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THERE IS NO HEALTHY LEVEL OF SMOKING

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SUMMARY – Cigarette smoking is the leading preventable cause of death in the world. Nicotine is a highly addictive substance. Nicotine dependence is a major barrier to successful smoking cessation. Smoking is a risk factor for 30 diseases with a high rate of morbidity and mortality. There is no safe level of smoking. Help and support to smoking cessation should be an integral part of treatment, particularly for cardiovascular and cerebrovascular diseases. Prevention of smoking and effective treatment for nicotine dependence can significantly decrease the risk of vascular and malignant diseases.

Key words: *Smoking – adverse effects; Smoking – prevention and control; Tobacco smoke pollution; Health status; Cerebrovascular disorders – risk factors*

Introduction

To quit smoking is by no means an easy task for many smokers because of the very strong connections relating them to cigarettes. These connections are of both chemical and psychological nature. In fact, cigarettes gradually, almost imperceptibly assume and maintain first place on the smoker's list of priorities. Most daily activities become inconceivable without cigarettes. In case of cigarette shortage, smokers can hardly overcome the unpleasant symptoms of abstinence. A new cigarette will then readily eliminate their nervousness, tenseness, desire, concentration difficulties, and other discomforts as the overt signs of nicotine dependence. In order to avoid these discomforts, smokers as a rule bring cigarettes always along and take care not to fall short of them.

Nicotine dependence poses great burden upon the person, which is accompanied by a number of diseases associated with daily tobacco smoke inhalation, i.e. malignant, cardiovascular and cerebrovascular diseases. Initially, diseases associated with cigarette smoking usually proceed without symptoms and have already reached an advanced stage at the time of diagnosis. Therapeutic options are considerably reduced due to the late detection of disease, which may result in lethal outcome; if not, smokers frequently spend the rest of their lives with some grade of disability.

Cigarette smoking remains the leading preventable cause of death worldwide, while smoking cessation is the most cost-effective health care intervention. Considering the magnitude and importance of the smoking problem, the International Convention on Smoking Control was adopted at the World Health Organization (WHO) session held in May 2003. In line with the Convention, the Croatian Parliament adopted legal regulations imposing a ban on smoking in indoor public premises in 2008, in order to prevent passive smoking and its unquestionable consequences. Passive smoking is not just a discomfort, but also a direct health risk for nonsmokers.

Deciding to quit smoking is with good reason considered one of the most important decisions in one's life. It should be firmly grounded, preferably not just on fear, but also on the many physical, mental, social and economic advantages associated with nonsmok-

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ing. Cigarette smoking is a type of dependence that has assumed pandemic character. Nicotine is a legalized drug with potent pharmacological action, thus the majority of smokers develop metabolic dependence on nicotine with time. In many cases, smoking cessation is difficult or even impossible to achieve due to physical or metabolic dependence on nicotine, along with concurrent psychological dependence and firmly rooted habit of smoking. To quit smoking is not an event but a process. Many smokers manage it after a number of attempts, whereas others are additionally discouraged by these failures[1]. The nicotine abstinence syndrome is a clearly defined addiction disorder (Diagnostic and Statistical Manual of Mental Disorders, DSM IV revision), which includes a number of symptoms such as irritability, frustration, anger, anxiety, restlessness, impatience, insomnia and other sleep disorders, increased appetite and weight gain, dysphoric or depressive mood, and concentration difficulties[2]. Most smokers continue smoking just because of these abstinence discomforts accompanying attempts to quit smoking.

Nicotine and the Brain

Nicotine is a tertiary amine obtained from the plant *Nicotiana tabbacum*. Nicotine reaches the brain in only seven seconds of tobacco smoke inhalation and binds to nicotinic acetylcholine alpha 4 beta 2 receptors in the ventral tegmental area (VTA), resulting in the release of the neurotransmitter dopamine into the nucleus accumbens, producing a short-lasting pleasant sensation (nicotinic buzz) in the smoker[3-5].

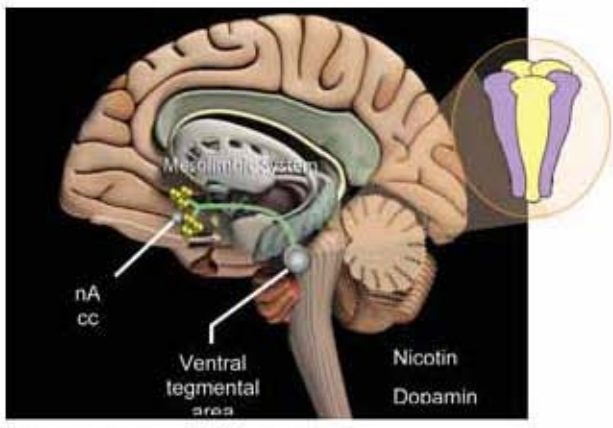

Fig. 1. Nicotine and the brain.

Long-standing repeated inhalation of tobacco smoke, i.e. chronic nicotine exposure results in the activation and desensitization of alpha 4 beta 2 nicotine acetylcholine receptors, with an increase in their count[6]. The need of nicotine increases with the development of nicotine tolerance. Nicotine has a half-life of only two hours. Rapid nicotine elimination leads to abstinence symptoms within several hours of the last cigarette. Therefore cigarette smokers do not make longer intervals of nonsmoking, but take every opportunity to satisfy their need of nicotine. The unpleasant abstinence discomforts such as anxiety, tension, restlessness, etc., accompanied by strong desire for nicotine, occur as soon as the level of dopamine declines. Then the smoker lights another cigarette to resume calmness and feeling good. Smokers are known to titrate their smoking habit to achieve maximal nicotine stimulation while avoiding abstinence symptoms and desire for nicotine.

Besides the addictive action of nicotine, environmental factors also play a role in the development, reinforcement and maintenance of nicotine dependence, which should be taken in consideration both in the prevention of sm oking and in the process of smoking cessation[7]. Behavioral science indicates the brain of addicts to be abnormally conditioned. Cigarette smoking is largely associated with certain situations, places and rituals (e.g., opening the box, lighting the cigarette, watching smoke rings, smelling), when desire for cigarette is present irrespective of dopamine level.

Dependence Identification

According to DSM IV criteria, nicotine dependence is present if three or more of the following symptoms are recorded during a one-year period:

- nicotine tolerance (decreased action and need for dose increase to achieve the same effect),
- abstinence symptoms upon smoking cessation,
- persisting desire for smoking in spite of all efforts at dose reduction,
- wasting an enormous amount of time for smoking and buying cigarettes,
- postponing work, social or recreational activities for smoking, and
- continuing smoking in spite of health discomforts.

Disease and Risk Factor

Cigarette smoking dependence is a chronic relapsing disease that frequently requires repeat interventions and multiple attempts at smoking cessation. At the same time, cigarette smoking has been identified as a major risk factor for some thirty diseases, as demonstrated by numerous epidemiological, clinical and experimental studies. The diseases associated with cigarette smoking include diseases of almost all organ systems. Respiratory system is, logically, at highest exposure to the action of tobacco smoke because of direct contact with the numerous and heterogeneous toxic substances of tobacco smoke. Tobacco smoke contains about 4000 different chemical substances that simultaneously enter the body upon smoke inhalation to be transported by blood to particular organs. Tobacco smoke contains some 300 substances with carcinogenic potential. Malignant, cardiovascular and cerebrovascular diseases occupy the first three positions on the list of morbidity and mortality in Croatia and worldwide. Cigarette smoking has been identified as a major individual risk factor for all these three groups of diseases. A combination of cigarette smoking with other risk factors significantly increases the likelihood of disease development and poor, frequently fatal disease outcome.

In Croatia, stroke ranks high, third cause of death and first cause of disability. It is widely known that, according to statistical data, one third of stroke patients recover, one third die, and one third survive with a minor or major disability. Many researchers have focused their studies on the treatment and prevention of stroke. New potential risk factors that contribute to the development of cerebrovascular disease are discovered on a daily basis. It seems that more efforts are invested in the detection of risk factors than in the use of efficient measures to eliminate removable risk factors and provide better control of those that cannot be eliminated.

Cigarette smoking definitely increases the risk of stroke and contributes to poorer treatment outcome. It is therefore necessary to prevent smoking, in order to reduce maximally the proportion of young people starting smoking, thus remaining beyond the risk groups. On the other hand, considering that many smokers wish to quit smoking, but only a minor proportion manage it on their own, the support and help offered to smokers in their efforts at smoking cessation should be integrated in regular therapeutic procedures performed by physicians at hospitals and outpatient clinics.

Short Intervention

WHO recommends short intervention according to which every patient should be asked whether he/she is smoking, and if so to advise smoking cessation, evaluate his/her readiness to do it immediately or within a month, help him/her determine the date of smoking cessation, and follow-up the course of abstinence, briefly a five-A schedule:

ASK	AID
ADVICE	ACCOMPANY
ASSESS	

In most cases, abstinence poses no problem for smokers in the acute stage of disease; however, many smokers resume smoking upon termination of the acute stage of disease. Short intervention by the physician generally proves inadequate in smokers with long-standing smoking habit, great number of cigarettes in their history, high-grade dependence, and failing attempts at smoking cessation. In such cases, a complex procedure is required, including the use of pharmacological agents in addition to behavioral approach. WHO recommends a combination of behavioral and cognitive strategy with the use of agents intended for the management of cigarette dependence as the most efficient therapeutic option for smokers.

Pharmacological Agents in the Treatment of Nicotine Dependence

The new non-nicotinic agent Vareniklin, developed and approved exclusively for the treatment of nicotine dependence and registered in Croatia in 2009, has proved significantly more efficient in the management of nicotine dependence as compared with nicotine substitution therapy and bupropione, previously used in the treatment of this type of dependence[8,9]. Vareniklin has a logical mechanism of action. It binds to the same acetylcholine nicotine receptors in the brain as nicotine and leads to partial dopamine release (agonist action), thus reducing the desire for nicotine and other abstinence symptoms. If the smoker using Vareniklin lights a cigarette, the sensation of delight and satisfaction associated with cigarette smoking will fail

because nicotine cannot induce new dopamine release since the respective receptors have already been occupied by Vareniklin (antagonist action). Vareniklin therapy takes twelve weeks.

Cigarette Smoking and Cerebrovascular Disease

Results of the Framingham Study that included 4255 subjects of both sexes, aged 36-68, followed-up for 26 years, suggest significant contribution of cigarette smoking to the occurrence of stroke, with the risk of stroke increasing with the number of cigarettes used daily. In heavy smokers (≥40 cigarettes daily), the relative risk of stroke was twofold that in moderate smokers (<10 cigarettes daily). At two years of smoking abstinence, the risk of stroke decreased significantly, and at five years of smoking abstinence the risk of stroke in former smokers was equal to the risk recorded in nonsmokers[10].

It is estimated that 12% to 14% of all stroke deaths are associated with cigarette smoking. In addition to smoking itself being a significant risk factor for stroke, in association with other known risk factors it potentiates their adverse effects. The acute effect of smoking on the circulatory system manifests as vasoconstriction and an increased likelihood of thrombus formation. The chronic effects of smoking are related to the atherogenic potential of smoking and progressive development of atherosclerosis[11]. The mechanisms of nicotine action are more or less known, whereas the action of some other tobacco smoke constituents and their interactions remain relatively obscure. Endothelial dysfunction and lesions[12], significantly elevated level of circulating tissue factor in atherosclerotic plaques[13], significantly higher leukocyte count, which has been related to cardiovascular events[14], and a considerably higher level of free F2 isoprostane as an index of lipid peroxidation[15] have been recorded in cigarette smokers as compared with nonsmokers.

Smoking accelerates the progression of atherosclerotic process in carotid arteries[16]. The progressive course of carotid artery atherosclerosis was demonstrated not only in active smokers, but also in nonsmokers exposed to passive smoking.

In women, the risk of lethal stroke outcome is considerably greater in female smokers than in female nonsmokers sustaining a stroke. The risk of lethal outcome increases with the number of cigarettes taken daily (2.5 in women taking up to 14 cigarettes daily *vs.* 3.8 in those with 25 or more cigarettes daily)[17]. In a study of lethal stroke outcome in men, smokers had a significantly greater risk of lethal outcome than nonsmokers with stroke[18].

The risk of hemorrhagic stroke due to either intracerebral or subarachnoid hemorrhage is increased in smokers[19]. On the other hand, positive correlation was found between smoking cessation and reduction in the risk of stroke[20].

Passive Smoking

Attention has been increasingly paid to the phenomenon of passive smoking, along with increasing concern about health risks to which some individuals may be exposed against their will, being for numerous reasons forced to inhale tobacco smoke. A nonsmoker found in some indoor premises together with smokers inhales tobacco smoke exhaled by smokers, along with the smoke blown off from the tip of the cigarette into the air. Passive smoking does not only mean a discomfort, but a direct health risk. Passive smoking increases the risk of developing some thirty diseases including stroke, which are directly associated with cigarette smoking. Nonsmokers at long-standing and intensive exposure to tobacco smoke as passive smokers have the same level of cotinine, a nicotine metabolite, as smokers taking up to ten cigarettes daily[21]. Determination of the mean coronary flow velocity reserve (CFVR) in nonsmokers exposed to passive smoking showed significantly lower mean CFVR upon second hand smoke inhalation[22].

The Benefits of Smoking Cessation

There are numerous benefits of smoking cessation, classified into several groups, i.e. physical, emotional, social and financial advantages. According to the time at which they become evident and experienced by the ex-smoker or demonstrated by some specific tests, these advantages are classified into the benefits that are observable immediately upon smoking cessation or after a short time of abstinence, and long-term benefits associated with smoking cessation. The latter include gradual reduction of the risk of disease development, improved course of the existing disease, and reduced risk of disease complications and lethal outcome.

A decrease in plasma fibrinogen concentration and a reduced fibrinogen synthesis were found after two-week abstinence from smoking[23]. Another study reports on a decrease in platelet aggregation also after two-week abstinence from smoking[24]. According to a study published in Nicotine Tobacco Research, the 17-week abstinence from smoking resulted in normalization of leukocyte count, improvement of lipid profile, increase in the level of protective high-density lipoprotein (HDL) and decrease in the level of atherogenic low-density lipoprotein (LDL) demonstrated in ex-smokers[25]. Cessation of smoking is associated with improvement in the hemodynamic parameters of arterial blood pressure and heart action[26].

The many benefits of smoking cessation include reduction in the risk of stroke, recurrent post-stroke coronary events, death from cardiac arrhythmia following myocardial infarction, death after aortocoronary bypass, and death after PTCA. The levels of inflammatory markers associated with progression of vascular disease, i.e. C-reactive protein, leukocytes and fibrinogen, decrease upon smoking cessation[27,28].

Prevention of smoking and treatment of nicotine dependence also imply prevention of some thirty diseases associated with smoking, including those occupying the first three positions on the list of morbidity and mortality in Croatia and worldwide, i.e. cardiovascular, malignant and cerebrovascular diseases.

There is no healthy level of smoking because each cigarette smoke contains 4000 different chemicals, some fifty of them with carcinogenic action. Each cigarette impairs breathing, paralyzes ciliary apparatus, causes oxygen deprivation, narrows blood vessels, accelerates heart action and elevates blood pressure, exerts biphasic effect on the central nervous system, impairs health in those found in the same room with the smoker, and leads to dependence or reinforces it if already present.

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Sažetak

NE POSTOJI ZDRAVA RAZINA PUŠENJA

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Pušenje je vodeći preventabilni uzrok smrti u svijetu. Nikotin je izrazito adiktivan. Ovisnost o nikotinu je glavna prepreka za uspješni prestanak pušenja. Pušenje je rizični čimbenik za tridesetak bolesti s visokim pobolom i smrtnošću. Ne postoji sigurna razina pušenja. Neophodno je integrirati pomoć i potporu za prestanak pušenja u redovitu terapiju, pogotovo tijekom liječenja kardiovaskularnih i cerebrovaskularnih bolesti. Prevencija pušenja i učinkovito liječenje nikotinske ovisnosti mogu značajno smanjiti rizik obolijevanja od vaskularnih i malignih bolesti.

Ključne riječi: *Pušenje – štetni učinci; Pušenje – prevencija i kontrola; Onečišćenje duhanskim dimom; Zdravstveno stanje; Cerebrovaskularne bolesti – rizični čimbenici*