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Working Group Report

Diagnosis and treatment of nicotine dependence with emphasis on nicotine replacement therapy

A status report

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Tobacco use is a global health care problem. Repetitive exposure to nicotine produces neuroadaptation resulting in nicotine dependence. Cigarette smoking is particularly addictive due to the repeated delivery of bolus doses of nicotine to the bloodstream. Although compulsive tobacco use is sustained by nicotine addiction, it is the toxic combustion products in tobacco smoke such as carbon monoxide and oxidant gases that adversely affect the cardiovascular system. Smoking cessation produces significant health benefits and is a very cost-effective intervention. Evidence that nicotine is the addictive component of tobacco provides the rationale for using nicotine replacement therapy to aid cessation. Nicotine replacement therapy doubles successful smoking cessation rates and evidence-based guidelines for the treatment of tobacco addiction recommend routine use of nicotine replacement therapy, particularly in heavily dependent smokers. Success rates of up to 40% can be achieved in specialist clinics. Despite early concerns regarding the safety of nicotine replacement therapy in smokers with heart disease, it is now clear that the health risks of using nicotine replacement therapy to assist such patients to stop, or significantly reduce, smoking far outweigh any treatment-related risks.
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Introduction

In 1994, the European Society of Cardiology (ESC), the European Atherosclerosis Society and the European Society of Hypertension published joint recommendations on the prevention of coronary heart disease in clinical practice[1]. Patients with established coronary heart disease or other major atherosclerotic disease were deemed the top priority for prevention.

Under the auspices of the ESC, a European survey (EUROASPIRE) was recently conducted to describe current clinical practice in relation to secondary prevention of coronary heart disease, and to ascertain to what extent the recommendations were being followed[2]. This study found that 55% of patients did not have controlled blood pressure and 43% did not have controlled cholesterol levels. Twenty-five percent of patients had a body mass index $\geq 30\ \mathrm{kg\,.\,m^2}$ and 20% were still smoking. Although the study examined medications for the treatment of hypertension and elevated cholesterol, it neglected the treatment of smoking.

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The Second Joint Task Force of the ESC recommendations on prevention of coronary heart disease in clinical practice emphasize life-style factors such as healthy nutrition, physical activity, non-smoking or smoking cessation[3]. The report recommends that physicians help patients to quit smoking, and that nicotine replacement therapy may be helpful, particularly in heavily dependent smokers. Although this is a step forward compared to the cautious comment on nicotine replacement therapy in patients with cardiovascular disease in the 1994 report[1], even the recent guidelines are not extensive with regard to the diagnosis and treatment of smoking, and fall short of the comprehensive recommendations concerning diagnosis and treatment of hypertension and dyslipidaemia[3].

It therefore seems timely to share recent developments in our understanding of nicotine dependence and its diagnosis and treatment with cardiologists and other health professionals.

Principles of diagnosis and treatment of nicotine dependence

If it were possible to prevent people in developed countries from starting to smoke, so that current smokers comprised the total smoking population, tobacco would still cause a quarter of a billion premature deaths among existing smokers[4]. Smoking results in an average loss of life of 9 years per person. This epidemic is sustained by tobacco use, which in turn is sustained by the addictive nature of nicotine[5]. Thus, the pharmacology of nicotine is important in terms of treating nicotine dependence and in the contribution of nicotine to other diseases.

At present, our understanding of the diagnosis and treatment of nicotine dependence is similar to that of hypertension and hypercholesterolaemia 30 or 40 years ago. The treatment of nicotine dependence is a key element of preventive cardiology, along with the management of hyperlipidaemia, hypertension and other risk factors for cardiovascular disease.

Understanding nicotine dependence

The nature of nicotine addiction may be unfamiliar to many specialists, including cardiologists. Many physicians find it difficult to consider tobacco use and nicotine dependence as a disease. However, smoking is an internationally classified disease according to the World Health Organisation International Classification of Diseases (code ICD F 17.2)[6].

Interestingly, there are many similarities between cocaine addiction and tobacco dependence. Nicotine affects mood and performance, reducing hunger and accelerating body metabolism. Smokers can easily regulate their mood by having one or two cigarettes. It is important to emphasize that nicotine itself does not cause cancer. Recent research also indicates that it does not cause myocardial infarction when taken in the form of pharmaceutical products[7–9]. Thus, caveats within the 1994 European Guidelines for Preventive Cardiology regarding the need for caution when using nicotine replacement therapy in patients with cardiovascular disease require revision.

Repetitive exposure to nicotine produces neuroadaptation[5,10]. Nicotine withdrawal is associated with symptoms typical of other addictions, i.e. irritability, restlessness, difficulty concentrating, impaired task performance, anxiety, hunger, weight gain, sleep disturbance, cravings and drowsiness[11].

Diagnosis of nicotine dependence

Nicotine dependence must be routinely diagnosed and treated appropriately. Smokers are not a uniform group and they can be differentiated according to their level of dependence.

One of the most important diagnostic tests is the Fagerström Test for Nicotine Dependence (FTND)[12]. One question in the FTND that is particularly important when assessing dependence is 'How soon after waking do you smoke your first cigarette of the day?' If the response is that he/she smokes his/her first cigarette within 5 min after rising then the individual is nicotine dependent. Another important question is 'Do you wake up during the night because of nicotine craving?'[13]. Individuals with high levels of nicotine dependence that involve nocturnal, sleep-disturbing craving are at high risk of developing tobacco-related disease.

There is often a direct relationship between nicotine dependence and the ability, or wish, to stop smoking[14]. This is important because health education is generally targeted at low dependent smokers, while those in whom the health risks are greatest are neglected.

Treatment of nicotine dependence in clinical cardiology

Benefits of smoking cessation in patients with cardiac disease

Epidemiological data indicate that smokers have a twofold higher risk of non-fatal myocardial infarction and a two- to fourfold higher risk of sudden death compared with that of non-smokers[15]. Importantly, the risk of myocardial infarction and sudden death fall rapidly following smoking cessation. For example, 20% of patients who continue to smoke after thrombolytic therapy for myocardial infarction will experience re-infarction within 1 year[16]. However, within 3 weeks of stopping smoking following thrombolysis this risk falls to a level similar to that observed in life-time non-smokers. Similar changes have been observed after angioplasty or coronary artery bypass surgery. Smoking

cessation produces health economic benefits far greater than those associated with other preventive or therapeutic strategies, and these costs and benefits should be taken into consideration during health care planning. Smoking cessation interventions are also very cost effective; a recent cost-effectiveness analysis estimated the societal cost of smoking cessation to range from £212–£873 per life year gained[17], compared to a median cost of £17 000 per life year gained for 310 other medical interventions[18].

General guidelines for smoking cessation

Evidence-based guidelines for the outpatient treatment of tobacco addiction have been developed by the US Agency for Healthcare Policy and Research[19]. The first step is to help patients develop a plan that includes the date on which they are going to quit smoking. Use of nicotine replacement therapy should always be encouraged (except where contraindicated) on the basis that the optimal strategy for maximizing the likelihood of cessation should be tried immediately. Patients should also be given appropriate advice, including an explanation of tobacco withdrawal symptoms and situations associated with a high risk of relapse. Finally, any necessary supplementary materials should be provided.

A similar approach is being used at the University of California, San Francisco, for nurse-managed smoking cessation in hospitalized cardiovascular patients. Treatment starts by getting the patient to acknowledge that he or she is a smoker and that this is a medical problem. Smoking cessation during hospitalization is encouraged, on the basis that withdrawal symptoms will peak during the first 2 to 3 days of hospitalization when smoking is not permitted. The relationship between smoking and cardiac disease is explained, along with the benefits of quitting. Finally, patients are provided with any materials they may need to help stop smoking, including medication such as nicotine replacement therapy.

Smoking and acute coronary events

Cigarette smoke contains a variety of chemicals that may adversely affect the cardiovascular system[9]. In addition to nicotine, tobacco smoke contains carbon monoxide, glycoproteins, oxidant gases and other toxic combustion products. Carbon monoxide and the oxidant gases are considered primarily responsible for most of the cardiovascular damage associated with smoking.

Oxidant gases oxidise low-density lipoproteins, making them more atherogenic, and cause endothelial damage, impairing nitric oxide release. Evidence suggests that oxidant gases also affect platelets, possibly causing the hypercoagulable state and associated thrombosis seen in smokers. In addition, carbon monoxide reduces oxygen transport in the blood and availability within the heart.

In haemodynamic terms, nicotine exerts mild sympathomimetic effects. It activates the sympathetic nervous system, which causes an increase in heart rate of about 7 beats . min^{-1} throughout the day in smokers compared with non-smokers. Blood pressure rises by approximately 5 mmHg after each cigarette as a result of increases in myocardial contractility and heart rate. Both these changes increase myocardial oxygen demand and consequently increase coronary blood flow requirements. However, nicotine may also constrict coronary arteries, the effects being blocked by α-adrenergic blockers[20]. Nicotine could therefore aggravate the discrepancy between blood supply and demand, which could aggravate ischaemia. However, the sympathomimetic effects of nicotine are no greater than those observed during mild exercise, and are unlikely to cause myocardial infarction.

An important aspect of the effects of nicotine is the delivery system. A cigarette delivers bolus doses of nicotine rapidly into the pulmonary circulation, producing peak concentrations in the heart and brain five times greater than those produced by other nicotine delivery systems such as transdermal patches or chewing gum. Importantly, the cardiovascular effects of nicotine exhibit a flat dose–response curve, which is probably related to the rapid development of tolerance.

The flat dose-response was demonstrated in a recent study of the effects of administering high doses of transdermal nicotine to healthy volunteer smokers[21]. Subjects received up to 63 mg of nicotine transdermally (equivalent to three patches) and were also allowed to smoke cigarettes simultaneously. Following administration of the 63 mg dose plasma nicotine concentrations approached 80 ng . ml^{-1}, which reflect those observed in arterial blood during smoking. However, no differences in heart rate or blood pressure were observed between patients when they either smoked or received 21, 42 or 63 mg transdermal nicotine. Moreover, 24-h urine adrenaline levels were similar irrespective of whether or not patients smoked during transdermal nicotine administration. This protective, flat dose–response curve explains why individuals who smoke concomitantly while using nicotine replacement therapy can have high plasma nicotine levels without experiencing any significant adverse effects.

There is no doubt that smoking predisposes to acute thrombosis. Burke *et al.* reported that 75% of men with post-mortem evidence of acute coronary thrombosis were cigarette smokers compared with 30% of those with stable plaques[22]. However, in contrast with smoking, nicotine replacement therapy does not appear to cause platelet aggregation. The effects of cigarette smoking and either a single 21 mg transdermal nicotine patch or a placebo patch on platelet activation in vivo have been compared, assessed by measuring urinary excretion of a metabolite of thromboxane A_2[23]. Thromboxane A_2 is released in vivo when platelets aggregate, and causes further platelet activation and vasoconstriction. Plasma nicotine concentrations produced by smoking and by using the transdermal nicotine patch were similar, but

only smoking resulted in a significant increase in urinary thromboxane A_2 metabolite levels.

In summary, although nicotine could contribute to smoking-related cardiovascular disease, other components of cigarette smoke probably play a more important role.

Safety of nicotine replacement therapy in cardiovascular patients

Concerns regarding the hazards of nicotine replacement therapy in smokers with heart disease were raised when transdermal nicotine patches were first marketed in the US. Within a 1-month period in July 1992, five men experienced myocardial infarction while using patches and smoking. However, the United States Food and Drug Administration (FDA) subsequently evaluated post-marketing surveillance data. On average, the rate of myocardial infarction in smokers is six per thousand person-years. As a total of three million smokers had used transdermal nicotine patches, each for an average duration of 1·5 months, the expected number of myocardial infarctions in nicotine replacement therapy users was 2250. In fact, only 33 serious cardiovascular events had been reported. Therefore, even taking into account that such events may be under-reported by a factor of 10, the number of myocardial infarctions reported was far less than that expected in a control population. The FDA therefore concluded that there was no evidence that transdermal nicotine patches contributed to an increase in the risk of myocardial infarction.

Several studies have assessed the cardiovascular safety of nicotine replacement therapy in the clinical setting. Mahmarian *et al.*[8] studied the effect of nicotine replacement therapy on myocardial ischaemia in 36 male smokers with severe cardiac disease awaiting bypass surgery. Patients were sequentially treated with 14 mg and 21 mg nicotine patches. Exercise–thallium tests were performed at baseline and during treatment with both patches to measure the perfusion defect size. Despite being instructed to quit, most of the patients continued to smoke cigarettes during treatment with nicotine replacement therapy, although they smoked fewer cigarettes . day^{-1}, with the result that their plasma nicotine levels increased (from 15·8 ng . ml^{-1} at baseline to 24·2 and 30·4 ng . ml^{-1} with the 14 and 21 mg patch, respectively) whereas their expired carbon monoxide levels decreased during treatment. In the setting of elevated plasma nicotine levels there was a significant reduction in the total perfusion defect size, which appeared to correlate with the reduction in blood carboxyhaemoglobin levels. These results suggest that carbon monoxide, or some other component of tobacco smoke, aggravates coronary ischaemia.

One key epidemiology study of transdermal nicotine used for smoking cessation in patients with cardiovascular disease has been conducted in the US[24]. Five hundred and eighty-four patients were randomized to receive either transdermal nicotine patch therapy or placebo for 10 weeks; many patients continued to smoke cigarettes during the study. The incidence of primary end-points (death, myocardial infarction, cardiac arrest, hospitalization for increased angina, arrhythmias or congestive heart failure) was similar in both treatment groups (nicotine 5·4% vs placebo 7·9%).

In conclusion, the health risks associated with nicotine appear to be much lower than those associated with cigarette smoking, even in individuals with cardiovascular disease. The health benefits of using nicotine replacement therapy to assist such patients to stop smoking, or even to significantly reduce cigarette consumption, far outweigh any treatment-related risks.

Neuropharmacology of nicotine

Nicotine has properties similar to those of other drugs of dependence, and smokers inhale sufficient nicotine to produce changes in the brain that can account for the tobacco withdrawal syndrome observed following abrupt cessation of smoking. Pharmacologically, nicotine is principally a psychomotor stimulant[25], somewhat like an amphetamine or cocaine. It also has other psychopharmacological effects, particularly anxiolytic and antidepressant properties, which may enhance its addictive properties in patients with an underlying anxiety or affective disorder[10].

Neuropharmacology of addiction

The 'rewarding' properties of addictive drugs are often investigated using self-administration schedules in which experimental animals are trained to respond for an intravenous injection of the drug. There is good evidence that experimental animals can be trained to respond for nicotine[26]. The self-administration of psychostimulant drugs of dependence, with behavioural properties similar to those of nicotine, depends upon their ability to increase the release of dopamine in the principal terminal field of the mesolimbic system, the nucleus accumbens[27]. This pathway is thought to form a pivotal component of the neural systems within the brain which respond to and encode for rewarding stimuli. Repetitive exposure to drugs which exert this effect results in the development of a close association between drug taking and their potent rewarding or euphoriant properties and, thus, to dependence. The ability of nicotine to serve as a reinforcer in a self-administration experiment also depends upon its ability to stimulate the dopamine-secreting neurones which project to the nucleus accumbens[28]. Repetitive administration of nicotine to experimental animals has also been shown to result in sensitization of its stimulatory effects on dopamine release in the accumbens[29]. Repetitive injection of other psychostimulant drugs of abuse also results in sensitization of their effects on dopamine release in the nucleus

accumbens[30] and it has been suggested that this property may be fundamental to the ability to cause addiction[31]. Although at the molecular level the mechanism by which nicotine stimulates dopamine release in the nucleus accumbens differs significantly from those which mediate the responses to amphetamine and cocaine[32], the effects of nicotine on the system resemble those of other psychostimulant drugs of abuse. It therefore seems reasonable to conclude that the effects of nicotine on this dopamine system are entirely consistent with it being a drug of addiction.

Cigarette smoking: the role of delivery system

A cigarette is a very addictive way to consume nicotine, because a smoker is presented with a discrete bolus of the drug each time nicotine is inhaled into the lungs. The drug is rapidly transferred into the brain, within approximately 10 s of inhalation[33]. Furthermore, nicotine is delivered frequently and repetitively.

Nicotine concentrations accumulate in the blood if individuals smoke frequently. Benowitz *et al.*[34] showed that plasma nicotine levels in smokers allowed to smoke ad libitum rise to approximately 20 ng . ml^{-1} during the smoking day, falling to around 10 ng . ml^{-1} or less during the night.

Regular smoking in humans, and constant nicotine infusion in experimental animals, produce changes in the brain that may be related more to withdrawal than the reward phase. For example, the density of nicotine receptors in many areas of the brain is increased in smokers compared with age- and sex-matched non-smokers[35]. In experimental rats receiving constant nicotine infusions, blockade of nicotine receptors using mecamylamine produces changes in the brain and behaviour which are thought to model nicotine withdrawal in humans. In these rats, characteristic behavioural changes are observed[36] and there is a decrease in dopamine release in the accumbens[37].

This decrease in dopamine has been associated with anhedonia, a feeling of dysphoria experienced during drug withdrawal. A number of mechanisms might account for this. For example, chronic nicotine administration in animals selectively reduces the concentration and biosynthesis of 5-hydroxytryptamine (5-HT) in the hippocampus[38,39]. At post-mortem, reduced hippocampal 5-HT is also observed in humans who smoked tobacco and it seems reasonable to suggest that this can be attributed to the nicotine present in tobacco smoke[40]. It seems likely that these reductions in 5-HT levels also reflect reductions in the formation and release of 5-HT and in 5-HT receptors, since the density of 5-HT$_{1A}$ receptors in the hippocampus of these subjects was increased, a change which normally reflects repeated or prolonged reductions in 5-HT release[40]. Again, this is selective to the hippocampus and also to the receptor sub-type as 5-HT$_2$ receptor density was unaffected.

The possible significance of the changes in hippocampal 5-HT evoked by nicotine are not understood. However, the pathway has been implicated in the mechanisms underlying both anxiety and depression[41–43], and it currently seems reasonable to suggest that the adaptive changes in 5-HT function in the hippocampus are associated with the dysphoria and anxiety experienced by many habitual smokers when they stop smoking.

Nicotine replacement: present and future

The evidence that nicotine is the principal addictive component of tobacco smoke is overwhelming, and this represents the basis for using nicotine substitution therapy to aid cessation[10]. Nicotine replacement therapy was developed in Sweden during the 1970s. Since then a range of delivery vehicles have been introduced, including nicotine chewing gum, transdermal patch, oral inhaler, nasal spray and sublingual tablet. However, these systems possess shortcomings that affect their acceptability as a replacement for cigarettes.

Drug uptake

One important drawback of existing nicotine replacement therapy delivery methods is their slow delivery of nicotine. Cigarette smoking produces high venous nicotine concentrations (10–12 ng . ml^{-1}) within 5 min of smoking a cigarette[10]. Arterial nicotine concentrations may be four to six times higher. While similar venous nicotine concentrations may (at most) be achieved with a piece of nicotine 4 mg gum, it takes approximately 30 min to achieve such levels[10]. Delayed and low-level nicotine release is unattractive to smokers and reduces their willingness to continue using nicotine replacement therapy. Moreover, slow delivery into the circulation is, for most psychoactive drugs, less efficacious as it may allow the development of tolerance. However, it should be borne in mind that rapid nicotine release from nicotine replacement therapy systems that are more acceptable to the smoker might have a higher abuse potential.

Effectiveness

Nicotine replacement therapy generally doubles successful smoking cessation rates compared to placebo, independent of the amount of counselling provided[44]. Nicotine replacement therapy combined with minimal intervention can achieve successful quit rates of around 10%. However, in intensive smoking cessation clinics, nicotine replacement therapy use may achieve a 40% success rate[19].

Puska *et al.*[45] assessed the relative efficacy of smoking cessation strategies in North Karelia. Sixteen thousand individuals participating in a vaccination campaign were asked whether they smoked and, if so, if they wished to stop. Almost 3000 individuals who wished to stop received brief advice and a leaflet and were randomised to receive either 30 pieces of Nicorette® gum, seven Nicorette® patches or no nicotine replacement therapy therapy. Twelve months later, 5·7% of those who received gum and 7·0% of those who received patches had stopped smoking, compared with 3·8% of those who received advice alone. This is a good example of a very cost-effective, minimal-intervention smoking cessation study in which nicotine replacement therapy approximately doubled the successful quit rate.

The success of smoking cessation is heavily influenced by the baseline level of dependence. While there is a good chance of success in individuals with low dependence, cessation is almost impossible without nicotine replacement therapy in highly dependent individuals[46]. Other factors that can reduce the likelihood of cessation include major depression and previous unsuccessful quit attempts.

Nicotine replacement therapy in practice

The choice of nicotine replacement therapy product should be based on the individual smoker's preference, as the various devices do not differ in their efficacy. Ideally smokers should be able to try each method before choosing their preferred product.

Smokers often under-dose nicotine replacement therapy during treatment, resulting in an insufficient dose of nicotine to prevent withdrawal symptoms[47]. Nicotine replacement therapy appears to be most effective if multiple delivery methods are combined. For example, as it is difficult to deliver an adequate dose of nicotine to highly dependent patients using a single formulation, the transdermal patch can be used to provide a baseline nicotine level that is supplemented with a flexible delivery system[47].

Another problem with nicotine replacement therapy is that smokers use it for too short a period. There are instances when a prolonged duration of use is desirable to maintain abstinence from smoking, e.g. in individuals with a clinical history of depression. Much research is ongoing to assess the efficacy of new antidepressant drugs such as specific serotonin reuptake inhibitors and monoamine oxidase inhibitors for the treatment of nicotine dependence. One antidepressant, bupropion, has been found effective and has been approved for smoking cessation[48]. In one study, the combination of bupropion plus nicotine replacement therapy showed a trend towards higher smoking cessation rates than bupropion alone[48].

Smokers who cannot or will not stop smoking may also benefit from nicotine replacement therapy. Consideration should be given to offering these individuals the option to reduce their cigarette consumption by concomitantly using nicotine replacement therapy[49]. This appears to increase their motivation to quit, which must remain the ultimate goal of nicotine replacement therapy, while reducing the risks of cancer and pulmonary and cardiovascular disease.

For smokers who are unwilling or unable to quit, controlled smoking reduction is a valid harm reduction goal because many tobacco-related diseases are dose related. The Danish health authorities have recently (August 1998) licensed nicotine replacement therapy for smoking reduction i.e. smoking fewer cigarettes while concomitantly using nicotine replacement therapy.

Future developments

Many interesting developments lie ahead in the treatment of tobacco dependence. Immunological approaches to antagonize nicotine have recently been proposed and there may eventually be a nicotine vaccine. Geneticists are poised to identify the genes that render some individuals highly susceptible to smoking addiction.

The future of nicotine replacement therapy lies in the development of better delivery systems, as the current products cannot compete with cigarettes. Greater and more rapid delivery of nicotine and a wider choice of administration methods are required. Importantly, nicotine replacement therapy must be de-regulated and made more widely available, as US estimates suggest that changing nicotine replacement therapy from prescription-only to general sale status resulted in 100 000–300 000 additional cessations[50].

Finally, new indications for nicotine replacement therapy will emerge, such as short-term nicotine replacement therapy use during situations of temporary abstinence (e.g. flights or hospitalization), harm minimization (i.e. smoking reduction), and long-term use for highly tobacco-dependent individuals.

Conclusions

Cigarette smoking is a major global health care problem. Smoking is an internationally classified disease (code ICD F 17.2) and as such it should be diagnosed and treated appropriately. The most widely used pharmacological treatment is nicotine replacement therapy, which doubles successful smoking cessation rates, and it is now recommended that nicotine replacement therapy should routinely be used during quit attempts.

The health risks of nicotine per se are clearly less that those of cigarette smoking, even in individuals with active cardiovascular disease and during pregnancy. Indeed, there is no evidence that nicotine has adverse cardiovascular effects in patients with heart disease. If nicotine replacement therapy can assist people to stop smoking, or reduce cigarette consumption in those who cannot stop, the health benefits far outweigh any risks.

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