

## FOR PRACTICAL DOCTORS

UDK (Universal Decimal Classification) 613.846-055.2+515.2.03:813.846

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### PHARMACOLOGICAL REMEDIES FOR ANTI-SMOKING FIGHT

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According to epidemiological studies, smoking is one of the main risk factors not only of cardiovascular but also bronchopulmonary diseases (in particular, cancer of lungs) as well as diseases of other systems and organs.

Based on the International Classification of Diseases, Injuries and Causes of Death (WHO, 1977), tobacco smoking is attributed to the same category of disorders as alcohol, Indian hemp, hallucinogens and barbiturates abuse. Acknowledgement of tobacco dependence as a disease similar to alcoholism and narcomania forms the basis for drug methods to control smoking as a part of preventive medicine.

Table 1

Results of studying the efficacy of Nicorette (with the nicotine content of 2 and 4 mg)

Authors of studies	Year of publication	Additional intervention	Duration of treatment, weeks	Number of smokers	Number of people who gave up smoking		
					Nicorette	placebo	P
Fee, Stewart	1982	Lectures	5	352	46	33	<0.02
Pushka et al.	1979	Group treatment	3	160	70	55	<0.05
Fagerström	1981	Individual treatment	4	98	89	59	<0.05
Jarvis et al.	1982	Group treatment	4	116	62	33	<0.01
Malcolm et al.	1980	Individual treatment	4	210	34	37	Invalid data
British Thoracic Society (BTS)	1983	No intervention	4	802	27	26	Invalid data
Christen et al.	1982	Group treatment	6	208	34	11	<0.001
Schneider et al.	1983	Group treatment	4	60	76	50	<0.05
Hjaimarson	1983	Group treatment	6	205	77	52	<0.001

In spite of different ways of tobacco usage (snuffing, chewing and smoking in the form of cigarettes, mouthpiece cigarettes and cigars), they all have something in common: nicotine reaches the central nervous system without undergoing any metabolism or inactivation. Nicotine as a chemical compound forming a part of tobacco has effect on special-purpose receptors located in the brain and muscular tissues.

The goal of any method of anti-smoking fight is, first, to help the smoker quit smoking (if a smoker gives up smoking fast, this results in the tobacco withdrawal syndrome, in particular, within the first 24 hours, in the form of the following several symptoms: craving for smoking, irritability, anxiety, nervousness, difficulty to concentrate attention, headache, sleepiness and functional disorders of the gastrointestinal tract), second, to prevent the return to smoking, especially during the first three months after the attempt to give up smoking when people return to this habit most frequently.

*Non-drug remedies of anti-smoking fight* are as follows: (a) psychotherapeutic intervention: group therapy, self-control development based on a program of special-purpose exercises, hypnosis, conditioned reflex impacts to develop aversion to smoking with the help of electric discharges and acupuncture. These methods are quite expensive and their efficacy does not exceed 15-25% within a year of observations; (b) replacement of nicotine-containing cigarette products with various kinds of confectionery (sweets, drops and chewing products in the form of plates or chewing gum without nicotine); (c) such counter-irritants as beads, watching movies, sport games, etc.; (d) administrative measures to ban smoking in public places and transport; (e) anti-nicotine propaganda including warnings on sold tobacco products informing that smoking is hazardous; (f) replacement of tobacco leaves in cigarettes with those of other nightshade plants (potato, eggplant, tomato, etc.); (g) modification of tobacco products by means of introduction of filtrates, special paper processing, etc. in them.

*Drug remedies of nicotine control* are as follows: solutions composed of silver salts, iron and copper sulfate for mouth rinsing before smoking to develop the negative conditioned reflex because the aforesaid solutions cause a strong foul taste in the mouth (this method is inconvenient for most smokers); chewing gums with nicotine to develop its low blood level. The low nicotine level in the blood is enough to prevent such abstinent symptoms as irritability, anxiety and distraction at the first stage after giving up smoking. At the same time, such a chewing gum does not satisfy the smoker as much as smoking. A low nicotine level in the blood is maintained with their help at the second stage when the smoker has already overcome the withdrawal syndrome to improve the efficacy of giving up smoking. Thus, nicotine chewing gums help quit smoking, too. The best results are achieved when these gums are used in a combination with non-drug methods of anti-smoking fight.

Results of short-term studies of the efficacy of chewing gums with nicotine as compared to placebo used for 3-6 weeks are given in Table 1. All of the authors applied the Nicorette chewing gum containing 2 mg of nicotine with the exception of Puska et al. who used gum containing 4 mg of nicotine. Results were verified using the CO determination method with the exception of the study conducted by Puska et al. The percentage of people who gave up smoking varied from 27 to 89. Authors of two studies only failed to obtain any reliable differences in the frequency of giving up smoking at the application of Nicorette or placebo.

Long-term results of most of the studies referred to in Table 1 are given in Table 2.

Table 2

Long-term results of studying the efficacy of Nicorette

Authors of studies	Duration of observation	Number of people who gave up smoking (in %) after taking		
		Nicorette	placebo	P
Fee, Stewart*	1 year	13	9	Invalid data
Pushka et al.	6 months	35	28	Invalid data
Fagerström	1 year	49	37	Invalid data
Jarvis et al.	1 year	47	21	<0.01
Malcolm et al.	6 months	23	5	<0.05
BTS	1 year	10	14	Invalid data
Schneider et al.	1 year	30	20	Invalid data
Hjaimarson	1 year	29	16	<0.05

\* There were only 18% of patients under a long-term observation.

A reliable reduction in the number of smokers after the application of Nicorette within six months - one year was established only in 3 studies out of 8. Persistent discontinuation of smoking was established in 23-43% of patients who received Nicorette. The placebo effect was discovered in 5-21% of patients in three of the above-mentioned studies, which is significantly lower than in the group of patients that were treated with the drug.

It is necessary to chew the chewing gum slowly 10-15 times, then make a break and keep it in the mouth for approximately 2 minutes, then chew it again 10-15 times. Each portion can be chewed this way for about 30 minutes. Then the chewing gum is to be removed from the mouth. In case of constant chewing, nicotine gets into the stomach all at once and does not have any effect. The chewing gum has quite an acrid taste, which is especially unpleasant in case of fast chewing. Usually 8-12 pieces a day being 2 mg each (seldom 4 mg) are enough for the first two months of treatment. However, it is necessary to reduce gradually the number of pieces up to 1-2 a day in the third month.

The chewing gum with nicotine can have various side effects: unpleasant taste; irritation of the mucous coat of the mouth and larynx (mucous ulceration of the mouth is quite possible), nausea; gastrointestinal disorders (pain in the field of stomach, eructation, constipation, diarrhea and meteorism), hiccup, pain in the jaw, tachycardia and nose bleedings. Chewing gum also frequently sticks to the teeth, gets between the teeth, produces a sugary (due to orange flavoring) or bitter taste in the mouth, and gives a feeling of specific odor. Transdermal nicotine plasters<sup>1</sup> are used to control smoking as a drug remedy. The first experiments were carried out with plasters containing 8-9 mg of nicotine; the peak nicotine concentration was achieved in the 90<sup>th</sup> minute after the plaster application. The concentration remained at a high level for three hours. It is expected that plasters with 50 mg of nicotine could maintain the nicotine blood level within 24 hours. Thus, this drug form is at the experimental and improvement stage.

Pills comprising alkaloids having an effect on nicotinic cholinceptors that is similar to that of nicotine due to the similarity of their structure with nicotine are also used. Competitive antagonism of these two chemical substances with nicotine takes place. The following alkaloids are used: cytisin (Tabex pills made in the People's Republic of Bulgaria), Lobeline (Lobesil pills) and anabasine hydrochloride. It is required to take into account such contraindications to their application as apparent hypertension and arteriosclerosis. Pills with anabasine hydrochloride 0.003 are taken eight times a day for five days and then 6-3-2-1 pills for 25 days. The following side effects are possible: unpleasant taste, nausea, headache, vertigo and rise of arterial pressure.

The chewing gum with anabasine (Gumibasine) 0.003 g is applied by long-term daily chewing at first one chewing gum (0.003) four times a day for 4-5 days. In case of the long-term effect, the treatment is carried on for 20 days based on the following regimen: one chewing gum 3-2-1 times a day. There are such side effects as nausea, light headache, vertigo, rise of arterial pressure and bleedings.

Anti-nicotine films with 0.003 g of anabasine hydrochloride or 0.0015 g of cytisin with polyanhydroglucuronic acid on the paper or fabric basis are also used. They are taken into the mouth from 4-8 to 1 times a day for 15 days. The area of films is 1 cm<sup>2</sup>. The drug gets into the oral cavity when the film is resolved. The paper or fabric basis that remains in the mouth is to be removed. Paper-based films stick together, and this hampers their application. Side effects can develop within the first hours after films application, in particular, headache, nausea and rise of blood pressure.

Anti-nicotine biologically soluble polymer films (All-Union Scientific Research and Experimental Institute of Medical Equipment (VNIIMT), Ministry for Health Care of the USSR) comprise 0.0015 g of anabasine, 0.0015 g of cytisin, or 0.00075 g of anabasine and cytisin. All three types of the above-mentioned films are thin films of the oval shape of white or light-yellow color being 9.5 x 4.5 x 0.5 mm in size in the blister package. Films are taken into the oral cavity on the gum beneath the upper lip according to the above-mentioned technique of taking trinitrolong. Films dissolve in the mouth completely and release the corresponding drug at the same time.

The effect of the film application was studied at the Institute for Preventive Cardiology, VKNTs, Academy of Medical Sciences of the USSR, in 74 people altogether (61 men and 13

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<sup>1</sup> Rose et al. Clin. Pharmacol. Ther. 1985, No. 38, p. 450-456.

women) with chronic nicotine addiction. The study program included: (1) acute pharmacodynamic study to examine their effect on the cardiovascular system and carbohydrate metabolism at one-time application as compared to that of placebo. It is well known that anabasine hydrochloride and cytisin in the form of pills were not recommended at hypertension and apparent arteriosclerosis before. That is why it was important to study the impact of the brand-new drug form on smokers with CHD, essential hypertension and diabetes mellitus; (2) course of treatment under clinical conditions; (3) course of treatment in a population; (4) long-term observations.

Films were applied to the mucous coat of the upper gum. The duration of films resolution made up 1.5 hours on average. Only films with cytisin caused side effects at one-time application: an unpleasant feeling in the mouth (in 1 patient), short-term numbness in the mouth (in 1 patient) and heaviness in the head (in 3 patients). Anabasine did not cause any side effects. One-time application of films did not result in the rise of arterial pressure or increase in the heart rate and did not have any effect on the frequency of heart strokes in CHD patients; according to daily ECG monitoring, no dynamical changes in the ECG including the impact on the heart rate were discovered.

As many as 41 patients underwent a course of treatment with films within 15 days under clinical conditions based on the following regimen<sup>2</sup>: the first 5 days - 4-6 times a day; from the 5th to the 8th day - 3 times a day; from the 9th to the 12th day - 2 times a day, and from the 13th to the 15th day - once a day. Patients were recommended to give up smoking beginning with the first day of the treatment with films. The effect was assessed to be absolutely positive when the patient gave up smoking at all and to be partially positive when the patient reduced the number of cigarettes he or she smoked by 2 times or more. As for the whole group, the absolute or partial effect was achieved in 90% of patients while the absolute effect was achieved in 56% of them. Films with cytisin or a combination of cytisin and anabasine turned out to be the most efficient ones under clinical conditions. Films did not have any undesirable effect on the mucous coat of the mouth. Side effects were rare and insubstantial, they emerged more frequently in case of applying films with anabasine: dry mouth (in 4 patients), unpleasant taste and bitterness in the mouth (in 4 patients), nausea (in 3 patients), hypersalivation (in 1 patient), single instance of vomiting (in 1 patient when he used a film with cytisin), vertigo (in 2 patients) and headache (in 1 patient). Films did not affect carbohydrate metabolism indices in diabetes mellitus patients.

As many as 21 people (mainly practically healthy people) underwent a similar course of treatment on an outpatient basis. They were people from a population of the Brezhnev region of Moscow (observations by the Multifactor Prevention Laboratory, head - Doctor of Medical Sciences L.V. Chazova). An immediate absolute or partial effect was observed in 47.% of cases including an absolute effect in 28.6% of cases i.e. twice less frequently than under clinical conditions. On the whole, an immediate absolute or partial effect was achieved in 79.8% of cases including an absolute effect in 46.8% of cases among 62 patients under examination from both of the groups.

There was an observation of 18 patients who underwent a course of treatment at the hospital lasting for 6-14 months. Among them, an immediate absolute effect of the course of treatment was observed in 12 people and a partial effect was observed in 5 people. An absolute effect was maintained in 5 people out of 12 by the end of the long-term observation; a partial effect was maintained in 3 people out of 5. Moreover, a partial effect was maintained in 3 people among those 12 people who had achieved an absolute effect before. At the same time, 4 people smoke as frequently as before the treatment in spite of an absolute or partial effect by the end of the course of treatment under clinical conditions.

Thus, it was shown at the Institute for Preventive Cardiology, VKNTs, Academy of Medical Sciences of the USSR, that anti-nicotine polymer films can facilitate dropping smoking when patients (or healthy people) want to give up smoking themselves.

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<sup>2</sup> The studies were conducted by T.P. Ostrovskaya, N.P. Filatova and A.V. Novikov.

The films do not have a negative impact on CHD patients and patients with moderate arterial hypertension. However, it is required to develop films with more long-term dissolution in the oral cavity to decrease the frequency of taking them during the first days of therapy. Further observations are also required.

The efficacy of the aforesaid anti-nicotine polymer biologically soluble films was also studied at five bases of the Pharmacology Committee, USSR's Ministry for Health Care including the All-Union Serbski Research Institute for Forensic Psychiatry in 201 people altogether. Both immediate and long-term (up to 6 months of observations) effect of the course of treatment was studied during the study. An absolute or partial effect of the course of treatment was observed in 50-75% of cases. Side effects were in the form of dry mouth, burning within the first 10-15 minutes upon application, headache, weakness, insomnia and nausea. The number of long-term observations was insubstantial.

When comparing the results of clinical studies of anti-nicotine biologically soluble polymer films with the results of the application of anti-nicotine drugs of home manufacture in the form of chewing gums with anabasine, paper-based films with anabasine or cytisin, efficacy and safety of biologically soluble polymer films and their advantages as compared to other drugs of home manufacture used for these purposes were emphasized. Due to it, three anti-nicotine biologically soluble polymer films (made by VNIIMT, Ministry for Health Care of the USSR) were approved by the Pharmacology Committee, USSR's Ministry for Health Care, for clinical application and recommended for industrial production along with the chewing gum with anabasine.

Thus, to reduce the withdrawal syndrome and prevent possible return to smoking, chewing gums with nicotine are used abroad while various drugs with anabasine hydrochloride, cytisin or a combination of both chemical substances are used in the USSR as drug treatment. Among drugs made in the USSR, three brand-new anti-nicotine films on the biologically soluble polymer basis to be applied to the mucous coat of the gum (in a similar way to applying trinitrolong) are of some interest. The aforesaid films turned out to be efficient in patients with cardiologic diseases who wanted to give up smoking more frequently than in healthy people under clinical conditions. They were tolerated well including CHD patients and those with moderate arterial hypertension and diabetes mellitus. The films turned out to be efficient on an outpatient basis as well, yet twice as less frequently in healthy people than in patients under clinical conditions. It is advisable to prescribe films only to those people who want to drop smoking.

Further comparative studies of nicotine treatment drugs in larger populations of patients and healthy people as well as further search for new drugs and improvement of the form of anti-nicotine drugs are needed.