nicotine levels as those who metabolize this substance more rapidly.

Recent studies show that patients with inactive CYP2A6 alleles compensate for the reduction in their nicotine metabolism by smoking fewer cigarettes per day.[84,85] These individuals become dependent on tobacco later (3 years later), they smoke for fewer years, and they find it easier to quit (1.75 times more likely).[86]

Just as certain polymorphisms of the CYP2A6 gene reduce the individual's abililty to metabolize nicotine, the administration of CYP2A6 inhibitor drugs could be used, either alone or in combination with NRT, to modulate the activity of this enzyme and treat tobacco addiction.

CYP2A6 inhibitors would make the concomitant administration of oral nicotine possible because they reduce the effect of first-pass metabolism in the liver (70%) and facilitate gastrointestinal tolerance. Normally, when nicotine is administered orally only 20% to 40% of the dose reaches the bloodstream; the remainder is metabolized in the liver by CYP2A6. This means that the nicotine dose required to reach blood nicotine levels high enough to treat withdrawal symptoms is precluded because it would produce severe gastrointestinal disorders (nausea and diarrhea), which contraindicate its use. Concomitant administration of CYP2A6 inhibitors could reduce hepatic nicotine metabolism and increase nicotine bioavailability, so that the dose required to produce therapeutic blood levels would be lower and therefore obtainable without the side effects.

Sellers et al[87] evaluated the effect in 17 healthy smokers of 4 mg of nicotine taken orally combined with methoxsalen (a CYP2A6 inhibitor) at doses of 3.5, 10 or 30 mg, or placebo. Patients who received placebo and nicotine reached plasma nicotine levels of 4 ng/mL, while those who received 10 mg or 30 mg of methoxsalen and nicotine reached plasma nicotine levels of more than 9 ng/mL. The same patients later participated in a double-blind, randomized crossectional trial which evaluated 4 treatments: methoxsalen 30 mg or placebo combined with 4 mg of oral nicotine or placebo. Exhaled carbon monoxide concentration was 47% lower (4.6 vs 8.7 ppm) in the group of smokers treated with methoxsalen 30 mg plus nicotine as compared to those treated with placebo plus placebo. The number of cigarettes smoked was 24% lower in the active-treatment group as compared to the placebo group. Despite the small number of patients studied, the data from this trial demonstrates that CYP2A6 inhibitors can reduce the hepatic metabolism of nicotine administered orally; it also shows how combined therapy (oral nicotine plus CYP2A6 inhibitors) can decrease tobacco consumption.

NRT continues to be a first-line treatment in tobacco cessation. Its efficacy is, however, limited because no form of NRT is capable of producing plasma nicotine levels of more than 50% of those achieved by smoking. Moreover, interindividual variation in nicotine metabolism make it difficult to predict the effect of a given dose of NRT. A pharmacotherapy that inhibits nicotine metabolism used in combination with NRT should improve the efficacy of the latter by increasing the plasma nicotine levels obtained with the same dose, thus prolonging the duration of the NRT action and reducing interindividual variations in nicotine metabolism.

Future research should be oriented towards understanding the genetic variants of CYP2A6 and their clinical consequences with a view to developing new ways to prevent and treat tobacco dependence.[84,85]

Central nervous system stimulants. While central nervous system stimulants, such as methylphenidate, ephedrine, and caffeine were at one time considered useful in the treatment of smoking dependence, subsequent clinical experience has not provided any evidence to support a recommendation for their use in tobacco cessation treatment.[88]

Drugs that act as agonists or antagonists of nicotine receptors could be a therapeutic option in the treatment of tobacco dependence withdrawal syndrome. One of the nicotine agonists that has been evaluated is clonidine, an α_2 post-synaptic agonist. Although the results of several meta-analyses are inconclusive, some clinical trials report abstinence rates at 5 months almost double those obtained with placebo. The current recommendation is that clonidine could be effective as long as it is used under a physician's supervision and only as a second-line treatment.[89-91]

Drugs, such as mecamylamine and naltrexone, which block nicotine receptors, have not been shown to be effective treatments in tobacco cessation.[92,93]

Tricyclic antidepressants. Tobacco cessation rates twice those obtained with placebo have been achieved with the tricyclic antidepressants nortriptyline (administered at a dose of 25 mg/8h) and doxepin (at a dose of 50 mg/8h).[94-97] However, the use of these agents is restricted to smokers who are unable to quit using first-line drugs and to patients in whom the use of NRT and bupropion are contraindicated.

Monoamine oxidase inhibitor. The administration of these agents in the treatment of tobacco dependence is based on the fact that the level of monoamine oxidase found in smokers is lower than that found in nonsmokers.[98] Some authors report abstinence rates in patients treated with selegiline or moclobemide similar to those obtained with NRT, and always on follow up at 1 year.[99,100]

Serotonin reuptake inhibitors. Fluoxetine has demonstrated its efficacy in depressed smokers (evidence = B). Fluoxetine increased abstinence rates, as compared to placebo, at 1 to 3 months in smokers with minor depression, but not among smokers not suffering from depression.[97]

Anxiolytics. The efficacy of benzodiazepine anxiolytics (ie, diazepam, alprazolam) as a tobacco cessation treatment has not been demonstrated, and prolonged use of such drugs may lead to physical and psychological dependence so that their use is contraindicated.[101]

The results of treatment with nonbenzodiazepine anxiolytics, such as buspirone, have been inconsistent, and the current recommendation is that this type of drug should be limited to use as an alternative, second-line treatment.[102]

Upper airway stimulants. Based on the work of Rose and Levine,[76] who demonstrated that stimulation of the sensory receptors located in the pharynx and larynx could contribute to tobacco addiction, inhaled preparations of ascorbic acid, citric acid and extract of black pepper have been evaluated although currently no results are available that justify their use.[103]

Antabuse effect. The combination of tobacco smoke with silver acetate gum causes an unpleasant sensation in the smoker which could be helpful in tobacco cessation treatment. However the trials carried out have not demonstrated that this treatment increases abstinence rates.[104]

High-frequency transcranial magnetic stimulation. The mesolimbic dopaminergic reward system plays a crucial role in reinforcing tobacco use behavior. High-frequency repetitive transcranial magnetic stimulation of frontal brain regions has been shown to efficiently modulate the mesolimbic and mesostriatal dopaminergic system in both animals and humans. Eichhammer et al[105] evaluated the usefulness of this technique as an aid to tobacco cessation in 14 smokers. High-frequency stimulation of the left, prefrontal cortex was shown to reduce the number of cigarettes smoked although levels of craving were unchanged. These initially encouraging results need to be corroborated by future clinical trials.

Conclusions

Bupropion and NRT are currently the only recommended treatments for tobacco cessation. However, a large number of studies describe new active agents, in particular CYP2A6 inhibitors, which offer hope for the future in the treatment of smokers who wish to quit.

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