2018

Guidelines for treating tobacco dependence

ENSP

European Network
for Smoking and Tobacco Prevention

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Declarations of Interests

The members of the Editorial Board of the ENSP Guidelines for Treating Tobacco Dependence declare the following declarations of interest:

Panagiotis K. Behrakis declares to have no conflict of interest with any pharmaceutical company;

Luke Clancy declares that his institute was awarded a research grant by Pfizer in 2010; he received consultancy fees from Pfizer and Pierre Fabre 2010, 2011, 2012; he received lecture fees from Pfizer and Novartis in 2010, 2011, 2012;

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Level of evidence of recommendations in the guidelines

Table 1: The current guidelines stratify the evidence into three categories, judging by the type, quality and quantity of the referred studies.

Levels of Evidence: Description		
Category of proof	**Sources of evidence**	**Definition**
A	Controlled and randomized trials (CRT). Large database.	**Great number of studies which imply a substantial number of participants.**
B	Controlled and randomized trials. Limited database.	**Studies include a limited number of patients, analysis post hoc or analysis of CRT sub-groups, or metaanalysis of CRT. The randomized trials are small, on various population groups, with inconsistent results.**
C	**Non-randomized trials. Observational studies. Expert consensus.**	**Proofs from non-controlled and non-randomized trials or observational studies.**

Levels of Evidence: Description		
Code	**Quality of Evidence**	**Definition**
A	High	Further research is very unlikely to change our confidence in the estimate of effect. Several high-quality studies with consistent results In special cases: one large, high-quality multi-centre trial.
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. One high-quality study. Several studies with some limitations.
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. One or more studies with severe limitations.
D	Very low	Any estimate of effect is very uncertain. Expert opinion. No direct research evidence. One or more studies with very severe limitations.

Preface

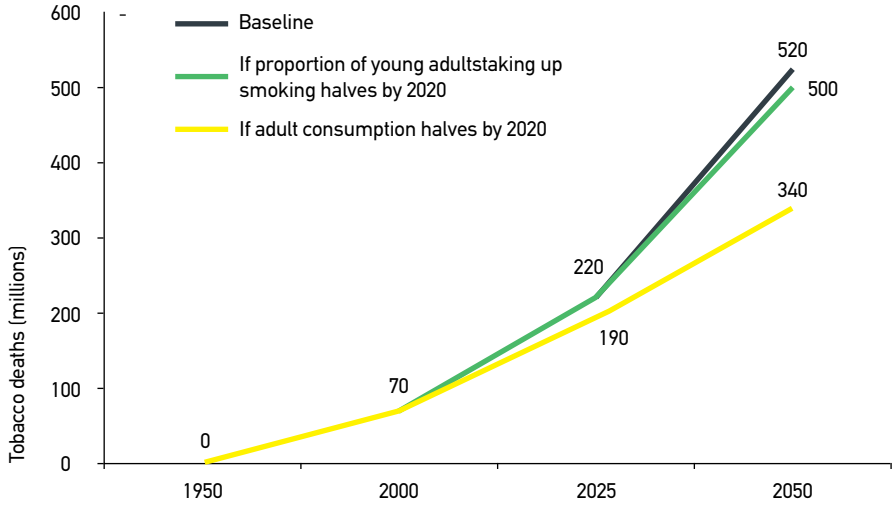
ENSP envisions a tobacco free future, in which no European will have to suffer from tobacco related illnesses and early death. All our constant efforts are concentrated towards providing children and young people the freedom to grow up independently and in good health, without being coaxed into a lifetime of addiction. Tobacco use not only constitutes a great addiction, but is also a fatal trap from which we want to help smokers escape. Our aim hence is to establish a wider coherence among smoking prevention activities, as well as promoting comprehensive tobacco control policies at a European and at the individual national level.

According to the Eurobarometer survey published in 2015i, almost a quarter (26%) of Europeans above the age of 15 smoke and 33% within the 25 to 39 age group are smokers. Tobacco kills half of its regular users, i.e. 700,000 Europeans every year[1].

In this context, there is an increasing consensus that tobacco dependence is a disease that must be treated by health care professionals. All health care professionals must understand that tobacco use is a medical condition, an ICD-10 addiction, and not a habit, vice, pleasure or lifestyle choice.

Cessation interventions have a more mid-term impact on the number of deaths and therefore must be encouraged. As explained in the World Bank report *Curbing the epidemic: Governments and the economics of tobacco control,* if smoking initiation is reduced by 50% by 2020, the number of deaths from tobacco will decrease from 520 to around 500 million in 2050. On the other hand, if half of the current smokers quit by 2020, the number of deaths from smoking would be reduced from 520 to 340 million in 2050 (Figure 1).

Figure 1: Unless current smokers quit, tobacco deaths will rise dramatically in the next 50 years. Estimated cumulative deaths 1950-2050 with different intervention strategies. (Source: The World Bank)



Article 14 of the WHO Framework Convention on Tobacco Control (WHO FCTC) states that:

"Each Party shall develop and disseminate appropriate, comprehensive and integrated guidelines based on scientific evidence and best practices, taking into account national circumstances and priorities, and shall take effective measures to promote cessation of Tobacco use and adequate treatment for tobacco dependence".

The guidelines for implementation of Article 14[ii]:

i. *Encourage Parties to strengthen or create a sustainable infrastructure which motivates attempts to quit, ensures wide access to support for tobacco users who wish to quit, and provides sustainable resources to ensure that such support is available;*
ii. *Identify the key, effective measures needed to promote tobacco cessation and incorporate tobacco dependence treatment into national tobacco control programmes and health-care systems;*
iii. *Urge Parties to share experiences and collaborate in order to facilitate the development or strengthening of support for tobacco cessation and tobacco dependence treatment.*

According to these aforementioned guidelines, effort should be focused on developing the infrastructure to support tobacco cessation and treatment of tobacco dependence among FCTC party members, with the FCTC recommending that *"Parties should implement the actions listed below in order to strengthen or create the infrastructure needed to promote cessation of tobacco use effectively and provide adequate treatment for tobacco dependence, taking into account national circumstances and priorities."*

These action steps can be summarised as follows
1. Conduct a national situation analysis
2. Create or strengthen national coordination
3. Develop and disseminate comprehensive guidelines
4. Address tobacco use by health-care workers and others involved in tobacco cessation
5. Develop training capacity
6. Use existing systems and resources to ensure the greatest possible access to services
7. Make the recording of tobacco use in medical notes mandatory
8. Encourage collaborative working
9. Establish a sustainable source of funding for cessation help

Within the current ENSP Guidelines for Treating Tobacco Dependence we aim to address mainly Step 3, taking however into account the national situation analysis of Step 1 and integrating to the extent possible Steps 5 (Training Capacity) and 7 (make the recording of tobacco use in medical notes mandatory).

According to the implementation guidelines "Parties should develop and disseminate comprehensive tobacco dependence treatment guidelines based on the best available scientific evidence and best practices, taking into account national circumstances and priorities. These guidelines should include two major components: (1) a national cessation strategy, to promote tobacco cessation and provide tobacco dependence treatment, aimed principally at those responsible for funding and implementing policies and programmes; and (2) national treatment guidelines aimed principally at those who will develop, manage and provide cessation support to tobacco users."

A national cessation strategy and national tobacco dependence treatment guidelines should have the following key characteristics:

- *they should be evidence based;*
- *their development should be protected from all actual and potential conflicts of interest;*
- *they should be developed in collaboration with key stakeholders, including but not limited to health scientists, health professional organizations, health-care workers, educators, youth workers and non-governmental organizations with relevant expertise in this area;*
- *they should be commissioned or led by government, but in active partnership and consultation with other stakeholders; however, if other organizations initiate the treatment guidelines development process, they should do so in active collaboration with government;*

- *they should include a dissemination and implementation plan, should highlight the importance of all service providers (within or outside the health-care sector) setting an example by not using tobacco, and should be periodically reviewed and updated, in the light of developing scientific evidence, and in accordance with the obligations established by Article 5.1 of the WHO FCTC.*

All our efforts and work are oriented to support the WHO FCTC, which we consider to be the tool towards fulfilling ENSP goals. This is the reason why in accordance with FCTC Article 14, these European Guidelines for Treating Tobacco Dependence have been developed and are freely provided to health care professionals and the public. We are confident that these Guidelines for Treating Tobacco Dependence will help equip health care professionals with the necessary skills to combat this fatal addiction and provide them with a wide range of vital tools in order to help them improve their smoking cessation strategies.

Finally, the present Guidelines constitute the result of constant and intensive work by the Editorial Board of both the 1st and 2nd edition, to whom ENSP is exceptionally grateful.

Francisco Lozano
President, ENSP

Panagiotis Behrakis
Chair, ENSP Scientific Committee

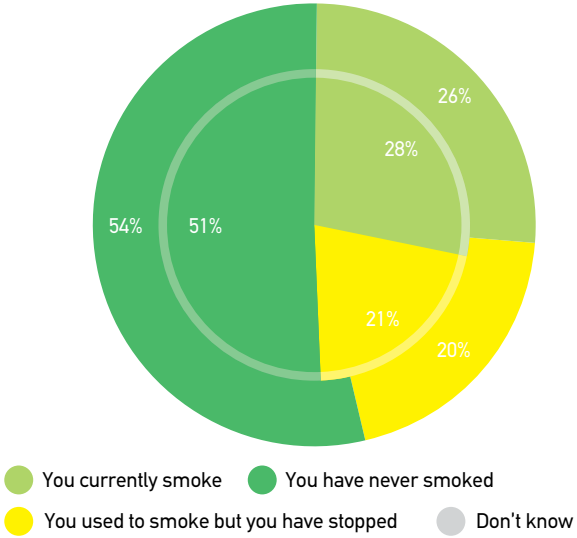
i) Special Eurobarometer 429 (2015). http://ec.europa.eu/public_opinion/archives/ebs/ebs_429_en.pdf
ii) WHO Framework Convention on Tobacco Control: guidelines for implementation, 2011
http://whqlibdoc.who.int/publications/2011/9789241501316_eng.pdf

PART ONE | Chapter 1

Assessment of tobacco use and tobacco dependence

1.0 Assessment of tobacco use and tobacco dependence

QC1. Regarding smoking cigarettes, cigars, cigarillos or a pipe, which of the following applies to you? In this question and the following questions in this section, smoking cigarettes does not include use of electronic cigarettes.



Inner pie: EB77.1 Feb.-Mar. 2012, Outer pie: EB82.4 Nov.-Dec. 2014

"Just over a quarter of respondents in the EU currently smoke boxed cigarettes, cigars, cigarillos or a pipe (26%), which represents a two percentage point decrease since 2012"
Eurobarometer 2015

1.1 Tobacco use is a disease

Tobacco use is the leading cause of premature death and disability in Europe.[1,2] Each year, more than 700,000 Europeans die from tobacco-related illness.[2] It is a known fact that a smokers' life expectancy is ten years shorter than that of a non-smoker and half of tobacco users will lose 20 years of healthy life before dying from a tobacco-related disease.[3]

Tobacco dependence is a disease, which drives the vast majority of tobacco use among adults. Tobacco dependence is associated with the long-term, daily use of tobacco-based products (cigarettes, pipes, cigars, bidis, hookahs, chewing tobacco etc.). Most smokers are unable to stop smoking at their own will. In medical terms chronic smoking is defined as: tobacco dependence, nicotine dependence, tobacco addiction or nicotine addiction.

Doctors and health professionals must therefore take into account that tobacco dependence is a medical condition and not a habit, vice, pleasure, or life-style choice.

The main etiological factor of tobacco dependence disease is nicotine. Nicotine is a highly addictive drug which is contained in tobacco and which determines dependence in those who use tobacco products chronically. Even though, depending on the intensity, duration of use and type of tobacco product used, not all tobacco users follow the same risk pattern, the response of health professionals to tobacco use must be one: to treat the smokers' tobacco dependence without delay.

As tobacco dependence is a disease, it must be diagnosed and treated in the same way as other chronic diseases. A health professional has the duty to intervene and initiate tobacco cessation. Prompt initiation of treatment for tobacco dependence is a good practice for doctors and health professionals, as tobacco consumption is mainly driven by tobacco dependence: only in very exceptional cases is tobacco smoking driven by a smoker's free choice of life-style. It is bad practice not to treat or arrange for treatment of tobacco-dependent patients. At minimum clinician's

Figure 1.1: Intervening with tobacco users in clinical settings

should provide brief counselling intervention to all patients who use tobacco (Figure 1.1).

Once tobacco use and dependence are correctly perceived as a disease, it follows suit that tobacco-dependent smokers require medical assistance offered by a health professional in order to quit, which is provided through tobacco dependence treatment. As is the case for other chronic diseases, medical aid consists of diagnosing chronic tobacco use and tobacco dependence, followed by regular treatment for remission of tobacco consumption and treatment of chronic tobacco dependence.

By way of conclusion, by smoking tobacco, individuals not only introduce nicotine into their own bodies and maintain or increase tobacco dependence, but also expose themselves to numerous severe illnesses, many of which are fatal, caused by the toxins contained in tobacco. The earlier tobacco dependence is treated, the earlier the patient quits smoking or using oral tobacco and tobacco smoke and the higher the health benefit for the patient.[3]

1.2 Definitions, classifications, terms and specific explanations

1.2.1 Tobacco dependence: an acquired industrial disease

Tobacco dependence is an addiction to tobacco caused by the drug nicotine. The smoker suffering from tobacco dependence cannot stop using the substance despite the fact that it causes him/her harm. Inhaled nicotine is known as a drug able to induce an addiction at least as strong as that of heroin or cocaine.[4] Tobacco users who took up smoking as teenagers are usually more addicted than those who took up tobacco use as adults.[5] Nicotine, a substance with psycho-active properties, creates the cravings for cigarettes, cigars, pipes, making smokers unable to quit easily and causes smokers to have physical and psychological symptoms when abstaining from smoking. While the nicotine contained in tobacco causes the nicotine dependence, the toxic effects are mainly due to other substances contained in the tobacco smoke.

1.2.2 Mechanism of induction of tobacco dependence

Inhaled nicotine reaches the arterial blood circulation of the brain via the lungs in as little as seven seconds.[6] Nicotine binds to specific acetylcholine receptors (mainly alpha4beta2 nicotinic acetylcholine receptor) in the nucleus accumbens area of the forebrain which stimulate the release of neurotransmitters, such as dopamine and noradrenaline which is perceived as pleasure by the tobacco user.[7, 8] The pleasure that the tobacco user perceive is in fact the relief of early withdrawal symptoms as nicotine levels rise and nicotine receptor stimulation occurs.

Nicotine dependence main feature is the desire to experience nicotine's pharmacological effects and avoid the possible withdrawal phenomena and conditioned associations, either positive (nicotine produces psychoactive stimulation) or negative (absence of nicotine results in discomfort).[7]

Each cigarette immediately decreases the craving but desensitizes nicotine receptors and increases their number, thus increasing the urge for the next cigarette.[8] This stimulation caused by tobacco use triggers chronic consumption.[7, 9] During the phase of tobacco dependence initiation, the smoker will have to raise the amount of nicotine administered in order to recreate the same intense sensations. After the initial adaptation period, the smoker needs his/her individual dose of nicotine in order to feel a neutral state and to prevent withdrawal symptoms. This morphologic adaptation occurring in the central nervous system corresponds to the development of a physical dependence.[7, 9]

1.2.3 Nicotine is not the only driver of tobacco dependence

Nicotine dependence has two components: physical dependence and psychological dependence.[10]

In addition to the physical dependence, the repeated use of tobacco products can become a habit. The social contacts and the situations associated with a certain daily routine can reinforce tobacco use. Over time, this behaviour becomes anchored in daily life. As such, it is recommended that tobacco use treatment be supported both by pharmacological treatment to alleviate the physical symptoms and by behavioural therapy aimed at addressing routines and triggers associated with an individuals tobacco use.

1.2.4 Nicotine dependence according to WHO

A person is considered as nicotine-dependent when he/she has a

history of chronic consumption with the following characteristics: substance abuse, continues to self-administer the substance despite perceived negative effects, high tolerance towards the substance and manifests withdrawal symptoms when trying to stop use.[6]

According to the criteria adopted by the World Health Organization (WHO) in the *International Classification of Diseases,* tobacco dependence is included in: *Mental and behavioural disorders due to tobacco use* and has the disease code F17 (Table 1.1).[11]

The dependence syndromes refer to a cluster of physical, psychological, behavioural and cognitive phenomena in which the use of a substance (in this case tobacco) becomes a priority for person concerned, disfavouring other behaviours, which in the past used to have a higher value for that person.

Nicotine withdrawal syndrome

While administering nicotine in the body, chiefly by inhalation, leads to nicotine dependence, conversely, when nicotine is no longer delivered to a nicotine-dependent person, nicotine withdrawal syndrome occurs.

Nicotine withdrawal symptoms are caused by suddenly stopping nicotine supply. Nicotine withdrawal can manifest itself in the first four to twelve hours after stopping smoking.

Symptoms include[12]:

- acute / uncontrollable need to smoke (craving);
- irritability / aggression / anger;
- anxiety;
- restlessness;
- tiredness;
- increased appetite;
- difficulty concentrating;
- depression;
- headaches;
- night time awakenings;
- light headedness/dizziness.

These symptoms vary depending on the individual: some smokers feel withdrawal more intensely than others. All these manifestations are temporary, reaching maximum intensity in the first 24 to 72 hours and decreasing over 3-4 weeks.[12] In

Table 1.1: Classification of tobacco dependence in the ICD10CM classification of diseases, WHO (Update effective October 1st 2015) Website for reference http://www.icd10data.com

Nicotine dependence F17	
Excludes (others specific codes)	
• History of tobacco dependence (Z87.891) • Tobacco use NOS (Z72.0) • Tobacco use (smoking) during pregnancy, childbirth and the puerperium (O99.33-) • Toxic effect of nicotine (T65.2-)	
F17	**Nicotine dependence**
F17.2	Nicotine dependence
F17.20	Nicotine dependence, unspecified
F17.200	…uncomplicated
F17.201	…In remission
F17.203	…nicotine dependence unspecified, with withdrawal
F17.208	…with other nicotine-induced disorders
F17.209	…with unspecified nicotine-induced disorders
F17.21	Nicotine dependence, cigarettes
F17.210	…uncomplicated
F17.211	…In remission
F17.213	…Nicotine dependence
F17.218	…With other nicotine-induced disorders
F17.219	…With unspecified nicotine-induced disorders
F17.22	Nicotine dependence, chewing tobacco
F17.220	…uncomplicated
F17.221	…In remission
F17.223	…with withdrawal
F17.228	…With other nicotine-induced disorders
F17.229	…With unspecified nicotine-induced disorders
F17.29	Nicotine dependence, other tobacco product
F17.290	…uncomplicated
F17.291	…in remission
F17.293	…With withdrawal
F17.298	…With other nicotine-induced disorders
F17.299	…With unspecified nicotine-induced disorders

approximately 40% of patients symptoms can last longer than 3-4 weeks.[12]

Nicotine withdrawal symptoms represent the sum of all changes induced by abrupt cessation of nicotine consumption, which is particularly difficult in the first two to six weeks and which must be accompanied by qualified medical assistance and psychological support. Thus the best strategy recommended by all smoking cessation guidelines for treating nicotine dependence is to combine pharmacological treatment with psycho-behavioural therapy.[13]

Smoking status

It is recommended that all clinicians appropriately assess of current and past tobacco use with patients.

The following definitions are used for the classification of smoking status:

- ***Non-smoker*** is a person who has not smoked more than 100 cigarettes in his/her life-time (or 100 g of tobacco, in the case of pipes, cigars or other tobacco products).
- ***Daily smoker*** is a person who has smoked on a daily basis for at least three months.
- ***Occasional smoker*** is a person who has smoked, but not on a daily basis.
- ***Ex-smoker*** is a person who has quit smoking for at least six months.

Some standard questions considered helpful in assessing smoking status are as follows:

1. Have you ever smoked cigarettes or used other tobacco products (e.g. pipes, cigars etc.)?

For current smokers:

2. How many cigarettes (or other tobacco products, e.g. pipes, cigars etc.) do you usually smoke per day?
3. How many years have you been smoking?
4. How many cigarettes have you smoked in your life? Is it more or less than 100?
5. Do you smoke every day/on certain days/in specific situations? Which situations?

For ex-smokers:

6. How many years/months has it been since you quit smoking?

1.3 Smoking is a chronic relapsing disease

1.3.1 Relapse patterns

Nicotine/tobacco dependence is a chronic relapsing condition, which is mostly acquired during adolescence.5 Tobacco dependence has many characteristics of a chronic disease with most smokers persist in consuming tobacco for years or decades.

"Relapse" is considered a return to regular smoking by someone who has quit. *Relapse* typically refers to a period of several days or more of continuous smoking after a period of abstinence. *"Failures"* or *"relapses"* mean daily smoking for at least three days after a period of at least 24 hours without any smoking.

A *"lapse"* or a *"slip"* denotes the use of tobacco after a prior period of abstinence that does not result in the return to regular smoking. This may be the case of quitters and ex-smokers who smoke less than one cigarette per day in up to three days in one week, or smoke any number of cigarettes one day in one week in the week before any scheduled visit. A lapse may be an isolated event that is followed by a renewal of abstinence, or it is a strong predictor of relapse.

Among ex-smokers relapse is common. Relapse most frequently occurs within the first few days of a quit attempt when withdrawal symptoms are the greatest. Over 75% of unaided quitters relapse within the first week making this a critical period of time.[12] Figure 1.2 depicts the likelihood of relapse within the first year of quitting.

Once patients are smoke free for two to three months their risk of relapse is much lower – but by no means gone. Even among tobacco users who may have succeeded in quitting for brief or longer periods of time the risk of relapse remains high. Patients who stay smoke free for at least 12-months have a 35% lifetime probability of relapse (See Figure 1.3).[14]

1.3.2 Treatment of tobacco dependence after cessation

Tobacco dependence may need persistent and repeated therapeutic interventions, as well as long- term follow-up until it is cured.[15]

Understanding its chronic nature implies long-term observation,

Figure 1.2: Relapse pattern in smokers who quit unaided[12]

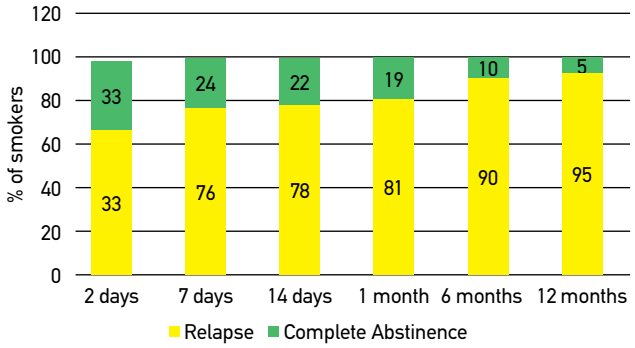


Figure 1.3: Probability of relapse by year[14]

and not simply interventions that are delivered during acute stages. Several pharmacological treatment cures might therefore be required after relapse, sometimes by alternating one medication with another, as well as educating patients and offering them psycho-behavioural support to avoid the risk of relapse. No effective treatment has yet been identified to treat tobacco dependence relapse in the abstinent smoker. Simply being an ex-smoker is no sure guarantee of the end of tobacco dependence.

Although many clinicians are able to treat patients with chronic diseases such as diabetes, arterial hypertension, COPD, etc., they feel less comfortable when it comes to treating tobacco dependence, because they ignore the fact that tobacco dependence is a chronic disease. Approaching tobacco use as a chronic disease accelerates the curative process and increases the success rate of cessation pharmacotherapy and reduces relapses.

We recommend to all practitioners who assist patients identified as smokers to approach tobacco use and tobacco dependence as a chronic relapsing disorder and to define it in medical terms as tobacco dependence.

1.4 Routine identification of smokers is mandatory in current medical practice

In order to achieve the best smoking cessation rates, all smokers must be systematically identified at any medical contact, whether or not the patient is in consultation for a tobacco-related disease. The best opportunities for this purpose are occasional or annual medical visits, as most citizens visit their own family doctor or general practitioner at least once a year, or regularly/occasionally visit a dentist or another doctor or health professional for various health or other reasons. All doctors, no matter what their specialty, should use these occasions to identify smokers and to organize cessation therapy.

Clinical evaluation of tobacco use is a mandatory medical act and must be legitimized as a routine intervention.

Smoking status and tobacco consumption as recommended by these smoking cessation guidelines must be recorded in the patient's medical records: e.g. hospital admission or discharge papers, referrals, laboratory reports etc. This recommendation is based on a meta-analysis of nine randomized studies about the impact of tobacco use screening on cessation rates.[13] Also, in a survey published in 2009, McCullough and colleagues showed that the number of patients registered for receiving cessation counselling was higher when doctors systematically asked about tobacco use and drew up a cessation plant.[16]

1.5 Assessment/diagnosis of tobacco use and dependence

Assessing smokers is a process consisting of a clinical and

biological assessment of tobacco smoke exposure, assessment of tobacco dependence, assessment of psycho-behavioural profile and health consequences of tobacco use.]

1.5.1. Clinical diagnosis of tobacco use and dependence

Clinical diagnosis is based on:

Smoking status

Smoking status (non-smoker, occasional smoker, daily smoker, ex-smoker).

Type of tobacco product used

The type of tobacco product used gives an idea about the level of addiction, since nicotine dependence is more severe in cigarette consumers, compared to those who use cigars, pipes, water pipes, e-cigarettes or oral tobacco.

Tobacco consumption

Tobacco consumption may be defined as:

- number of cigarettes smoked per day;
- number of cigarette packs/years (no. of PY). The number of pack/years is calculated by multiplying the number of cigarettes packs smoked/day by the number of years of smoking (e.g. if someone smokes 15 cigarettes per day for 15 years, this 15 equals 15x15/20 = 11.2 PY).

Tobacco dependence assessment

Tobacco dependence could be diagnosed in accordance with the WHO definition. Tobacco dependence is defined by the presence of at least 3 out of 7 definition criteria, if present at a moment during the past 12 months.[17]

- strong desire to smoke,
- difficulty in controlling quantity,
- withdrawal symptoms when reducing or quitting tobacco,
- continued consumption despite obvious harmful effects,
- priority of smoking over other activities,
- high tolerance,
- physical tobacco withdrawal symptoms.

In daily routine, nicotine/cigarette dependence is mainly assessed using the Fagerström nicotine dependence test, FTND (Table 1.2) that provides not only a yes/no answer but also a final

Table 1.2: Fagerström Test for nicotine dependence (FTND)[18]

1. How soon after you wake up do you smoke the first cigarette?
Under 5 minutes (3)
6-30 minutes (2)
31-60 minutes (1)
More than 60 minutes (0)
2. Does it feel difficult for you to abstain from smoking in places where smoking is banned (e.g. church, cinema, train, restaurant etc.)?
Yes (1)
No (0)
3. Which cigarette would it be the most difficult for you to give up?
The first cigarette in the morning (1)
All the others (0)
4. How many cigarettes/day do you smoke?
10 or fewer (0)
11-20 (1)
21-30 (2)
31 or more (3)
5. Do you smoke more frequently in the first hours after you wake up than in the rest of the day?
Yes (1)
No (0)
6. Do you smoke if you are so ill that you are immobilized in bed most of the day?
Yes (1)
No (0)

The patient may fill in the questionnaire directly. The range of scores is from 0 to 10. This enables precise evaluation of nicotine dependence, based on which a therapy will be elaborated:

Score 0-3: no or low tobacco dependence
Score 4-6: medium tobacco dependence
Score 7-10: high tobacco dependence

score, which categorizes tobacco users as having either low, medium, or high levels of nicotine dependence.[18] The higher the score, the higher the nicotine dependence of an individual. The level of nicotine dependence can be used to guide the design of treatment plans for patients.

The key questions are questions 1 and 4: the number of cigarettes smoked daily and the time of the first cigarette after waking up in the morning. These questions may be asked by a doctor during consultation and constitute the short version test, scored from 0 to 6, with the same score values as the 10 questions version of FTND.[18]

In specialized smoking cessation clinics the use of additional assessment tools to profile tobacco users level of dependence is optional. Such an evaluation is possible using several instruments, i.e. the Nicotine Dependence Syndrome Scale (NDSS)19 and the Wisconsin Inventory of Smoking Dependence Motives (WISDM).[20]

1.5.2 Analysis of previous quit smoking attempts

Past experience with quitting has been shown to be highly predictive of future quit attempts and can be used to guide future treatment.[21] It is recommended that clinician's assess:

- the number of past quit attempts,
- longest smoking abstinence period,
- any previous cessation treatment and what the treatment consisted of,
- any history of withdrawal symptoms,
- any relapsing risk factors,
- positive aspects described during abstinence.

These features are important to anticipate treatment success or failure risk factors, as well as treatment compliance and patient's capacity to overcome withdrawal.

1.5.3 Motivation to quit smoking

Assessing the motivation of a smoker to quit is recommended. All health professionals should assess motivation of patients. There are a variety of methods that can be used to assess motivation to quit which we describe here.

Motivation can be assessed through direct questions including:

- Do you want to quit smoking (now)?
- If you decide to quit smoking, how confident are you that you would succeed?
- What are your reasons for wanting to give up smoking?
- How important is it for you to quit smoking?

According to J.O. Prochaska and C.C. DiClemente's well known Transtheoretical Model (TTM) of Behaviour Change the psychological process of smoking cessation goes through five stages (Figure 1.4):[23]

- *Pre-contemplation:* the patient is fully satisfied by his/her smoking behaviour and he/she does not feel any need for a change;
- *Contemplation:* the patient feels the need for a change, but this is not strong enough to push himself/ herself to action or to make an action plan
- *Preparation:* the patient has decided to try to change his/her smoking behaviour and is ready for this change in the near future
- *Action:* the patient starts the smoking cessation attempt.
- *Maintenance:* abstinence for 6-months or longer.

Figure 1.4: Stages of change for smoking cessation according to Prochaska model[23]

Source: Di Clemente C.C., et al. J Consult Clin Psychol, 1991; 59: 295-304

Typically stage of change is assessed using the question: "what are your feelings about quitting smoking right now?: response options include: a) I would like to quit in the next 30 days, b) I would like to quit in the next 6-months, c) I am not planning on quitting smoking in the next 6-months

It is important to note that individuals do not necessarily pass through the stages of change in a linear fashion; rather, they move back and forth between stages as a function of motivation, readiness, and other factors influencing change.

Simple scales, in which clinicians ask patients to rank on a scale from 1 to 10, their motivation to quit smoking, can also be useful in busy clinical practice (Figure 1.5).

There are additional published instruments to measure the motivation including the Motivation to Stop Smoking Scale.[23]

Regardless of the patient's readiness to quit or motivation, smoking cessation treatment should be initiated by a physician for all patients who report tobacco use. In the case of smokers with comorbidities and patients with tobacco dependence the health professional has to communicate to the patient the risk of continued tobacco use and the need to quit immediately. As is the case with all medical decisions, the patient remains free to refuse treatment, but the health professional has to propose smoking cessation treatment and thus have the same conviction as when proposing a treatment for diabetes or for hypertension.

1.5.4 Patient's medical history

The patient's medical history is relevant in the choice of therapeutic option, with regard to any drug interaction or any incompatibility required by a concurrent disorder/comorbidity. Acute cardiovascular events, history of seizure, kidney disease, current or history of addiction etc. may also impose caution in prescribing some pharmacological treatments; thus the need to note them in the smoker's medical records.

1.5.5 Pregnancy/ Breast Feeding/ Contraception

It is also very important to check the physiological status in women (pregnancy, breast-feeding, contraception methods etc.) to organize smoking cessation effectively. Pregnancy is associated with significant increases in the rate of nicotine metabolism.[24]

Figure 1.5: Easy to use scale of motivation

1.5.6 Patient's anxiety and depression history

1.5.6.1 Initial Screening

Generally, depression and anxiety are the most frequent conditions described in heavy smokers. Very often such syndromes impose caution or raise awareness about the side effects of cessation medication. Two simple questions from the Primary Care are recommended as a screening tool for depression.[25]

- *Have you felt sad, depressed, desperate in the past month?*
- *Have you had the feeling that you do things with neither pleasure nor interest in the past month?*

A positive answer to both questions may be interpreted as a strong sign of depression.

Another faster way to quantify depression can be just one question:

- *Have you felt sad on most of the days over the past two weeks?*

If the answer is yes, again we can consider this a strong indication that the patients may be suffering from depression.

All patients responding yes to this question should be screened for suicidal ideation using simple screening tools or validated assessment tools.

- *Have you had any thoughts of death?*

1.5.6.2 Clinical Assessment of Anxiety and Depression

The use of validated clinical tests can be used as required in clinical practice to assist with the diagnosis of depression and anxiety and assess severity:

- The Anxiety and Depression Scale,[26]
- Hamilton Depression Subscale,[27]
- Patient Health Questionnaire(PHQ),[28] and
- Beck Depression Scale – II[29]

1.5.7 Laboratory diagnosis of tobacco dependence

Smoking status as defined based on clinical criteria may be also evaluated by biochemical laboratory tests to assess biomarkers of tobacco smoke exposure, such as carbon monoxide concentration in exhaled air and level of cotinine (a metabolite of nicotine).

Biochemical validation is generally used in research to confirm self-reported rates of smoking abstinence and as such is not recommended as standard practice in clinical settings.

Carbon monoxide (CO)

Breath CO is the easiest biomarker to monitor; in the absence of CO in the environment, it is a well accepted measure of tobacco consumption. Breath CO is easily measured by asking a smoker to exhale into a commercially available hand-held CO analyzer (Figure 1.6). CO is measured in ppm (parts per million), a measurement unit that can be converted as carboxyhemoglobin equivalent.

CO's half-life is approximately, 2-6 hours.[30] The CO levels in exhaled air of a smoker may achieve 10-20 ppm (i.e. 2-5% carboxyhemoglobin).30 There is a dose relationship between the number of cigarettes per day consumed and CO measurements; however significant individual variation should be expected.[30] The level of CO is also influenced by physical effort.[30]

Figure 1.6: Carbon monoxide expired monitoring devices (CO)

In the 24 hours following smoking abstinence, CO reaches normal values. Normally, CO concentration in exhaled air of a non-smoker does not exceed 4 ppm. Exposure to second hand smoke will influence CO values. The recommended cut-off value to separate smoker and non-smoker is 9 ppm.[31] A reading of 10 ppm or more signifies smoking. However research suggests cut-offs of 2 or 5 ppm provide the highest degree of accuracy of whether or not someone smoked in the past 24 hours.[32,33]

CO concentration in the morning (after several hours of sleep without smoking) are usually lower than measurements taken in the afternoon. For this reason it is recommended to measure CO in the afternoon, when it will represent a more true tobacco exposure biomarker.[30]

CO concentration among smokers with chronic obstructive pulmonary disease (COPD) has been found to be higher than in the general population.[34] In these subjects, a higher CO ratio is either explained by the production of carbon monoxide as a result of the chronic airway inflammatory processes in COPD, or it is simply due to the more intense smoking described in this category of patients.

Clinical utility of CO monitoring

CO measurement has been used as a tool to enhance patient motivation to quit.[35] The fast conversion of CO to normal values encourages the smoker to be abstinent and thus demonstrates lower CO values at each follow-up visit, which supports the quitting attempt. There is however insufficient evidence to support the use of CO monitoring in comparison to standard treatment.[35] However, due to its value as a motivational tool it is recommended that specialized smoking cessation centers should be equipped with a CO analyzer. The use of CO analyzers in other settings such as primary care is also a good practice.

Cotinine

Cotinine is the main metabolite of nicotine and is a biomarker of exposure to tobacco smoke. By monitoring the concentration of cotinine in the body, one can assess an individual's tobacco smoke exposure. Cotinine can be measured in blood, hair, saliva and urine.

The half-life of nicotine is about two hours; however nicotine

concentration can vary depending on the time of the day when the last cigarette was smoked.[30] Cotinine has a half-life of 15-20 hours and as such can be used to measure 24-48 hour smoking abstinence.[30] In smokers, plasma cotinine is about 200 ng/ml, but may reach up to 1000 ng/ml depending on the intensity of smoking.[31] There is considerable variation among individual smokers in levels of cotinine and daily intake of cigarettes.[30] Rates of nicotine metabolism are genetically determined and can influence cotinine levels.[36]

A cut-off of < 15 ng/ml for saliva and of 50 ng/ml for urine is recommended.[30, 31, 37]

In situations where the patient is using nicotine replacement therapy, measurement of cotinine is not recommended. In these cases CO monitoring is the preferred method of validation.[31]

The use of cotinine levels has not been found to be more sensitive than using clinical symptom monitoring to adapt the therapeutic dose of cessation medications.[38] As such, cotinine assessment is not at the present time recommended as a tool for guiding clinical practice.

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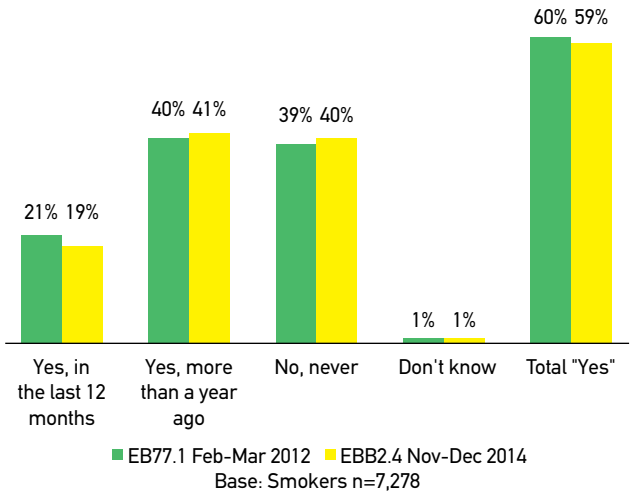
General recommendations for the treatment of tobacco use and tobacco dependence

2.0 General recommendations for the treatment of tobacco use and tobacco dependence

QC17. Have you ever tried to quit smoking? (Multiple answers possible).



"In the last twelve months in the EU, almost one in five smokers have tried to quit smoking (19%), while a further 41% tried to stop further in the past. In total, 59% of smokers in the EU have tried to quit"
Eurobarometer 2015

This chapter briefly presents general recommendations for the treatment of tobacco use and tobacco dependence.

2.1 Tobacco use

Tobacco consumption is mainly due to tobacco dependence, a chronic disorder primarily acquired during adolescence, but all health professionals must consider all tobacco use (smoked or chewed) as a health hazard, even if there is no tobacco dependence. Few adult people smoke only as a behaviour without tobacco dependence.[1,2] Health professionals must inform these patients about the health risks involved and must advise them not to use tobacco, and support cessation using available evidence-based treatments.

Health professionals should be proactive in addressing tobacco use with adolescents to prevent initiative and support cessation among those adolescents who use tobacco. Adolescents who smoke without tobacco dependence should be a target for intervention, given consumption during adolescence becomes tobacco dependence towards the end of adolescence.

2.2 Tobacco dependence disease

In nearly all adult smokers, smoking is driven by a disease acquired during adolescence. This is tobacco dependence, a chronic disease with no complete cure. Still, tobacco use may be halted for a short period or for life, resulting in significant health benefits.[3]

Tobacco-dependent smokers light up most cigarettes once the level of nicotine has declined in the brain, typically 20 to 60 minutes after the last cigarette.[4] Tobacco consumption is not driven by the brain cortex, but rather by a non-conscious part of the brain not controlled by will *(accumbens nucleus)*.

As with all chronic diseases, after diagnosis and assessment, health professionals should develop a treatment plan to support cessation. The patient may refuse treatment, but health professionals must act to cure the patient of a disease that kills half of patients suffering from it.[5] Just as health professionals carry out treatment of diabetes mellitus, hypertension or any other chronic disease, so health professionals must treat tobacco dependence once a diagnosis has been made. Smoking cessation treatment has been studied in depth and tools exist to help smokers and other tobacco users to quit tobacco.

2.3 Smoking cessation

The key components of successful cessation (remission) are combinations of therapeutic education, behavioural support and pharamacotherapy.[2,6]

A tobacco user's preparation, motivation to quit, nicotine dependence, age, comorbidity and numerous personal factors will affect the chances of success.[2]

2.3.1 Therapeutic education

- Explain tobacco dependence disease
- Explain the reasons for lighting up a cigarette
- Explain the health consequences of smoking
- Explain the benefits of quitting smoking
- Explain tobacco cessation treatment
- Explain chronic tobacco dependence management to prevent relapse
- Present tools available locally to smokers.

2.3.2 Behavioural support

- Identify the behavioural causes of smoking, the long-term and immediate smoking stimulation factors.
- Increase motivation to quit and decrease fears of quitting and of becoming a non-smoker
- Learn how to deal with emotions.

2.3.3 Medications

- Nicotine replacement therapies are available in transdermal form (patches), oral form (gum, lozenge, sublingual tablets, inhaler) and in some countries as nasal spray. Compared to the past, dosage is more adaptable, fixed dosing is rarely used and combinations of patch and oral NRT formulations are largely used to increase the dose of nicotine close to the level of nicotine received by cigarettes.
- Varenicline is a partial agonist of alpha4 beta2 nicotine receptor used as smoking cessation monotherapy with an efficacy versus placebo, which has been found to be greater than other first line monotherapies. Varenicline and combined high dose nicotine replacement therapy are equally effective.[6]
- Bupropion is a medication used initially to treat depression that has shown to be effective for smoking cessation.[2,6] This drug can be combined with NRT.
- Nortriptyline (a tricyclic antidepressant) and cytisine (a nicotine receptor partial agonist) are second line smoking cessation therapies available in some countries and have been shown to be effective.[2,6] These medications tend to be less expensive.

2.3.4 Tobacco cessation

The initial aim of the treatment is to quit tobacco.

- A quitter is a smoker who has voluntarily not smoked a single cigarette.
- Abstinence has to be monitored when possible together with monitoring of expiratory carbon monoxide (CO).
- The maximum recommended level of CO in breath required to validate abstinence is 7 ppm.

For clinical practice, we recommend that abstinence should be confirmed after six weeks of tobacco abstinence post quit date, with an allowed grace period of two weeks. Also, abstinence is established when a subject's self-declaration not to have smoked or used tobacco is confirmed by CO reading below 7 ppm. A "grace period" is a period immediately after the quit date or intervention in which continued smoking is not counted as a failure. A routine six-month assessment of abstinence is recommended to assess cessation and early relapse.

2.4 Treatment of tobacco dependence after cessation

Tobacco dependence is a chronic disorder with a high risk of relapse after tobacco cessation. Half of new ex-smokers relapse in the following year.[7] The relapse rate is higher in the first weeks of cessation so in clinical practice long-term follow-up is recommended for at least six months and preferably 12 months in order to confirm abstinence and to cover the period of highest relapse risk. Even after several years of abstinence, the risk of relapse remains high.[8] Further studies are needed to identify those at high risk of relapse.

Craving is a major factor of relapse. Uncontrolled cravings should be treated with improved counselling (support) and/or optimization of pharmacotherapy. Cravings and withdrawal symptoms should be assessed at each contact. Uncontrolled craving/withdrawal

symptoms should be treated with increased counselling (support) and/or optimization of pharmacotherapy. To treat cravings, acute formulations of NRT could be combined with standard treatments, but new assessment studies and new effective treatments for craving are required. However, evidence suggests that relapse prevention interventions are likely to be highly cost-effective.[9]

2.5 Prevention of relapse

After quitting smoking, relapse is defined as smoking ≥ 7 cigarettes for seven consecutive days or for two consecutive weeks. Smoking less is defined as a lapse. (For more specific definitions for clinical practice, please refer to Chapter 1.3.1).
After the quit date, treatment should be tailored to the level of craving and risk of relapse. There is an urgent need for studies validating tools and treatments for this purpose. A high craving score is an important factor in predicting the risk of relapse.
Once lapses have occurred, the following provided interventions may prevent or treat relapse:

- Increasing CBT sessions in time, format and number sustains the effectiveness of treatment;
- Using nicotine patches for more than 14 weeks plus short acting NRT formulations when needed;
- Prolonging the use of varenicline from 12 to 24 weeks;
- Prolonging the use of bupropion;
- Combing medications.

Treatment of chronic tobacco dependence after cessation in ex-smokers has been widely assessed and remains a challenge.[10] No validated tools exist to identify ex-smokers with a high risk of relapse and no validated treatments are proposed except continuation of cessation treatment and cognitive behavioural therapy (CBT) to prevent relapse in high-risk relapsing situations.[10] New studies are needed to assess new strategies to treat tobacco addiction in non-smokers and to prevent relapse.

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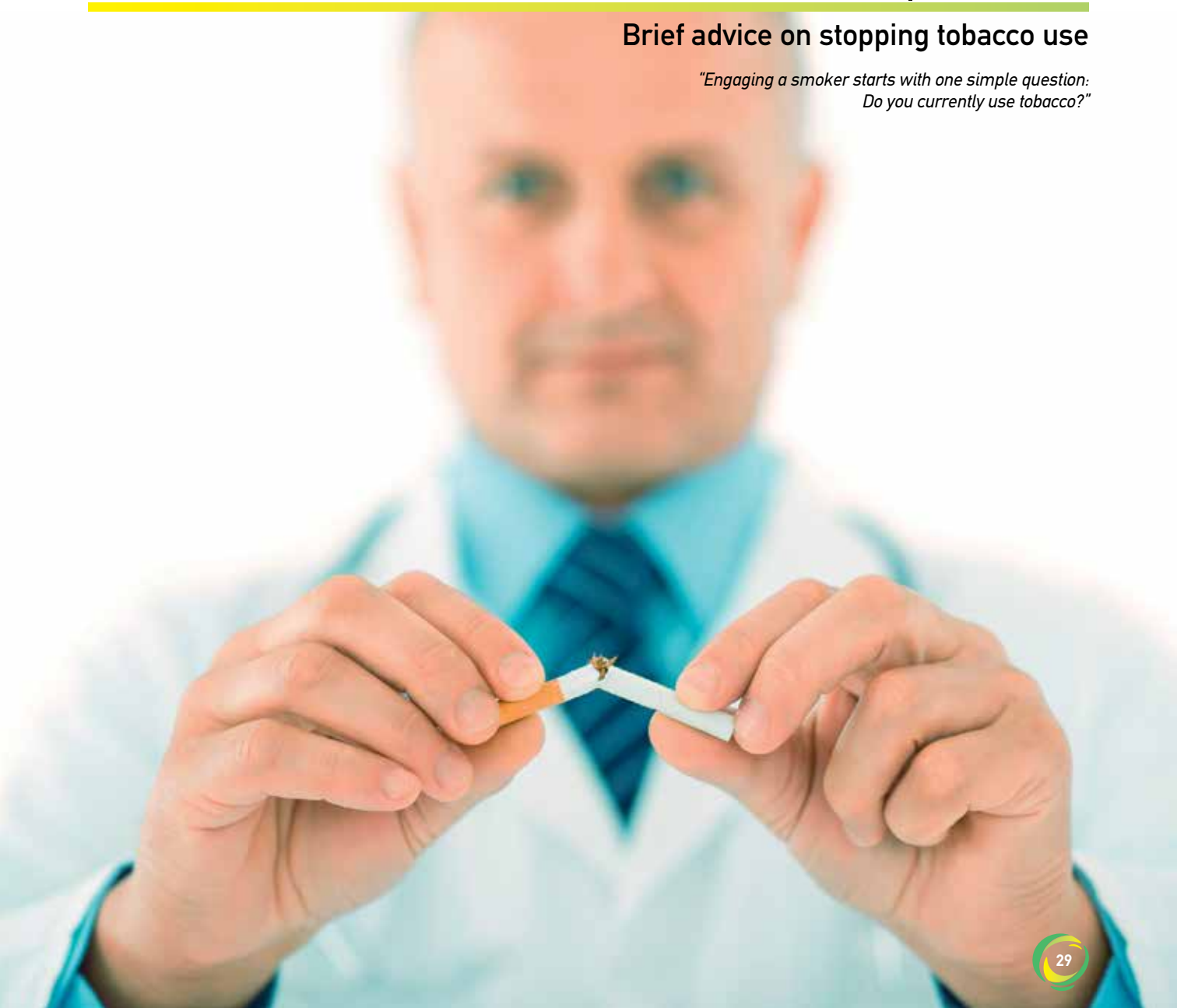
Brief advice on stopping tobacco use

"Engaging a smoker starts with one simple question: Do you currently use tobacco?"



3.0 Brief advice on stopping tobacco use

It is mandatory for all health professionals to provide a minimum of brief advice on quitting smoking to all patients. Not tackling the issue of tobacco use with a smoking patient is bad practice and aggravates the tobacco dependence of the patient.

3.1 General recommendations

Clear but brief smoking cessation advice provided by any medical service provider significantly increases patient motivation to quit and smoking abstinence rates.[1,2] Analysis of the duration of the contact time between doctor and patient for this purpose indicates that minimum counselling (3-5 minutes) offered by various clinicians increases long-term smoking abstinence.[1,2] There is some evidence that offering assistance with quitting to all smokers, regardless of readiness to quit is more effective than offering advice on medical grounds in increasing patient quit attempts.[2]

Minimum counseling (also known as brief advice) can have a substantial public health impact due to the great number of smokers who consult with clinicians every year. All health professionals, i.e. general practitioners, family doctors, occupational doctors, specialized doctors, surgeons, nurses, midwives, dentists should offer minimal counseling to tobacco users. Dentists and dental technicians can be effective in evaluating and counselling smokers to quit.[3]

Recommendations:

- All doctors should recommend quitting tobacco products to all tobacco consumers. Scientific evidence indicates that advice from a doctor significantly increases quit attempts and smoking abstinence rates (level of evidence A).[1,2]
- The efficacy of brief advice (3-5 minutes) from a doctor or other health professional leads to an increased long-term smoking abstinence ratio (level of evidence A).
- Offering of support with quitting to all tobacco users is a recommended practice (level of evidence B).[2]

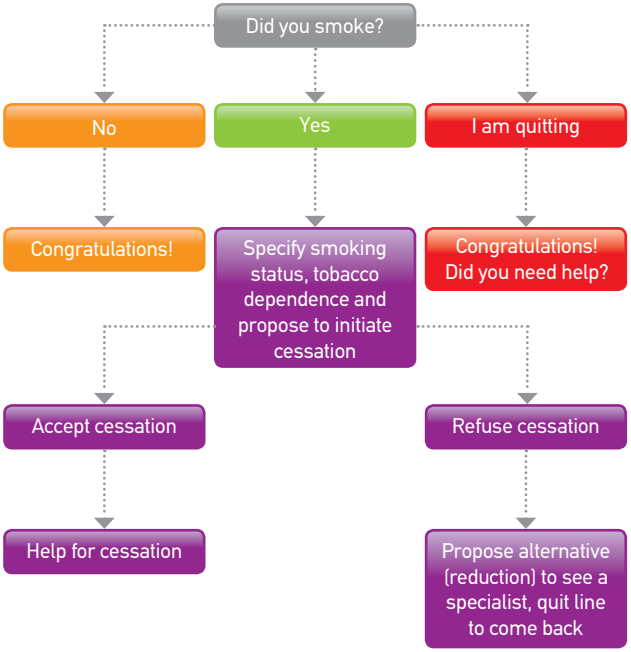
3.2 Intervention plan for medical personnel involved in assisting smokers

- Evaluate the smoking status, for every patient, at each medical visit
- Assist all smokers who wish to quit smoking.
- Provide those who are willing to quit with specialized counseling.
- Whenever and wherever possible, direct smokers to a specialized smoking cessation service or quitting.
- Recommend to tobacco-dependent smokers willing to quit the use of nicotine substitutes or prescribe medication and offer them specific information and advice about therapy and counselling.

3.3 Recommendations for general practitioners

- All general practitioners or family doctors must routinely advise smoking patients to quit smoking, offer support with quitting, and recommend the use of available quit smoking medications. It is recommended to note the patient's behaviour in his/her medical records and, if needed, to refer patients for specialized therapy and counselling (level of evidence A).
- All family doctors and nurses should have training in delivering minimal smoking cessation counselling and be prepared to assist patients with a quit attempt and recommend appropriate treatment (level of evidence A).
- Smokers who cannot quit smoking merely by primary action (own willpower, brief medical advice, pharmacotherapy) should receive specialized treatment as a second stage. This strategy is not yet unanimously applied in current practice, but a smoking cessation counselling programme should be initiated as part of primary care and should be continued with second line interventions in a specialized centre (level of evidence C).

Figure 3.1: Minimal counseling in general practice



- Brief advice gives smokers a pre-quitting motivation when none exists and at the same time it has been shown to increase smoking cessation rates.[1,2] Many smokers cannot quit smoking without medical aid; the most part of heavy smokers who are at a higher risk of developing smoking-related diseases have the greatest need for qualified therapy.

3.4 Recommendation for hospitalized patients

Intervening with smokers while in hospital has been shown to be effective in supporting cessation in particular among those patients with smoking related diseases but also in other groups of patients.[4]

- It is recommended that all categories of medical personnel in hospitals should assess smoking status and should provide brief smoking cessation advice for all hospitalized patients who smoke (level of evidence A).
- Patients should be informed about hospitals' smoke-free status (level of evidence C).
- For hospitalized patients who are current smokers, it is recommended that support should be provided with managing craving and withdrawal while in hospital as well as assistance with cessation from qualified medical staff (level of evidence A).
- High intensity interventions that provide at least 1 month of supportive contact post-discharge are most effective in increasing abstinence rates (level of evidence A).

3.5 Recommendation for pregnant women

- It is recommended that all categories of medical personnel dealing with pregnant women (gynecologists, midwives, nurses and GPs) should assess smoking status and provide smoking cessation advice for all pregnant women who smoke (level of evidence A).
- It is vital for the mother- to quit smoking as early as possible during the pregnancy and maintaining cessation is particularly important after the first trimester, due to the fact that the strongest adverse effects of smoking occur during the second and the third terms of pregnancy (level of evidence C).[5]

3.6 Recommendation for patients with elective surgery

Tobacco use doubles the risks of complications such as wound healing, bone healing scarring, infection, and other side effects.[6,7] It is also shown that stopping smoking after an acute operation and maintaining abstinence for 6 weeks reduces the risk of complications by half.[6,8]

- It is recommended that all patients quit smoking 6 to 8 weeks

before surgery in order to reduce risk of complications (level of evidence A).[6]

- It is essential to inform all patients of the need to quit smoking until the end of the healing process (three weeks for minor surgery and three months for orthopedic surgery) in order to overcome other risks (level of evidence A).[6,8]

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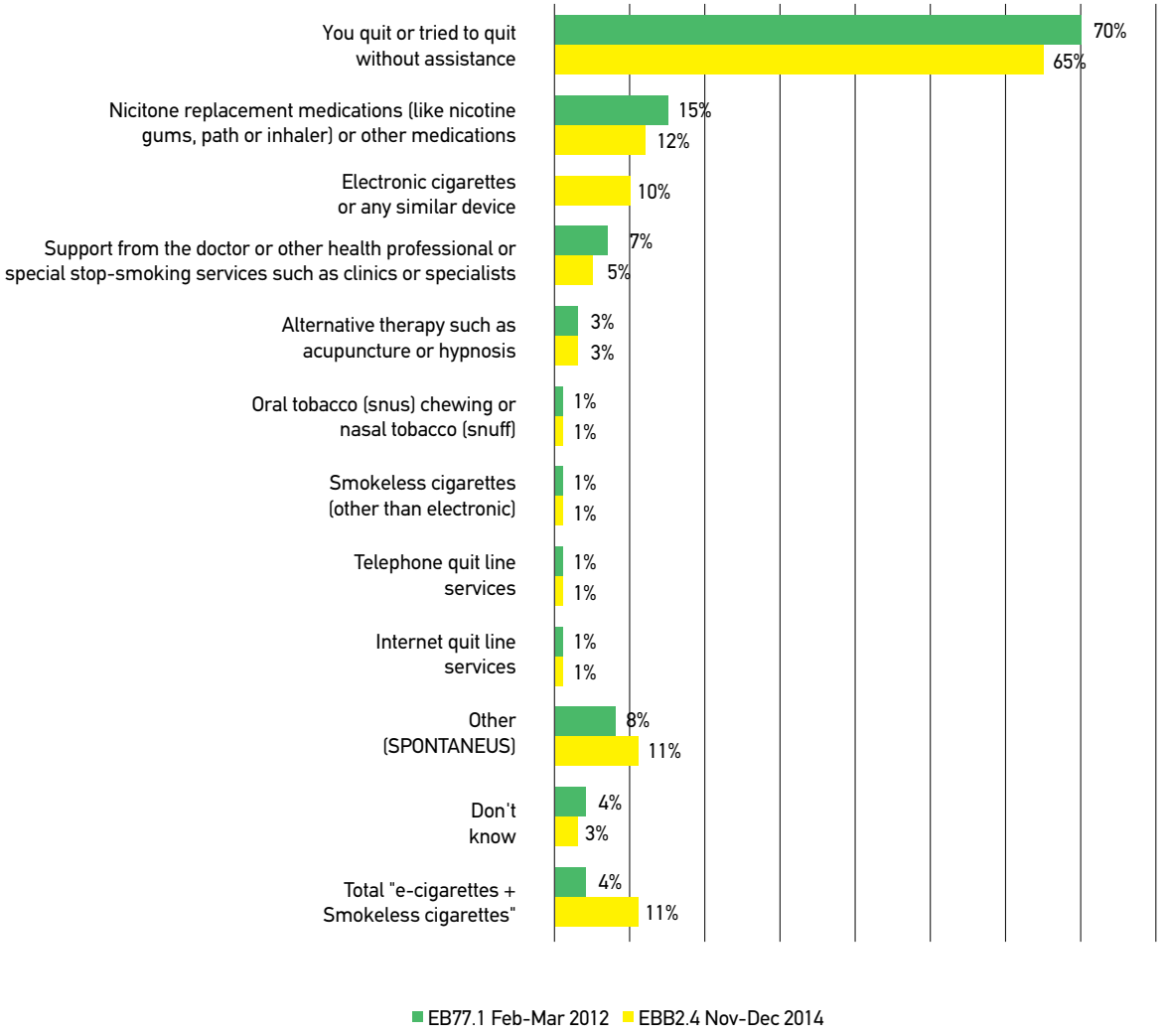
Standard tobacco treatment interventions

4.0 Standard tobacco treatment interventions

QC18. Which of the following did you use in order to quit or to try to quit smoking? (Multiple answers possible)



"According to the 2015 Eurobarometer, 65% of smokers and ex-smokers reported that they quit or tried to quit without assistance, 12% used nicotine replacement medications such as patches, 10% used e-cigarettes, while only 5% used support from a doctor or health professional".

4.1 Therapeutic interventions for tobacco use and tobacco dependence

4.1.1 Therapeutic intervention to stop smoking is mandatory

Article 14 of the Framework Convention on Tobacco Control1 states that every country should provide smoking cessation assistance, and implementation of this approach is now being considered by many countries.[2] Assistance with quitting should be a major part of every European country's tobacco control strategy.

In an editorial, West and colleagues[3] countered four fallacies in a constructive debate about the role of cessation assistance.

"Most smokers stop without help, so providing assistance may seem unnecessary."

This is incorrect as the fact that most smokers who stop do so without assistance does not mean that this is the most effective method of stopping; it only reflects the fact that the numbers attempting to stop without assistance are considerably greater than those trying to stop with it, but evidence shows unassisted attempts are four times less effective.

"Promoting help with stopping may make smokers think they are addicted, so fewer will try to stop."

This is false, as evidence shows smokers who believed they were addicted were actually more likely to make quit attempts than other smokers.[2]

"The results of research into assisted cessation do not apply to the real world."

This is false, as an evaluation of the English smoking cessation services has found that nearly one in seven smokers (14.6%) were carbon monoxide-validated quitters one year after receiving treatment, a proportion similar to the outcomes found in clinical trials,[4] and substantially higher than those achieved without support.

"Other tobacco control interventions are more cost-effective, particularly mass media campaigns"

This is not true, as cost-effectiveness of interventions to assist cessation has been evaluated rigorously from randomized controlled trial data supplemented by data from the 'real world' and found to be excellent,[2] while many other tobacco control interventions' estimates of effectiveness rely upon more circumstantial data and interferences. Also, a false dichotomy between clinical interventions and other tobacco control interventions should not be created, as long as different interventions serve different functions and they work in synergy with each other. The appropriate mix of interventions will depend upon particular circumstances in every country/region at any given time.[5]

Hence, as health benefits of smoking cessation are well-documented and helping people quit is cost-effective compared with other measures in the health sector,[6] it is mandatory that any smoker identified through a medical visit be offered the opportunity to receive medical aid to stop smoking.

Smoking cessation services across Europe vary widely. For the moment, while the UK has put greater emphasis on assisting smokers to stop than other countries, in many European countries, most of the smokers that address a smoking cessation centre, have not previously benefitted from brief advice or any other qualified intervention to assist them for smoking cessation. A minority of smokers are aware of the dangers of continuing smoking or having received minimal verbal recommendations to quit, maybe even pharmacotherapy or counseling.

Countries must set realistic performance targets for both the number of people using cessation services and the proportion who successfully quit smoking. These targets should reflect demographics of the local population. Services should aim to treat at least 5% of the estimated local population of people who smoke or use tobacco in any form, each year, and also aim for a success rate of at least 35% at four weeks, validated by carbon monoxide monitoring. This figure should be based on all those who start treatment, with success defined as not having smoked in the third and fourth week after the quit date.

Success should be validated by a CO monitor reading of less than 7 ppm at the four-week point. This does not imply that treatment should stop at four weeks.[7]

All health professionals are concerned

An overview of the available smoking cessation guidelines showed that it is unanimously recommended to all doctors and all health professionals to regularly identify smokers and note patients' smoking status in their medical records as a routine procedure at each visit.[8]

An overview of the literature demonstrates that results are very modest in patients quitting by their own willpower alone: even though most smokers (80% to 90%) want to quit[9,10] only 30% report a serious attempt to stop using tobacco in the past 12 months and these attempts are successful only in 5% of the cases.[11] Moreover, smokers too often do not use evidence-based treatments and about 90% to 95% of unaided attempts to quit end in failure.[12] Finally, non-adherence to medications and counseling is common, which reduces the chance for successful smoking cessation.[5] Patients typically receive only about 50% of recommended doses of medication and often complete less than half of scheduled counseling sessions.[13]

Addressing tobacco use with patients should be a priority of all health professionals. Heath professionals should be prepared to treat tobacco dependence as a standard of care, as they would treat any other chronic disease.

Recommendations

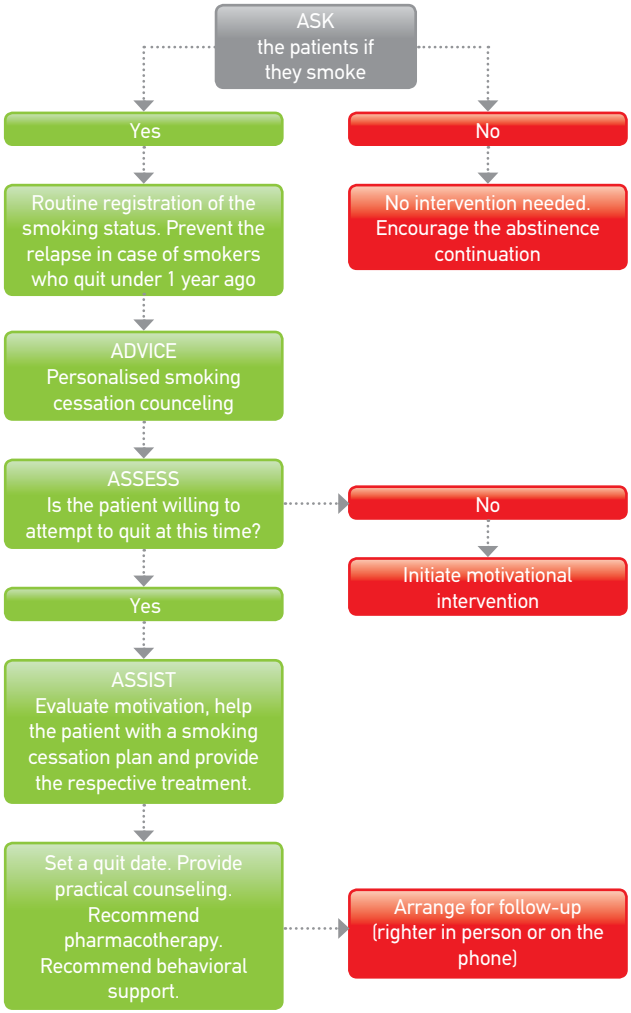
- All doctors and other health professionals should recommend smoking cessation to each smoking patient. There is evidence according to which medical advice increases significantly the smoking abstinence ratio (level of evidence A).
- During regular medical visits, general practitioners have the obligation to advise the smoking patients to completely stop smoking, to prescribe them treatment for nicotine dependence/to refer them to a specialized smoking cessation centre, at least once a year. These medical gestures must be noted in the patient's medical records (level of evidence A).
- Any time possible, current smokers who are hospitalized must receive from their clinician the same interventions recommended to general practitioners: brief quit smoking advice/smoking cessation counseling, prescription of pharmacotherapy for nicotine dependence or referral to a specialized smoking cessation counselor/centre (level of evidence A).

4.1.2 Standard approach to quitting smoking

The 5As

Five strategies are recommended for addressing tobacco use in clinical settings. Known as the 5As these strategies are:[14]

Figure 4.1: The 5As algorithm for tobacco treatment delivery in clinical settings



- ***Ask*** all patients about smoking status;
- ***Advise*** patients who smoke to quit;
- ***Assess*** readiness to quit;
- ***Assist*** with making a quit attempt, including providing behavioral counseling and prescribing first-line smoking cessation medications; and
- ***Arrange*** follow-up.

The 5As model is an evidence-based approach to increasing smoking cessation. The 5As methodology has been used in a variety of smoking cessation intervention programs. Figure 4.1 outlines the 5As algorithm.

Clinicians should ask about smoking status at each visit and document smoking status in the patient's medical record.

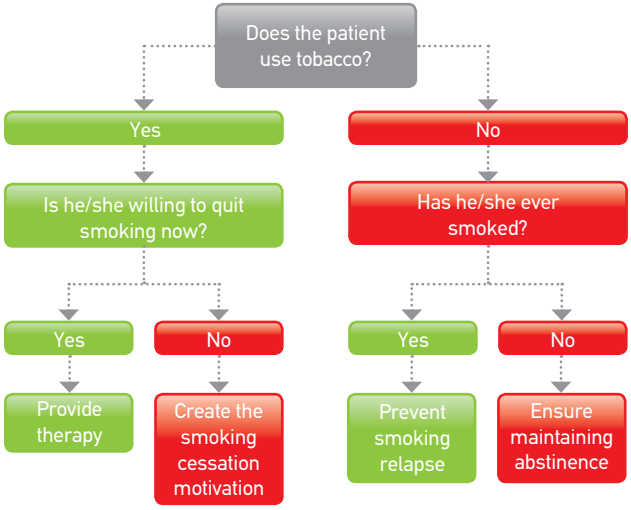
The doctor must advise all patients reporting current smoking to quit, evaluate the patient's readiness to quit smoking and assist the patient during the quit attempt, either by himself/herself (if he/she is trained to), or by referral to a specialized smoking cessation service.[15]

Health care professionals should care for all smokers either motivated or not: all patients should receive medical assistance to quit smoking. Four situations are more frequently encountered in current practice, as shown in Figure 4.2, depending on the smoking status and the motivational stage.

For each of these situations, a suggested approach is outlined below:

1. For tobacco users who want to quit smoking at the moment of assessment it is recommended to provide them with pharmacotherapy and cognitive-behavioral counseling immediately.
2 For tobacco users who do not want to quit smoking at the moment of assessment it is recommended to use the motivational interview strategy, in order to: encourage quitting / promote pro-cessation motivation / precipitate decision towards stopping smoking as soon as possible in the close future. A meta-analysis of 14 randomized trials showed that, as compared with brief advice or usual care, motivational interviewing increased six-month cessation rates by about 30%. Cessation rates in the two studies involving physician counselors (who typically received ≥ 2 hours of training) were about 8% with motivational interviewing versus 2% with brief advice or usual care.[16] Also, cessation rates were higher if smokers received two or more counseling sessions rather than one session and if the sessions lasted longer than 20 minutes.

Figure 4.2: Quitting smoking in current practice – most important situations



Interventions especially designed for this category of patients proved efficient to strengthen motivation to quit. The 2008 U.S. Public Health Service guideline used components of motivational interviewing to develop an abbreviated intervention that can be used more easily.[14]

Helping non-motivated smokers to quit

Motivation for quitting smoking is crucial in choosing the therapeutic method for the treatment of tobacco dependence. Some specialists consider that it is preferable to provide therapy only for a motivated patient, many specialists now support quitting, without any preamble or based on the so-called" catastrophic pathway". Such theories have been put forward by Larabie, as well as by West & Sohal, who found a higher success ratio in unplanned attempts compared to those planned in

advance.[17,18] These authors state that, especially in patients with respiratory diseases, it is all about a tension accumulation, so that an adverse event, even if minor, can precipitate the change towards the decision to quit.[17,18]

From a public health perspective, it is much more effective that all tobacco-dependent smokers receive treatment to quit whatever the motivation is than to treat only the small proportion of smokers motivated to quit, because there is no clear disadvantage in the success of cessation to be initially non-motivated, if the doctor helps the smoker to quit.

The 5Rs strategy

The 5Rs counseling strategy focuses on personally relevant reasons to quit, risks associated with continued smoking, rewards for quitting, and roadblocks to successful quitting, with repetition of the counseling at follow-up visits.

The 5Rs strategy, as applied in the case of a smoker not willing to stop smoking immediately, consists of:[14]

- ***Relevance:*** When discussing with the patient, the doctor should try to answer the question: "Why is smoking cessation important for you in a personal plan?"
- ***Risks:*** The doctor should try to identify personalized potential health risks of the smoker and to stratify both acute (exacerbations of COPD) and long-term (infertility, cancer) risks.
- ***Rewards:*** The doctor should show to the patient the personal benefits of stopping smoking.
- ***Roadblocks:*** The doctor should ask the patient to identify the barriers or obstacles that might impede the success of a quit attempt.
- ***Repetition:*** Smoking cessation interventions should be delivered repeatedly, whenever the doctor finds the patient is not willing/ready enough to quit smoking.

Interventions that aim to raise motivation towards smoking cessation that are grounded in motivational interviewing methods as outlined below:[19]

- Expressing empathy through open questions exploring attitude towards smoking ("How important do you think smoking cessation is for you personally?")
- Using reflective listening techniques ("So, do you think smoking helps you keep your current weight?")
- Supporting the patients right to reject change ("I understand that you're not ready to stop smoking right now. When you are willing to try, I will be here to help you.")
- Developing discrepancies between the patients" current behavior and their personal values ("You say your family matters a lot to you. How do you think your smoking affects your wife and children?")
- Building commitment to change ("We are going to help you avoid a heart attack, like your father had.")
- Empathetic attitude ("Are you worried about possible withdrawal symptoms?")
- Asking for permission to provide information ("Do you agree to learn together with me a few behavioral strategies that will help you face situations that make you smoke?")
- Providing simple solutions, as small steps on the way towards abstinence: a phone number (toll-free quit line, leaflets to present tips about changing behaviors etc.)

See section 4.2.3 for additional information on motivational interviewing.

Smoking reduction

If the standard approach to cessation fails, encouraging smokers to reduce their daily smoking "as much as possible", either alone or in combination with nicotine-replacement therapy (NRT) is recommended.[20]

See section 4.7 for more information on reduce to quit approaches.

Tobacco users who are recent quitters

As recent quitters are still vulnerable to relapse, especially in the first three to six months after ending treatment, it is recommended that the doctor ask them systematically, at each visit, if they still smoke sometimes or feel the urge to smoke. Their potential risk of relapse to smoking has a maximum intensity at two weeks around quit date, and decreases within the coming weeks. This risk must be evaluated as early as possible. The following questions are very important for this aspect:

- "Do you still feel the need/urge to smoke?";
- "How hard is it for you to refrain from smoking?"

Patients with major relapse risk should be assisted more intensively, including by recommending them to repeat the initial treatment course, if it is considered useful.

For successful recent abstainers, it is recommended to encourage abstinence maintenance, to congratulate every small victory and to monitor any risk of relapse carefully.

All patients who recently quit smoking must benefit from a follow-up period with qualified support in order to maintain non-smoking status. Thus, the doctor will provide them with minimal interventions like cognitive-behavioral counseling to maintain abstinence and to prevent smoking relapse.[9] In case patients notify withdrawal symptoms or increasing smoking appetite, it is indicated to provide them with more intensive counseling in a specialized centre. For those patients who have stopped smoking but do not experience cravings or withdrawal symptoms, follow-up can be done adequately in primary care services.

For never tobacco users

The doctor will reconfirm at each visit the initial non-smoking status and will make brief recommendations, through health-generating messages, to maintain this status. These minor interventions are simple and can be done by any doctor, whether he/she is specialized in smoking cessation or not.

Recommendations

- It is recommended to assess the patient's motivation to quit smoking, once identified and advised to quit (level of evidence C).
- Clinicians should use motivational techniques to encourage those smokers not willing to quit (level of evidence B)

Interventions that use motivational techniques are considered efficient in determining if the patient makes a future cessation attempt, but all tobacco-dependent smokers have to be treated for cessation regardless of their level of motivation (level of evidence C).

4.1.3 Effectiveness of treatment for tobacco use and dependence (Assist)

Combined counseling and medication treatments

Research provides strong evidence to support the effectiveness of combining counseling and pharmacological interventions, in increasing smoking-cessation rates among patients who are willing to quit.[14,2,3] Counseling and medication are effective when used by themselves, but the combination of counseling and medication is more effective than either used alone and increases abstinence rates.[14,21,22] The clinician providing medication does not need to be the clinician providing the counseling. It may be that a physician, a dentist, physician's assistant or nursing practitioner could prescribe medicines, and counseling could be provided by another tobacco treatment specialist (doctor, nurse, psychologist, quit lines worker etc.).

A 2016 Cochane review of 53 trials (25,000 participants) compared the efficacy of the combined use of counseling and pharmacotherapy fo smoking cessation. There was high quality evidence that the combined use of pharmacotherapy and behavioural counseling was superior to brief advice or usual care (RR 1.83, 95% CI 1.68 to 1.98).[22] There is a consistent relationship between more intensive counseling (with respect to both the duration and number of counseling sessions) and abstinence from smoking, however the optimal number of sessions has not been determined.[22]

Recommendations

- The combination of counseling and medication is more effective for smoking cessation than either medication or counseling alone. Therefore, whenever feasible and appropriate, both counseling and medication should be provided to patients trying to quit smoking (level of evidence A).
- There is a strong relationship between the number of sessions of counseling when it is combined with medication and the likelihood of successful smoking abstinence. Therefore, to the extent possible, clinicians should provide multiple counseling sessions, in addition to medication, to their patients who are trying to quit smoking (level of evidence A).

4.1.4 Follow-up Support (Arrange)

The patient's long-term follow-up, by monitoring the cessation process and the possible side effects of pharmacotherapy, is very important. Smoking status must be checked at each follow-up visit and objectively assessed by determining carbon monoxide concentration in the exhaled air. Measuring the cotinine in urine,

blood, saliva or hair also provides useful information about the organism's exposure to tobacco, but this needs to be adjusted in the case of smokers under nicotine substitution therapy, as pharmaceutical nicotine adds to nicotine from tobacco, if the patient still smokes.[19,23]

Adherence to treatment

Adherence to combined treatment (both medication and counseling) is also an important factor to consider for smoking cessation success. It has been suggested that pharmacological and non- pharmacological approach complement each other and this is supported by a meta-analysis showing that behavioral therapy can improve people's skills in dealing with situations when they would normally smoke, while pharmacotherapy eases physiological withdrawal symptoms.[14] Furthermore, pharmacotherapy helps patients overcome the acute phase of quitting, when withdrawal symptoms are most intense, while behavioral therapy provides coping mechanisms to maintain long-term abstinence. Therefore, combining both treatments may improve compliance with each method.[14]

Many smokers will not engage in counseling, especially if it involves long sessions or multiple visits. Therefore, patients should be offered options for quitting, including brief and accessible counseling. Non-adherence to medications for smoking cessation is common and is linked with beliefs that they are dangerous, ineffective, and should not be used if a person has had a relapse. Because non- adherence to medication is related to failure to quit, the clinician should discuss with the patient any concerns regarding medications for smoking cessation and should encourage his/her adherence to a given regimen.

Research has shown that making treatment easily available and reducing barriers to treatment increases treatment acceptance. For instance, when treatment is delayed and occurs at a separate location, only 10% or fewer of smokers initiate it, whereas as many as a third of patients enter treatment that is readily accessible.[24] Acceptance of treatment may also be increased by offers to help that are repeated over time, since smokers' interest in quitting can change along lifetime.[25]

In other words, there is no miraculous smoking cessation recipe. Any method is welcomed if it results in tobacco abstinence and, implicitly, in a health-generating benefit. In this respect, the way the doctor communicates with a patient who asks for smoking cessation aid is very important. The doctor must take into account that most of the times, smokers who come to a smoking cessation centre, especially if out-patients, do not consider themselves as ill persons, do not even realize that they suffer from an addiction and need medicines as treatment for what they consider more like "a weakness, a lack of will, a bad habit" etc. It is recommended to allocate a separate space where discussion will take place, by stimulating the smoker to talk, without blaming him/her and trying to establish a relationship of collaboration and mutual trust, while all the methods to quit are put at the patient's disposal.[27]

Recommendations

- As there is a strong dose-response relationship between the duration of face-to-face sessions and the success of smoking cessation therapy, intensive interventions are more efficient than less intensive ones and should be used whenever possible (level of evidence A).
- Clinicians should encourage all patients to use efficient medications for treating tobacco dependence (level of evidence A).
- Clinicians should provide all smokers willing to quit with treatment in a format of minimum four face- to-face counseling sessions. This has proven efficient in increasing the abstinence ratio (level of evidence A).
- The combination of counseling and pharmacotherapy for treating nicotine dependence is more efficient for smoking cessation than each of the two methods taken separately. That is why it is recommended to associate both methods any time when possible (level of evidence A).
- When it is not possible to use pharmacological treatment, using non-pharmacological therapy remains recommended, so that all smokers will receive therapeutic support, given that treatment of tobacco dependence was proved to be efficient (level of evidence A).

4.1.5 Health care systems approach for tobacco use and dependence treatments

The consistent, effective delivery of an intervention for stopping

tobacco use requires support from the health care systems. Smokers are significantly more likely to make an attempt to quit if tobacco treatment is covered by health insurance.[26] Because of the health and cost benefits of smoking cessation, more insurance companies now plan to cover evidence-based cessation treatments; for example, in 2010, the US company Medicare expanded its counseling coverage to all smokers (4 million persons), not just to those with a smoking-related disease.

Moreover, the use of electronic health records to prompt physicians and clinic staff to systematically identify and treat smokers has been associated with increased rates of documentation of smoking status and may also increase the use of treatments for smoking cessation.[27] Clinician training and performance feedback, dedicated staff to deliver treatments, and "fax to quit" programmes that link patients with tobacco quit lines nationwide, also increase cessation rates.

The health care systems worldwide take into consideration ensuring the minimal conditions to assist smokers towards cessation, depending on their existing local possibilities and resources: identifying smokers, recommending them to stop smoking, facilitating access to therapy. There is scientific evidence about successful cessation when free of charge treatments are available.[28]

4.1.6 Types of smoking cessation interventions

In current practice, there are two major types of cessation interventions: minimal intervention and specialized cessation treatment.

4.1.6.1 Minimal (brief advice)

This type of intervention lasts for a maximum of 3 to 5 minutes (as level 1 intervention) and is recommended in primary medical care, and family doctors, dentists, all categories of specialists.

Brief advice represents "a sum of verbal indications to stop smoking, given in medical terms and by adding information about harmful effects of smoking". When applied alone, it has a very low impact: just 1 out of 40 smokers succeed in quitting smoking.[29] When routinely administered to all patients, as a basic, systematic intervention, followed by referral to a specialized centre, it becomes a very strong therapeutic tool.

Minimum advice is recommended to all categories of smokers, ex-smokers, as well as to those who have never smoked. Providing a brief period of counseling (3 minutes) is more effective than simply advising the patient to quit, and doubles the cessation rate, as compared with no intervention.[7]

The health care system should offer treatment as a backup to brief opportunistic interventions for those smokers who need more intensive support. This support can be offered either individually or in groups, and should include coping skills, training and social support.

4.1.6.2 Specialized individual interventions towards stopping smoking

As a level 2 intervention, tobacco users should receive specialized individual treatment to address tobacco use from their own trained doctor, nurse, or psychologist, if available. Alternatively patients can be referred to a specialized smoking cessation service if available in the community.

The treatment consists of medication that has been proven to be effective in treating nicotine addiction and a series of cognitive-behavioral counseling sessions delivered individually. Specialists use the term "counseling" to define the specific cognitive-behavioral assistance given to patients under treatment to quit smoking. The counseling sessions have the role to provide smokers with knowledge about the smoking cessation process and with solutions for overcoming obstacles during the quit attempt.

Usually provided by a team (doctor, nurse and – optionally – psychologist) trained in the field of smoking cessation, the specialized intervention entails assisting an already informed patient having received minimal quitting advice, but now asking for qualified help. The doctor has the main role in this process, since he/she has the responsibility to recommend and advise pharmacotherapy; the nurse helps filling in the documentation, completing the database, laboratory tests etc. and can even provide minimum advice. The psychologist helps the intervention by adding elements of psychological support and cognitive-behavioral techniques.

Optimally, individual smoking cessation strategies combine advice

(i.e. recommendation to quit smoking) with pharmacological treatment (varenicline, bupropion, NRT etc.) and with cognitive-behavioral therapy. Usual format intervention consists of several (minimum four) sessions lasting 20-45 minutes through 9-12 treatment weeks.

In the first consultation, the patient is briefly introduced to the available treatments, warned about withdrawal symptoms and agrees on the most suitable solutions. The initial contact must be an opportunity for assessing chances for success and the risks of relapse.

During the 9-12 week standard treatment, regardless of therapy indicated, it is recommended to follow up all patients (at least two visits) in order to be certain that the patient follows the correct treatment, in standard doses in the case of pharmacotherapy, address psycho- behavioral difficulties or withdrawal symptoms and there are no adverse effects of medication. Follow-up visits allow the doctor to obtain an update of the smoking status, to monitor biomarkers of tobacco use and to prevent lapses or relapses. These visits offer an opportunity to provide prompt support – the doctor can intervene right on time in case the smoker is discouraged or has a slip after a short temporary abstinence. The most important visit is the first one – it is recommended to schedule it immediately after the target-quit day.

Most specialists recommend setting the quit date in the second week of treatment. However, depending on both the doctor's expertise and the smoker's profile, it should be noted that the specialist may recommend another quit date, for example in weeks 3 to 6, as the case may be.

The final treatment consultation takes place when the treatment ends, usually two to three months after the initial consultation, and aims mainly to evaluate tobacco abstinence as a result of the treatment. On this occasion, the smoking status should be again evaluated clinically and biologically. The smoking appetite should also be assessed, as well as the way the subject faces challenging situations in relation to smoking. Withdrawal symptoms and the side effects of pharmacotherapy must be audited. At the same time, the patient who has stopped smoking should receive counseling with the aim of maintaining abstinence and preventing smoking recurrence. Patients who have not succeeded in stopping smoking should be re-assessed, in order to start another quit attempt.

The specialized smoking cessation intervention in its individual format is the most recommended approach for treating tobacco dependence. An intensive programme with weekly visits, personal consultations with a respiratory physician and use of pharmacotherapy may increase the cessation rate of motivated smokers trying to quit, and this can be more easily provided by specialized tobacco cessation centers. However, as tobacco smoking involves an addiction to nicotine, the highest one- year quit rate to be expected is 25% to 40%.[7]

Research has demonstrated that evidence-based smoking cessation services are a highly cost- effective way of helping smokers to stop smoking. From NHS smoking cessation clinic data and controlled trials, it has become clear that if smokers receive support from specialist clinics, with treatment in groups along with access to combination NRT or varenicline, they will be more likely to succeed than those smokers receiving treatment in primary care and those receiving one-to-one and single NRT.[30]

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4.2 Behavioural Counselling

We review here evidence related to behavioral counseling for smoking cessation. In addition to the overall evidence we review two effective counseling techniques for addressing tobacco use with patients: cognitive behavioral counseling and motivational interviewing.

4.2.1 Psychological support for smoking cessation

Besides pharmacological treatment and counseling, the patient who wants to stop smoking can benefit from psychological assistance, as needed. Every smoker should be advised to make his or her own effort to quit. If this effort fails, or if the smoker feels unable to quit without help, then psychotherapy techniques must intervene in supporting stopping smoking.

The recommended elements of treatment are derived from behavioral therapy; there is inadequate evidence to support psycho-dynamically oriented treatments, because of the lack of relevant controlled trials. Cessation programmes are based on the premises that psychological dependency arises by operant and classical conditioning, and that cognitive processes, own personal values, and the functionality of tobacco consumption play a major role in maintaining smoking behavior. Such programmes combine psychological education and motivational techniques with behavioral- therapeutic elements. These interventions can be provided either by group therapy or in an individual therapeutic setting. In one popular model, a smoking cessation group of 6 to 12 patients undergoes treatment together in 6 to 10 sessions

consisting of two 90 to 120 minute therapeutic units each.[1]

Psychological support is carried out in a systematized and standardized approach. It starts with an evaluation of the patient's psychological characteristics, and assists patients in comparatively evaluating benefits over disadvantages in a personalized manner, as well as the influence that their tobacco dependence will have on their own life perspectives (Table 4.1, Table 4.2).

Then, the content of the written analysis is discussed with specialists, concerning both advantages and disadvantages, in order to reveal the positive outcomes. Emphasis should be placed on positive achievements and it is recommended to support the patient's own self-confidence strongly.

A personalized smoking cessation treatment plan is then drawn up, through a doctor-patient collaborative process. The first step consists of agreeing on a quit day. As of that day on, the patient must not keep cigarettes in his/her pocket, bag, suitcase, at home, etc. This is necessary as we know scientific proofs reveal that the overwhelming need for smoking lasts seven minutes and then, even if the need for smoking still remains, it will manifest itself on more bearable levels. Since patients do not have any cigarettes at hand, until they can eventually get them, those seven minutes of extreme pressure pass and they may face this challenging situation from a more powerful position.[1]

While the patient still smokes, but has also started pharmacological treatment, the following actions are recommended:

- announce to all friends, family etc. his/her initiative to give up smoking;
- write on a piece of paper the reasons why he/she wants to quit smoking, and post this piece of paper in a place where it can be seen frequently – on the fridge door, in the bathroom, on the computer monitor etc.;
- identify what he/she will optimally replace the smoking gesture with: this may be a glass of water, tea, coffee etc. – and drink it little by little; other tips may be also helpful to postpone smoking: using anti-stress balls, chewing gum or eating biscuits/carrots, etc.;
- define a support person – the person that he/she commits to contact by telephone before possibly relapsing to smoking;
- imagine a type of reaction for the situations when the desire to use tobacco appears: drink water, go for a walk etc.;
- change his/her daily life, habits or space when and where he/she used to smoke at other times.[1,2,3]

See Table 4.3.

Table 4.1: Patient analyzes himself/herself

The Tobacco dependence that I am suffering from, generates for me:	
Short and long-term advantages	Short and long-term disadvantages

Table 4.2: The patient predicts the influence of the tobacco dependence status upon the objectives he/she wants to achieve

Five years from now, I will be ... years old	
What would I like to be and to do?	What will happen if I do not quit smoking?

Table 4.3: Common elements of intra-treatment supportive interventions

TREATMENT COMPONENT	**EXAMPLES**
Encourage the patient in the quit attempt	- Note that effective tobacco dependence treatments are now available and that one-half of all people who ever smoked have now quit. - Communicate belief in patient's ability to quit
Communicate caring and concern	- Ask how the patient feels about quitting - Directly express concern and willingness to help as often as needed. - Ask about the patient's fears and ambivalence regarding quitting.
Encourage the patient to talk about the quitting process	Ask about: reasons the patient wants to quit for, concerns or worries about quitting, success achieved or difficulties encountered while quitting.

Recommendation

- Psychological support for smoking cessation must be integrated in the medical treatment of the patient addicted to nicotine (level of evidence A).

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4.2.2 Cognitive-behavioural therapy (CBT)

Principles of CBT

The principles of CBT are as follows: initiating a collaboration relationship between doctor and patient; avoiding conflicts; active listening – which refers to re-phrasing what the patient says; valuing success; creating positive appreciation skills concerning the benefits of quitting smoking.

This treatment aims at changing the individuals' inadaptable behaviors and at de-conditioning and moving towards adapted behaviors. Using CBT in smoking cessation centers helps smokers learn to take note of their smoking behavior and evaluate themselves, given that smoking is a learned behavior, subsequently maintained through a dependence constantly influenced by environment stimuli.[1] This technique developed from treatments for anxiety and depression (so-called cognitive behavioral therapy) attempts to change habitual ways of thinking and feeling about smoking and oneself and provides encouragement and advice on ways of minimizing and managing the desire to smoke.[2]

Counseling also provides an opportunity to warn the patient about obstacles or hurdles to quitting and encourages the patient to plan to use coping strategies for avoiding and resisting the need to smoke. The clinician should assess and counsel the patient regarding factors that pose especially great challenges to quitting, such as living with a smoker, excessive alcohol use, and fear of gaining weight. Counseling should be empathic and supportive, not confrontational.[1] Counseling remains underused, and a key goal is to increase its use in clinical practice either in person or through referral to a telephone quit line.[3]

Through CBT the smoker will learn practical techniques for dealing with smoking-inciting situations and will benefit from psychological and behavioral support for encouraging him/her to stop smoking completely. Data show that the same standard counseling can rarely be applied to all patients; some cognitive-behavioral therapy models are associated to a certain therapeutic strategy; in the majority of studies in this field, there is no correlation with any control group. Cognitive-behavioral therapy contributes to an increased abstinence ratio by evaluating the motivation for quitting smoking, by building communication skills and a doctor-patient dialogue based on respect and understanding and by evaluation of nicotine dependence (analysis of the smoking appetite, explaining the tobacco dependence concept). Most smokers do not have accurate knowledge about what happens in their brains when they smoke and the reasons why it is difficult to quit smoking, even if they are highly motivated. A discussion with a specialist about the effects of nicotine on the brain and the way nicotine dependence manifests itself can spectacularly increase the patient's initiative towards giving up smoking.[4,5,6] The intervention also allows in-depth analysis of concerns and fears related to the smoking cessation process and creates an opportunity for agreeing with the patient on the adequate therapeutic strategy.

Efficacy of CBT

Meta-analysis of 64 studies about the effectiveness and the estimated abstinence rates for various types of counseling and behavioral therapies showed statistically significant increases in abstinence rates compared to no contact in the following categories of counseling: (1) providing practical counseling, such as problem-solving/skills training/stress management; (2) providing support during a smoker's direct contact with a clinician (intra treatment social support); (3) intervening to increase social support in the smoker's environment (extra treatment social support); and (4) using aversive smoking procedures (rapid smoking, rapid puffing).[7]

See table 4.4.

Table 4.4: Common elements of practical counseling (problem-solving/skills training)

TREATMENT COMPONENT	EXAMPLES
Recognize danger situations – Identify events, internal states or activities that increase the risk of smoking or of relapse.	Negative effect and stress. Being around other tobacco users. Drinking alcohol. Experiencing urge to smoke. Smoking cues and availability of cigarettes.
Develop coping skills – Identify and practice coping or problem-solving skills. Typically, these skills are intended to cope with danger situations.	Learn to anticipate and avoid temptation and how to trigger situations. Learn cognitive strategies that will reduce negative moods. Accomplish lifestyle changes that may reduce stress, improve quality of life, and reduce exposure to smoking cues. Learn cognitive and behavioural activities to cope with smoking urges (e.g. distracting attention; changing routines).
Provide basic information – Provide basic information about smoking and successful quitting.	The fact that any smoking (even a single puff) increases the likelihood of a full relapse. Withdrawal symptoms typically peak within 1-2 weeks after quitting, but may persist for months. These symptoms include negative mood, urges to smoke, and difficulty concentrating. The addictive nature of smoking.

How to manage behavioral smoking addiction

Successful interventions to quit tobacco need to tackle an interacting constellation of factors – personal, family, socio-economic, pharmacological and behavioral – that sustain use and can act as major barriers to cessation. Sometimes, if the complexity of this condition is not taken into account, the patient will struggle to achieve long-term abstinence and this process extends over years or decades. So, besides both the physical and psychological addiction, the behavioral addiction must also be addressed, as in some smokers this aspect may seriously intervene.

It is now unanimously recognized that cigarette smoking is a primary manifestation of nicotine addiction and that smokers have individually characteristics preferences for their level of nicotine intake, as they regulate their own way of puffing and inhaling to achieve their desired nicotine dose.

Recommendations

- CBT must be included in planning all types of medical interventions for smoking cessation as an efficient method, which contributes to increasing the smoking cessation success ratio (level of evidence B).
- Two types of counseling and behavioral therapies result in higher abstinence rates: (1) providing smokers with practical counseling (problem solving skills/skills training) and (2) providing support and encouragement as part of treatment (level of evidence B).
- These counseling elements should be included in smoking cessation interventions (level of evidence B).

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4.2.3 Motivational interviewing (MI)

Motivation is essential for every smoker who plans to stop using tobacco. Therefore, methods for strengthening a patient's motives to quit are important research objectives.

What is motivational interviewing?

Motivational interviewing (MI) is a method developed by US psychologist William R. Miller in the 1980s as he was treating patients with problems of abuse. Miller showed that empathic listening could reduce a client's intake of alcohol. Studies indicated that resistance and denial are phenomena that arise in the relation between client and counselor.

The first MI book, written by Miller in collaboration with Stephen Rollnick, a psychologist from the UK, was published in 1991.[1] Rollnick later developed shorter versions of MI suitable for use in health care. In essence, the method aims to offer interested clients information on health risks coupled with a specific dependence, and evoke interest for change. MI is now practiced in many countries for treatment of abuse such as alcohol, tobacco, as well as for those who need improved nutrition and exercise. MI is also widely used for gambling problems, for treatment compliance and in the criminal system.

MI describes what you as counselor can do in order to increase the probability that the client can achieve behavior change. It builds on improving the counselor's understanding of how we communicate and relate better to the patient. MI seeks to avoid an aggressive or confrontational approach and tries to steer people towards choosing to change their behavior, and to encourage their self-belief.[1]

- The counselor acts as a collaborator and sees himself/herself as an equal.
- The counselor searches for and evokes the client's own thoughts and ideas about his/her smoking and how to change it.
- The counselor shows respect for the client's autonomy and his/her right and capacity to make decisions.

Underlying principles of MI[1]

- *Show empathy.* The counselor clearly shows an interest in trying to understand the patient. This is done through reflections and summaries.
- *Highlight discrepancies.* The counselor helps the patient to become aware of the gap between the present situations and how it might look taking into account the patient's goals and values. The feeling of wide discrepancies is a strong driving force for behavioral change provided that the client/patient has the ability to change. Avoid arguing. So-called resistance is respected as a natural sign of anxiety or doubt about change.
- If the counselor confronts this or starts arguing, the patient's resistance will increase. The counselor
- "rolls with" the resistance when it appears, but tries to prevent such situations from arising. *Support self-reliance.* The counselor supports the patient's self-reliance by showing trust in the
- Client/patient's ability to change. The counselor shows that he/she appreciates the patient's efforts.

Some important features of MI

- *Asking for permission.* A conversation about tobacco is rarely seen as offensive by patients but it is always wise to approach the subject by asking for permission to bring it up.
- *Ambivalence.* Ambivalence is a natural phase of change. There are always pros and cons for changes, the effects of which may be playing out in a distant future. The counselor should aim at helping the patient to express his/her reasons for change.
- *Open-ended questions.* Closed questions ask for yes or no responses; open-ended questions ask for longer answers or elaboration.
- *Change talk.* It is important for the counselor to pick up "change talk", words and thoughts expressed by the patient that might lead to change.
- *Affirm positive talk and behavior.* The patient will be more ready for change if positive signs or thoughts are identified and affirmed.
- *Reflect upon what you are hearing or seeing.* At their core, reflections are guesses as to what a patient is saying or thinking. Reflections do not confirm agreement with the patient; rather, they tell the patient that the counselor has

been listening and help the patient hear what he/she has been saying.

- *Summarize what has been said.* A summary is a special form of reflection. Summaries remind the patient about major discussion points, the plan of action, and the patient's own reasons for taking action. Summaries are useful in two ways. If the patient slows or stops talking, summaries can act as a bridge to help him/her continue. Summaries may also help remind the patient what he/she has said or point out a connection between his/her statements.

Motivational interviewing in clinical practice

In many ways MI breaks with counseling traditions in medicine. MI reduces the authority of the "expert in a white coat" who talks down to the patient and tells him/her what to do. MI is more akin to inviting the patient to a dance in which patient and counselor hold each other and follow each other step-by- step across the dance floor. The roles have changed. Some health professionals have a natural talent to talk to patients in a non-judgmental and understanding way and can easily adopt MI. More often, however, health professionals revert to old habits and start ordering the patient around. Hence, to master MI well, a lot of training is needed and expert follow-up of adherence to counseling procedures is important (and expensive).

In order to make MI more accessible and more usable a simpler version has been developed called rapid engagement.

Rapid engagement (RE). Rapid engagement is an abbreviated and simplified version of MI designed for use in a busy doctor's office.[2] RE uses a simple set of questions. A VAS-scale may be used to visualize the degree of motivation, but is not necessary as similar assessments can be made verbally.

The importance of change. Question 1: How important is it for you to quit smoking on a scale from 0 to 10 (0 = not important at all, and 10 = very important)? The response steers the ensuing discussion. The counselor may follow up by "provoking" the patient by saying "I would have thought a lower number". This often results in a discussion where the patient takes the lead and is eager to convince the counselor that the suggestion was wrong.

Self-reliance. Self-reliance may depend upon successes or failures of earlier attempts, the achievements by others, knowledge and support. Again, the patient assesses on a scale 0 to 10 his/her chances of success to quit smoking (or the same scale expressed in words). If the patient assesses his/her own chances above 0, the counselor should ask why the patient does not choose a lower number than the one chosen, the intent being that the patient is inspired to soul-search for his/her ability to mobilize internal resources. The better this mobilization, the stronger the self-reliance. Even more "change talk" can be evoked by asking: "What would it take to further increase your chances?" The will and the ability to change behavior are two different, but related aspects of motivation, which are not easily distinguishable. Some patients may find it easier to define what they do not want rather than admit to a low level of self-reliance. For others it may be the opposite ("I want to, but it won't work!"). It is important that the counselor is able to understand what the patient actually means.

Evidence of efficacy

A Cochrane review from 2015 identified 28 studies published between 1997 and 2014, involving over 16,000 smokers which examined MI compared to brief advice or usual care.[3] Trials examined involved one to six sessions, with the duration of each session ranging from 10 to 60 minutes. The meta-analysis found that MI versus brief advice or usual care yielded a modest but significant increase in quitting (RR 1.26; 95% CI 1.16 to 1.36). Sub-group analyses suggested that MI was effective when delivered by primary care physicians (RR 3.49; 95% CI 1.53 to 7.94) and by counselors (RR 1.25; 95% CI 1.15 to 1.63), and when it was conducted in longer sessions (more than 20 minutes per session) (RR 1.69; 95% CI 1.34 to 2.12). Multiple session treatments may be slightly more effective than single sessions, but both regimens produced positive outcomes. Evidence is unclear at present concerning the optimal number of follow-up calls. The evidence examining MI is of moderate quality and some caution is warranted due to the heterogeneity of study characteristics.

Scientific evidence is lacking for the rapid engagement method, but clinicians report that the method is useful even in a busy practice and that it makes discussions about behavior change much more relaxed.

Recommendations

- Motivational interviewing or its variants, widely used as counseling techniques can be effective in assisting patients with quitting smoking (level of evidence B)

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4.2.4 Delivery Format

A variety of formats have been tested for delivering smoking cessation treatments including: individual counseling, proactive telephone counseling, group counseling, web-based, and self-help.

4.2.4.1 Individual smoking cessation counseling

A meta-analysis involving 30 trials found that such individual anti-smoking counseling is more effective than simple counseling (13.9% v. 10.8%, RR = 1.39, CI 1.24–1.57).[1] According to a meta-analysis of 35 randomized trials, six-months abstinence rates increased significantly with minutes of total counseling contact: about 14% for 1 to 3 minutes of counseling, 19% for 4 to 30 minutes of counseling, and 27% for 31 to 90 minutes of counseling, versus 11% for no counseling. (Some studies included pharmacotherapy across all counseling conditions, so medication also contributed to these success rates.) Successful counseling boosts the motivation to quit by personalizing the costs and risks of the patient's tobacco use (by tying it to the patient's health, economic status, and family situation). There is a consistent relationship between more intensive counseling (with respect to both the duration and number of counseling sessions) and abstinence from smoking.

4.2.4.2 Group smoking cessation counseling

Group behavioral therapy implies scheduled meetings where groups of people who smoke receive information, advice and encouragement and some form of behavioral intervention (e.g. cognitive behavioral therapy).[2] This therapy is offered weekly for at least the first four weeks of a quit attempt (i.e. for four weeks following the quit date). Normally, group counseling is combined with pharmacotherapy.

There are two ways to approach conducting a group. One is scholastic, with the health professionals acting as teachers and giving information about how to achieve and maintain abstinence from smoking. The other one seeks mutual support among group members in order to achieve abstinence.

A review by the Cochrane Collaboration found 16 trials that compared a group programme with a self-help programme.[3] There was an increase in cessation with the use of a group programme (OR 1.98; 95% CI 1.60-2.46). There was no evidence that group therapy was more effective than individual counseling with a similar intensity. Limited evidence was found that addition of group therapy to other forms of treatment, such as advice from a health professional or nicotine replacement, produced any extra benefits.

Data from a study interviewing both key personnel and smokers in three types of cessation services (specialized teams, community-based health care workers and combination of both) suggest that the service structure, the method of support, the health care professionals involved and the pharmacotherapy, all play a role in successful quitting.[4] Group support resulted in the highest quit rates (64.3% for closed groups v. 42.6% for one-to-one support offered by specialists). Services must be tailored to support individual needs with patient choice and with access to varied services, including group counseling.[4]

Numerous smoking cessation programmes include group strategies based on interactive educational methods and better access to treatment and psychological support. A well-tested group format includes around five one-hour sessions over one-month duration with follow-up visits. Intensive support should include the offer or encouragement to use pharmacotherapy (as appropriate) and clear advice and instructions on how to use it.[5] Group counseling should be done by specially trained counselors,

able to make smokers interact and share own withdrawal fears and barriers, but at the same time learn from collective experience. This can also be delivered as weekly sessions and with the help of auxiliary personnel (nurses, trained facilitators, psychologists etc.). In any case, a group approach may be kept as an alternative for those patients who communicate better in a group, but where available it can also be integrated into individual treatment in order to consolidate the therapeutic intervention.

It is advisable to offer individual (i.e. face-to-face) and group interventions to better suit and satisfy patients, who should be screened to diagnose major psychiatric disorders. Exclusion criteria for group treatment could be personality disorders or pronounced psycho-pathological traits (e.g. narcissistic or histrionic disturbances, anxiety, social phobia, strong manipulative attitudes, schizophrenic behavior or multi-problematic cases as in the case of multiple dependencies). Widespread group models usually consist of 5-10 sessions over a two- to three-months treatment period.

Recommendations:

- Group counseling is effective for smoking cessation. Inclusion of social support in a group intervention and the types of cognitive-behavioral components included in the group do not influence its efficacy (level of evidence A)
- Group counseling is similar in terms of effectiveness to that of individual counseling and patient preference may be used to determine if group of individual treatment is preferred (level of evidence B).

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4.2.4.3 Telephone support and quit lines

In many countries, a toll-free phone service exists, known as 'Quit lines' or 'help lines'. Patients who call this phone number can receive information about access to local smoking cessation centers and can receive advice on how to quit with minimal or full counselling.[1] Using the telephone to deliver cognitive-behavioral therapy is similar to the structure of traditional face-to-face contact, but is more flexible.

One important advantage of quit lines is their accessibility. A telephone operation eliminates many of the barriers of traditional cessation classes, such as having to wait for classes to form or needing to arrange for transportation. Appointments can be arranged at suitable times, including lunch breaks and in the evening and Saturday. Participants can choose whether to be contacted at home or on their own mobile phone and are offered telephone support to guide them in putting into practice various quitting strategies and in making positive changes in their own daily lives. Telephone calls are in general 20-25 minutes long, but this is flexible and can be adapted to meet individual needs.[2] Quit lines are particularly helpful for people with limited mobility and those who live in rural or remote areas. Due to their quasi-anonymous nature, telephone-based services may also appeal to those who are reluctant to seek help provided in a group setting.

Quit lines also offer, proactive calls, defined as telephone counseling in which at least some of the contacts are initiated by the quit lines counselor to deliver tobacco cessation interventions, including call-back counseling.

There is a large body of randomized controlled trial evidence examining the efficacy of 'quit line' services.[3,4] A meta-analysis involving 70 trials published by the Cochrane collaboration found that receiving multiple proactive calls from the quit line increased rates of smoking abstinence (RR 1.37, 95% CI 1.26, 1.50).[4] A minimum of two calls appears to be associated with increased cessation. It is not clear if increasing the number of calls beyond two further increases quit rates. Reactive quit lines, which only respond to callers' immediate requests have also been shown to be effective in increasing quitting relative to self-help (RR 1.27, 95%CI 1.20, 1.36).

The overall evidence indicates that quit lines have the potential not only to provide effective assistance to those who seek it, but also to increase quitting among tobacco-users generally. Is a

good way to let tobacco-users, wherever they are, know that help is available.[4]

Recommendations:

- There is good evidence that proactive telephone counseling is an effective intervention for smoking cessation (evidence level A)
- A minimum of two sessions appear to be important for increasing quit rates. The benefits of increasing the number of calls beyond two is not clear (evidence level B)

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4.2.4.4 Self-help materials

This category includes: booklets, leaflets, manuals, media materials, reactive telephone help lines, computer/ web-based programs, and various community programmes. Self-help interventions are defined as "any manual or programme to be used by individuals to assist a quit attempt not assisted by health professionals, counselors, or group support."[2]

The following contains a sample of a brief explanatory leaflet destined for smoking patients, to help them become familiar with the basic notions about treating tobacco use and dependence.

Example of checklist and questions for self-aid material

Why use tobacco?

- What, therefore, is the explanation for continuing smoking, despite so many tobacco control efforts to stop morbidity and mortality caused by tobacco?
- Can we assume that smokers have no regard for their health or do they imagine "this harmful effect cannot happen to me"?
- Are they not capable of realizing the harmful effects shown in educational materials? Or is it something else that makes them unable to quit smoking despite being aware of the dangers?
- Could this be the complex psycho-behavioral and physical changes determined by a chemical substance contained in tobacco? Clearly this is the case.[3,4]

Tobacco dependence

- The intensity of nicotinic dependence is very high, higher or similar to heroin and cocaine, much more addictive than alcohol, cannabis or LSD and similar drugs.
- Chronic tobacco use, or in simple terms "smoking", has been recognized by all psychiatric medical bodies as a disease in itself, inducing physical and psychological as a chronic disease, i.e. tobacco dependence or nicotine dependence.
- Most cigarettes are smoked not by free choice but by dependence on nicotine, a highly addictive drug present in all tobacco products.[5]
- Chronic tobacco exposure has been proven to cause a wide range of diseases and death due to the numerous toxins and carcinogenic compounds present in tobacco.
- Tobacco manufacturers use many strategies to increase nicotine dependence in tobacco products: additives, flavorings, filter characteristics etc.
- The tobacco industry constantly invests in new markets to target vulnerable categories of potential clients, i.e. children and young people who are the most exposed.
- The best method to react to the tobacco industry is to provide individuals with knowledge and skills based on scientific evidence in order to face this challenge.

Individual implications of tobacco use[5]

- One out of every two tobacco users will die prematurely as the result of a tobacco-related disease.
- Tobacco use is the single largest cause of preventable death.

- More than half of these deaths occur in people aged 35-69 years.
- Every day around the world this number of deaths is equivalent to fifty jumbo jets crashing.
- Tobacco use accounts for: 87% of lung cancer deaths, 82% of COPD (chronic obstructive pulmonary disease) incidence, 21% of CHD (coronary heart disease) incidence and 18% of stroke incidence.
- Tobacco use has been shown to cause complications during pregnancy.
- Tobacco use makes a person's breath, hair and clothes smell bad, causes teeth, fingernails and skin to become stained and causes clothes to become ruined or burnt.
- Tobacco use decreases athletic performance.
- Tobacco is a major cause of fires and accidental deaths.
- Tobacco use is a gateway to other drug use, and addiction to tobacco may make a person more susceptible to trying other dangerous drugs.

Implications for family, friends, and co-workers of tobacco users[6]

- You are exposing your family, friends and co-workers to environmental or second-hand tobacco smoke.
- Second-hand tobacco smoke increases the risk of lung cancer by 30%. This results in 3000 additional cases of lung cancer per annum.
- Infants and children chronically exposed to second-hand smoke have an increased risk of asthma, other respiratory diseases, malignancies and other health issues. These diseases result in increased hospitalizations and school absence.
- Exposure to tobacco smoke increases the risk of low birth weight babies and sudden infant death syndrome.
- Non-using adults exposed to second-hand smoke are also more likely to have respiratory diseases and symptoms that contribute to absenteeism from work and other activities.
- Spouses of smokers have a higher risk of heart disease and lung cancer.

Benefits of quitting tobacco use

1. Short term benefits

- After 20 minutes blood pressure and pulse rates return to normal.
- After 8 hours carbon monoxide and oxygen levels in the blood return to normal.
- After 24 hours carbon monoxide is eliminated from the body; lungs start to clear out mucus and smoking debris; chances of a heart attack are decreased.
- After 48 hours no nicotine is left in the body; nerve endings start to re-grow; and the ability to smell and taste is improved.

2. Long-term benefits

- Improved breathing.
- More physical energy.
- Better skin tone.
- Reduction in risk of tobacco related diseases, such as:
  - Lung cancer,
  - Emphysema,
  - Chronic Obstructive Pulmonary Disease (COPD),
  - Sudden death heart attack,
  - Coronary Heart Disease (CHD)
  - Atherosclerosis (narrowing of the arteries)
  - Stroke,
  - Chronic Bronchitis

Preparation to quit

The better prepared to quit you are, the higher the likelihood of success.[6] Some suggestions include:

- Decide positively that you want to quit.
- Make a list of reasons, including personal reasons, medical effects, health benefits, financial advantages and obligations to others.
- Repeat one of these reasons to yourself several times each morning.
- Start conditioning yourself physically with a modest exercise routine. Get lots of rest and drink more fluids.
- Set a target date for quitting within the next two weeks.
- Identify barriers to quitting. What will make it difficult? What situations make you desire tobacco? What can you do to change that?
- Make a list of people who can support your intentions to quit,

such as family, friends and co- workers. Discuss your plans with them.

- If any of these people are smokers, ask them to refrain from using tobacco around you or, better yet, ask them to join you in quitting.
- Clear the places where you usually smoke of anything that would remind you of cigarettes like:
  - Lighters
  - ashtrays or
  - matches.
- Clean your house and car; try to remove the smell of smoke as much as possible.
- Make a list of activities, hobbies, and interests that you can do to keep your mind off smoking.
- Prepare yourself with knowledge about the withdrawal symptoms and ways to cope with them.
- Be prepared to face difficult quitting. Learn about "withdrawal syndrome".
- Nicotine withdrawal consists of symptoms due to suddenly stopping the nicotine supply. Nicotine withdrawal can manifest from the very first 4-12 hours since smoking cessation, through symptoms like:
  - acute/uncontrollable need to smoke (craving);
  - irritability;
  - restlessness, anger, feelings of anxiety;
  - tiredness;
  - increased appetite, especially for sweets, weight gain;
  - difficulty concentrating/ poor memory;
  - depression;
  - headaches;
  - insomnia;
  - dizziness.

Therapies that help to quit smoking

- The two components that have proven efficient in treating tobacco dependence are: counseling and pharmacotherapy.
- Pharmacological therapy is crucial and it comprises a generous offer of medications, from nicotine substitutes used in various forms (gum, patch, nasal spray, inhaler, sublingual tablet), to anti-depressants, nicotine receptor antagonists etc.
- You must ask your physician or pharmacist to prescribe or recommend medication to quit smoking.
- Combination of various pharmacological therapies can be used with the help of health professionals, the therapy duration can be extended, and dosages can be adjusted to avoid side effects.
- Leaflets, posters, brochures, different educational and self-help written or media materials, together with Internet tools

Table 4.5: Some practical tips to avoid smoking[7]

EXAMPLES OF BEHAVIOURAL STRATEGIES/TIPS TO AVOID SMOKING
- Learn to refuse the first cigarette!
- Throw away you "smoker kit": lighter, matches, cigarettes package;
- Change your daily routine!;
- Avoid the use of coffee, cola or tea;
- When you feel the need for smoking, drink a big glass of water or natural fruit juice;
- Eat 3-5 meals/day;
- Breakfast: natural juices, milk products, possibly meat, eggs; be careful to the irreplaceable cigarette next to the morning coffee!
- Lunch and dinner: preferable raw fruit and vegetables, green vegetables, fruit;
- Before going to sleep – a glass of water or tea;
You must avoid: eating between meals, eating too much sweets; pastry, candies, chocolate;
- Do not hesitate to drink more than 2 liters of water/day
- Physical exercises, walks in open air, learn relaxation techniques;
- Start practicing a new sport;
- Avoid getting in contact with smokers situations when you could be tempted to smoke;
- Save the money you used to spend on cigarettes – buy yourself a present instead!

or phone lines may help.

- CBT is a therapeutic technique that attempts to change habitual ways of thinking and feeling about smoking and oneself and provides encouragement and advice on ways of minimizing and managing the desire to smoke.
- Optimally, individual smoking cessation strategies combine advice (a recommendation to quit smoking) with pharmacological treatment (varenicline, bupropion, NRT etc.) and with cognitive- behavioural therapy (CBT).

Efficacy of patient educational materials

Several studies prove the efficacy of educational material included in programmes for cessation.

A total of 2000 adults were tested using a standard 13-page self-quitting guide (the control group) against the 28-page Free & Clear (F&C) self-quitting guide, the F&C guide and social support instructions for family and friends of the smoker and the F&C guide and social support instructions and four telephone calls with specialists.[7] The F&C telephone counseling programme plus self-help materials was found to be an effective strategy for assisting self-quitters. Use of self-help guides and social support instructions for family and friends did not significantly improve a person's likelihood to quit in comparison to use of the F&C four-call programme.[7]

In a meta-analysis that addressed the impact of self-help brochures, either used as the sole intervention or in addition to counseling, self-help did not significantly boost abstinence rates over other minimal interventions such as advice from a healthcare professional, or nicotine replacement therapy.[2] Materials which are tailored appear to be superior to generic materials.[2]

Recommendations:

- Access to information for individuals who are attempting to quit smoking is needed.
- There is no evidence that self-help materials produce incremental benefits over other minimal interventions (level of evidence B).
- Materials which are tailored for the individual smoker are more effective than generic materials, however impact on smoking cessation rates is small (level of evidence B).

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4.2.4.5 Computer/web-based

Computer or Internet-based interventions have the potential to be accessed by a large percentage of the smoking population, may better address special categories like young people and are cheap to deliver. Such interventions may be used as single or adjuvant treatments, by typically collecting information from the patient and then using algorithms to tailor feedback or recommendations. Current applications permit multiple iterations of feedback, development and monitoring of a quit plan, and proactive e-mail prompts to users.

Positive effects have been reported for a population study using computer-generated reports based on the stages of change mode and a website study offered in a worksite programme. A study with adolescents reported positive results due to access to a complex intervention that comprised an interactive computer intervention, advice from a clinician, brief motivational interviewing and telephone booster sessions (the control condition was information about eating more fruit and vegetables).[1]

A recent review found evidence that Internet and web-based smoking cessation programmes can assist with increasing

smoking cessation, however consistent effects were not documented and evidence was at risk of bias.[2] Internet intervention programmes that provide individually tailored information and support may be more effective than a static website and likewise those that offered interactivity appear to be more efficacious. The Internet may have an additional benefit when used alongside other interventions, such as NRT or other pharmacotherapy. Innovative smoking cessation interventions delivered via the Internet may be more attractive to young people and women who smoke, and less attractive to smokers reporting depression.[3] Additional research is required to better understand the value of Internet based intervention programs.

Recommendations:

- Further research is needed before internet-based smoking cessation interventions can be recommended.

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4.3 Pharmacological treatment of tobacco dependence

Since smoking is a chronic disease, it imposes a therapeutic intervention with multiple components, amongst which pharmacological therapy is crucial. In different European countries, various European and national regulatory bodies are involved in approval of medications. Two categories of medicines are indicated for smoking cessation: first line medication and second line medication.

First line medications have been found to be effective in treating tobacco dependence, have a higher safety level and are approved by European Medicines Agency (EMEA). First line medication must be the first option for any clinician treating nicotine dependence. Three categories of medications are approved for smoking cessation are considered first line therapies and include: nicotine replacement therapy, varenicline and bupropion (See Table 4.6).

Second line quit smoking medications include the partial nicotine-receptor antagonist cytisine (approved for this indication in Eastern European countries). The tricyclic anti-depressant nortriptyline, and the anti-hypertensive agent clonidine are registered in many countries, but not for smoking cessation. Nortriptyline is approved as an anti-depressant, but not as a smoking cessation drug. Second line medication recommended for smoking cessation is represented by medicines with proven efficacy, but to a smaller extent than in the case of first line medication, either because they are not EMEA-approved for tobacco dependence treatment or because they are suspected of having greater side effects than first line medication. Generally, they are recommended when first line medication cannot be used for various reasons (lack of efficacy, contra-indications etc.). Significant progress has been made concerning the efficacy of drugs used for quitting tobacco over the last few years. In addition to mono-therapy, a combination of various pharmacological therapies can be used to increase success with quitting. Additional strategies such as prolonging the therapy duration, adjusting the dosages to avoid side effects, and combing medications have been shown to increase efficacy of these treatments.

Efficacy of First Line Medications

A 2008 meta-analysis of 83 randomized trials examining the effectiveness of various medications, with respect to the rate of abstinence at six months after treatment, showed that most smoking cessation medications (nicotine patch, gum, lozenge, nasal spray, inhaler, and sustained-release bupropion) approximately doubled the odds of achieving abstinence (See Table 4.7).[1] The estimated six-month abstinence rate among patients randomly assigned to placebo was about 14%, compared to 19% or to 26% across most pharmacotherapies. Since some studies included counseling among other study interventions, these effectiveness rates reflect also some counseling benefit.

Table 4.6: First line quit smoking medications (adapted from Fiore M.C.)[1]

PHARMACOLOGICAL TREATMENT OF TOBACCO DEPENDENCE		
MEDICATION	**DOSE**	**INSTRUCTIONS**
BUPROPION	Days 1-3: 150 mg each morning; day 4-end: 150 mg x 2/day (at least at 8 hours) for the rest of the cure	Start 1-2 weeks before quit date; Use for 2-6 months
NICOTINE GUM	2 mg – patient smokes ≤ 24 cigarettes/day 4mg – patient smokes ≥ 25 cigarettes/day The unanimously recommended dose is 8-12 gums chewed/day	Use 3-6 months
NICOTINE INHALER	6-16 cartridges/day, a cartridge can deliver 4 mg of nicotine throughout 80 inhalations	Use up to 6 months; taper at end
NICOTINE LOZENGES	Doses of 1, 2 and 4 mg; 1 piece every 1-2 hour initially, then taper 2 mg if patient smokes 30 min. or more after waking and 4 mg if patient smokes < 30 min. after	Use 3-6 months
NICOTINE NASAL SPRAY	0.5 mg / nostril, initially 1-2 doses/hour; limits: 8-40 doses/day	Use 3-6 months
NICOTINE PATCH	7, 14, 21 mg/24 hr (or 10/15/25 mg/16) If patient smokes 10 cigarettes/day, 21 mg/day for 4 weeks, then 14 mg/day for 2 weeks, then 7 mg/day for 2 weeks; If patient smokes <10 cigarettes/day, start with 14 mg/day for 6 weeks, then 7 mg/day for 2 weeks	Use new patch every morning for 8-12 weeks Evidence of increased efficacy when used for 3-6 months
VARENICLINE	Days 1-3: 0.5 mg every morning; Days 4-7: 0.5 mg twice daily; 8-end: 1mg twice daily	Start 1 week before quit date; Use 3-6 months
COMBINATION THERAPIES – only the combination of bupropion SR + nicotine patch has been approved by the FDA for smoking cessation		
NICOTINE PATCH + BUPROPION	Follow instructions for individual medications above	Follow instructions for individual medications above
NICOTINE PATCH + INHALER **NICOTINE PATCH + LOZENGES** **NICOTINE PATCH + GUMS**	Follow instructions for individual medications above	Follow instructions for individual medications above

Varenicline and the use of combination nicotine-replacement therapy (nicotine patch plus a short-term form of NRT such as nicotine gum or lozenge, used for more than 14-weeks) were associated with the greatest estimated abstinence rates of 33% and 37%, respectively.[1] These rates were significantly higher than the rate associated with a representative mono therapy (nicotine patch). The superiority of these two medications has also been shown in head-to-head trials in which they were compared with single agents such as the nicotine patch or bupropion.[2,3]

A second recent meta-analysis by the Cochrane Collaboration which examined evidence to support smoking cessation pharmacotherapies found similar conclusions.[4] In short combination NRT (oral + patch) and varenicline provide similar benefits terms of efficacy, and both outperform mono therapy

Table 4.7: Efficacy of First Line Quit Smoking Medication Monotherapy and Combination Therapy

PHARMACOTHERAPY	ESTIMATED OR (95% CI) OF ABSTINENCE	ESTIMATED ABSTINENT RATE (95% CI)
Placebo	1.0	13.8
Mono therapy		
Nicotine Patch	1.9 (1.7 - 2.2)	23.4 (21.3 - 25.8)
High Dose Patch	2.3 (1.7 - 3.0)	26.5 (21.3 - 32.5)
Nicotine Inhaler	2.1 (1.5 - 2.9)	24.8 (19.1 - 31.6)
Nicotine Gum	1.5 (1.2 - 1.7)	19.0 (16.5 - 21.9)
Bupropion	2.0 (1.8 - 2.2)	24.2 (22.2 - 26.4)
Varenicline	**3.1 (2.5 - 3.8)**	**33.2 (28.9 - 37.8)**
Combination Therapy		
Patch + Inhaler	2.2 (1.3 - 2.6)	25.8 (17.3 - 36.5)
Patch + Gum	2.6 (2.5 - 5.2)	26.5 (28.6 - 45.3)
Patch + Bupropion	2.5 (1.9 -3 .4)	28.9 (23.5 - 25.1)
Patch (long-term; > 14 weeks) + ad lib NRT (gum or spray)	3.6 (2.5 – 5.2)	36.5 (28.6 – 45.3)

Source: Treating Tobacco Use and Dependence, U.S. Clinical Practice Guideline, 2008 Update.[1]

with NRT or bupropion.

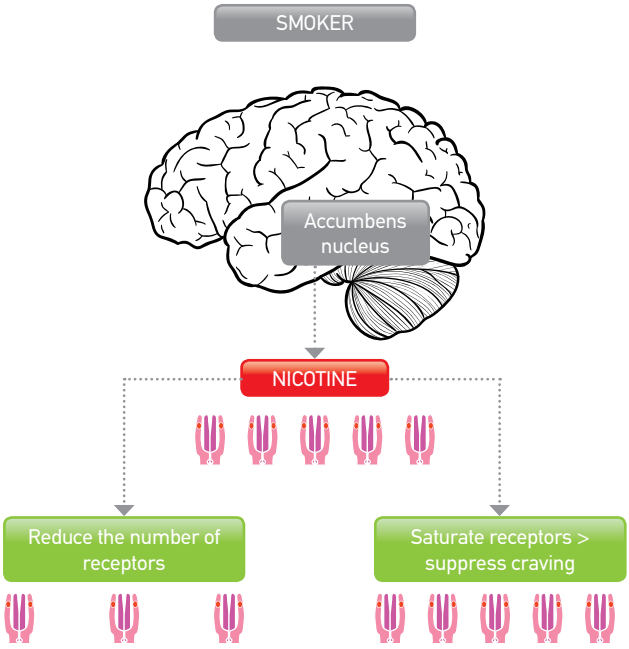
Medications for smoking cessation have been shown to be effective in real-world health care settings and in smokers with various co-existing conditions (substance abuse and depression).[1,5]

4.3.1. Treatment with NRT

4.3.1.1 Indications

- Nicotine replacement therapy is proposed as first-line treatment for smoking cessation in tobacco users motivated and not motivated to stop.
- It is also a product that can be used for a time to reduce smoking prevalence when quitting is not possible or accepted by the tobacco user.

Figure 4.3: The two objectives of nicotine replacement therapy: decrease withdrawal syndrome (acute) and reduce addiction by reducing the number of nicotine receptors (chronic)



4.3.1.2 Mechanism of action

Nicotine delivered by tobacco smoke or chewing and nicotine delivered by NRT is the same nicotine, but the kinetics of delivery to the brain is radically different changing dramatically the effects.

Nicotine replacement therapy has two aims:

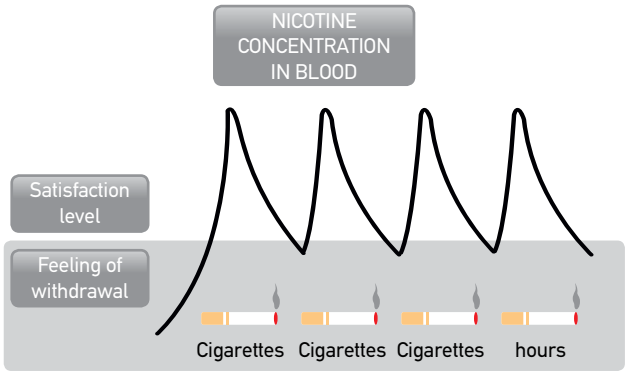
- stimulate the nicotine receptors to remove the craving and other withdrawal symptoms: the effect is immediate;
- reduce the number of nicotinic receptors: this decline continues over weeks and reduces tobacco dependence.

See Figure 4.3.

When smoking a cigarette, nicotine reaches the smoker's brain within 7 seconds and saturates nicotine receptors ("shooting effect"), (Figure 4.4).

The cells in the involved brain area react by desensitizing the

Figure 4.4: Evolution of nicotine levels in the arterial system with repeated nicotine consumption



receptors and multiplying their number and thus the need for another cigarette appears. Smokers have many more nicotine receptors than non-smokers, explaining the high tolerance to nicotine in smokers, as well as their strong nicotine addiction. These receptors are so many that they could be highlighted by positron emission tomography: a centre of nicotine addiction that brightens the area of the nucleus accumbens and the anterior tegmental area where the nicotinic receptors are mainly located in the brain.

Nicotine replacement therapy delivers nicotine to the brain much more slowly than cigarettes, producing no peaks. NRT stimulates nicotine receptors, reducing or eliminating the need for nicotine, thus producing progressively fewer receptors, which after three months of NRT will return to normal number. However, these structures retain the memory of smoking and could be multiplied very rapidly on the cell membrane if smoking is resumed: tobacco dependence is therefore a chronic relapsing disease.

4.3.1.3 Clinical evidence for the efficacy of NRT

As with the treatment of all chronic diseases, treatment of tobacco dependence has been the subject of many randomized trials made in the past 40 years.

Two major meta-analyses have summarized available evidence regarding the efficacy of NRT in supporting cessation. The first meta-analysis was conducted by the U.S. Surgeon General, co-ordinated by Michael C. Fiore.[1] The second meta-analysis was conducted by the Cochrane Collaboration and has been recently updated.

The Cochrane Collaboration identified 150 trials of nicotine replacement products, 117 trials involving over 50,000 participants compared the different types of nicotine replacement therapy to a placebo or a control group without nicotine replacement therapy.[6]

The relative risk (RR) of abstinence from all forms of substitutes versus control is 1.60 (95% confidence interval [CI]: 1.53 to 1.68).6

The RR for each type was:[6]

- 1.49 (95% CI 1.40 to 1.60, 55 trials) for nicotine gum;
- 1.64 (95% CI 1.52 to 1.78, 43 trials) for nicotine patch;
- 1.95 (95% CI 1.61 to 2.36, 6 trials) for oral tablets/lozenges;
- 1.90 (95% CI 1.36 to 2.67, 4 trials) for nicotine inhaler;
- 2.02 (95% CI 1.49 to 2.73, 4 trials) for nicotine nasal spray
- 2.48 (95% CI 1.24 to 4.94, 1 trial) for oral spray.

The observed difference in efficacy between patches and oral forms may be dose-related, because it is more common to examine dosage with oral forms that are given in fixed dose clinical trials.

There was evidence that combining a nicotine patch with a rapid delivery form of NRT was more effective than a single type of NRT (RR 1.34, 95% CI 1.18 to 1.51, 9 trials).[6]

In the case of highly dependent smokers, there was a significant benefit of 4 mg gum compared with 2 mg gum, but evidence of a benefit of higher doses of patch are lower in the studies currently available.

The Cochrane Collaboration authors concluded that all commercially available forms of NRT (gum, transdermal patch, nasal spray, inhaler and sublingual tablets) can help smokers in their quit attempts and increase their chances of success. NRT increased smoking abstinence rates of 50%-70%, regardless of type and dose.[6]

The effectiveness of nicotine replacement therapy is not fully independent of the intensity of the additional assistance provided to the smoker. The more support there is, the greater the benefit, but even in the absence of any support nicotine substitutes are effective.

NRT in combination with pharmacotherapy

The Cochrane Collaboration has shown that combining nicotine patches with oral forms is more efficient than using a single type of nicotine replacement.

- NRT may be used in combination with oral and transdermal forms;
- NRT may be used in combination with bupropion or nortriptyline;
- Current clinical practice guidelines do not recommend using NRT in combination with varenicline for smoking cessation. This is primarily because it is thought that NRT similar to tobacco nicotine was blocked by varenicline.
- In patients who continue to smoke cigarettes after 2 to 6 weeks of varenicline monotherapy there is no contra-indication to replace theses cigarettes with NRT. Recent clinical trial evidence suggests there may be a benefit to combing NRT and Varenicline, however results are mixed.[4] Additional research is required to support the efficacy of this approach as a standard practice. Likewise the addition of varenicline to NRT mono therapy follows the same guidelines.

4.3.1.4 NRT Patch

The patch was developed to avoid the difficulties associated with the use of gum. It also has the advantage of providing more stable nicotine concentrations, more favorable to smoking cessation, but less favorable than oral forms to meet urgent nicotine needs.

The nicotine contained in the patch will gradually be administered via the skin and subcutaneous tissue, migrating from the skin to the blood and brain. Even when the nicotine patch is removed, it continues to spread from skin to brain.

The patch allows for good compliance due to the ease of use. To reduce the risk of local skin reaction, the user must change the patch application site daily, alternating arms, shoulders, and chest. There are patches to be worn for 24 hours to deliver a maximum dose of 21 mg of nicotine per day and systems that can be worn for 16 hours which deliver a maximum dose of 25 mg of nicotine. So the 21 mg/24h systems deliver approximately 0.9 mg of nicotine per hour, while the 25 mg/16h systems deliver 1.4 mg/h (Table 4.8).

Type of patch

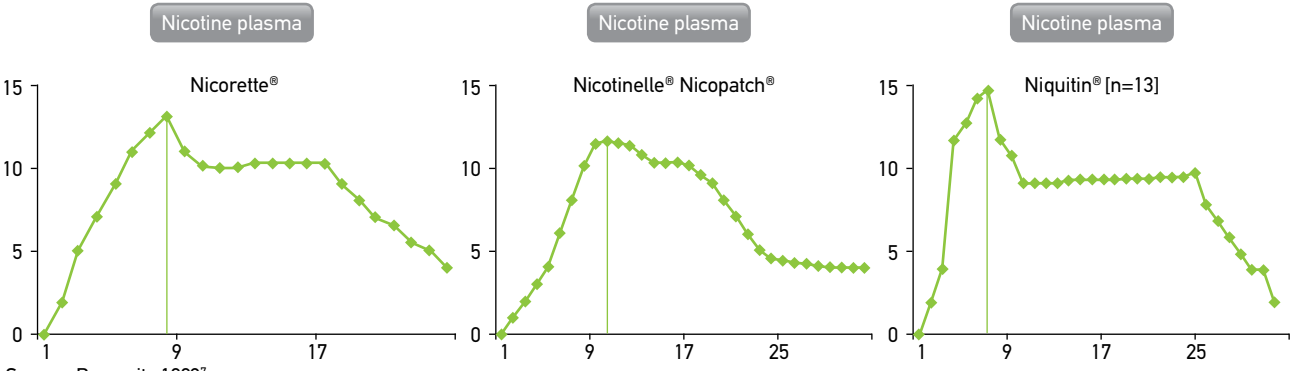
Patches are all based on the same principle, but have small kinetic differences (Figure 4.5).[7]

Each form of patch thus has small advantages and disadvantages. It is possible to adjust the treatment for each patient.

Table 4.8: Equivalence of nicotine delivered patches at 16 and 24 hours

	0.3 MG/H	0.6 MG/H	0.9 MG/H	1,6 MG/H
16 hours	5mg	10 mg	15 mg	25 mg
24 hours	7 mg	14 mg	21 mg	

Figure 4.5: Kinetics of nicotine over 24 hours according to patch used



Source: Benowitz 1993[7]

How to apply patches

The patch is applied in the morning before or after showering (being careful not to use surface-active agents that decrease nicotine absorption. The user should avoid sticking patches in places of high pressure. If the patch becomes detached in the course of the day, it is possible to re-use the same patch using e.g. a sticking plaster.

General tolerance of patches

Like all nicotine replacement products, tolerance of patches is much better among highly dependent smokers who usually have no side effects even with multiple patches, while in a non-smoker one patch may produce almost constant side effects. These side effects are dose-related to nicotine and are strongly linked to withdrawal symptoms.

One side effect specific to the patch is skin allergy: a red skin reaction to the patch is common, often reflecting irritation. But a larger allergic reaction is possible in some patients allergic to adhesive patches. Doctors must inquire of any possible allergies to sticking plasters. If symptoms are moderate, it is possible to change the brand of patch, as different patches use different adhesives.

If a skin reaction occurs after the patch is applied, remove the patch and abandon use, except in very specific situations.

4.3.1.5 Oral nicotine replacement

Many forms of oral nicotine replacement therapy are on the market. There are four oral forms:

- Chewing gum,
- Sublingual tablets (placed under tongue),
- Lozenges,
- Inhalers, which look like cigarette holders.

All of these nicotine replacement products are absorbed through the oral mucosa.

The absorption of nicotine through the oral mucosa occurs only if the mouth pH is neutral, so the user should avoid eating or drinking, especially sodas (which are acidic) 30 minutes before taking an oral form of nicotine replacement therapy.

The amount of saliva absorbed in the stomach has to be minimized as much as possible because it may cause irritation and hiccoughs. Increased salivation and swallowing of saliva is particularly important with chewing gum used by smokers who have not used chewing gum before and chew too quickly.

Bioavailability of oral nicotine

Nicotine is absorbed through the lining of the mouth when chewing begins, throughout the duration of chewing and after a few minutes or for 15 to 30 minutes.

So the progressive rise in arterial blood nicotine is much less abrupt than with cigarettes or nasal spray, thus explaining why it is preferable to maintain a certain level of nicotine concentrations with sustained dosages, so that if a sudden lack occurs, taking an oral form only has to provide additional adjustment for serum as minimal as possible. At the peak nicotine concentrations produced by gum, it is possible for a few minutes beyond the level of nicotine necessary to satisfy the receptors, which can cause a desensitization of these receptors and the awakening of new receptors that may persist in time explaining that some patients find it difficult to stop gum six months or a year or more after quitting. It is totally incorrect to sustain that gum makes them addicted to nicotine. They had been addicted to cigarettes, but it is true to say that oral intake of nicotine contributes to the maintenance of nicotine dependency in this case. Such a phenomenon does not exist, e.g. with patches that produce the least steep pharmacokinetic curve of nicotine, most likely to regress to dependence, but at the cost of occurrence of cravings at certain times of the day.

All nicotine contained in gum is not delivered to the mouth, and 2 mg of gum does not deliver 2 mg of nicotine to the oral mucosa and blood, but rather less than 1.5 mg, with variations from one brand to another (all forms are 1.5 mg to 2 mg gum quasi bioequivalent to 2 mg). The individual variations depend greatly on how the gum is chewed. Kinetic variations from one subject to another and from one outlet to another are generally greater in the case of patches as compared to oral forms, but are much less significant than in the case of cigarettes. Even smoking from one moment of the day to another can result in doses ranging from 1 to 5 of nicotine in the same cigarette.

These kinetic changes are not so significant in practice because the dose of oral forms is determined by the patient taking the amount needed to make cravings disappear.

In any case it is clear to the patient that the gum should not be used as chewing gum, but, conversely, chewed slowly, and that saliva should not be swallowed.

Gum

Chewing gum exists in dosages of 2 mg to 4 mg. The 2 mg gum is available to low and medium- dependent smokers, the 4 mg to highly dependent smokers with a score of 7 or more). Gum has either natural taste or is flavored with mint, cinnamon, orange or other fruit flavors.

Chewing gum requires a good technique in order to be effective and to avoid causing side effects: pain in the mouth, jaws, stomach pain or hiccoughs. Gum taken orally is chewed once or twice, then left against the cheek for 3 minutes, and then chewed once a minute for twenty minutes. Once completed, the gum must be disposed of out of the reach of children because like cigarettes it is a nicotine containing product.

Sublingual tablets

These 2 mg tablets are small-uncoated tablets that must be placed under the tongue. They may cause a stinging sensation, but have no taste. As there is no need to chew or suck the tablets, excessive drooling is avoided (which may cause hiccoughs). They melt in the mouth in 15-30 minutes.

Lozenges

Lozenges are available in dosages of 1 to 4 mg and oral absorption is better than gum. Administration of lozenges is simple, as they are film-coated. They are sucked slowly without chewing.

Inhalers

An inhaler consists of a white plastic tube resembling a cigarette holder that opens up to contain a nicotine cartridge. As you inhale, as the smoker does with a cigarette, a small amount of nicotine is projected onto the oral mucosa where it is absorbed. The cartridges contain 10 mg of nicotine. Some heavy smokers consume the cartridge within an hour; others can keep the same inhaler all day and do not finish the cartridge by the evening. This form of substitution maintains/allows both the gesture of smoking cigarettes and of taking nicotine.

Nasal spray

Nasal sprays sold by prescription are available in some countries. These nasal sprays have the advantage of being very effective in suppressing withdrawal symptoms. They have two major drawbacks: the first is that they cause nasal irritation (sometimes major), the second is that they administer nicotine to the brain abruptly, almost as fast as cigarettes, which explains persistent addiction to this product outside of smoking cessation.

4.3.1.6 Prescribing instructions

Choose the initial dose of nicotine replacement therapy

When quitting, the key is to replace nicotine to a level close to what was taken with the cigarette (80- 90%). This quantity is difficult to determine a priori, because, with a cigarette, some smokers are 10 times more nicotine-dependent than others.

The initial dose of nicotine replacement products can be easily determined by the amount smoked per day, and time to first cigarette (Table 4.9).[8] Less dependent smokers may not require pharmacological treatment, the most dependent may require two patches associated with oral forms.

The amount of nicotine provided by the strongest patch is, for many smokers, similar to that provided by a pack of cigarettes, but for some rare smokers, it may be too much nicotine, whilst for others it may not be sufficient.

When a high dose of nicotine is needed, the most frequently recommended method is a combination of patches and oral forms or using more than one patch.

It is possible to associate a patch to oral forms in a staggered administration to alleviate cravings that may persist, as is done to relieve severe pain of cancer patients, who are administered morphine long term allowing patients the opportunity to make cross-doses to relieve persistent pain. As long as one has a craving, there is no danger in associating patches and oral forms. Mixed nicotine replacement is less dangerous than mixing cigarettes and cigars.

Of course nicotine concentrations, urinary cotinine or expired CO levels may sometimes contribute to a finer adjustment of the dosage, but this table suggests a dose, which is frequently close to the final dose.

Table 4.9: Proposed initial doses of nicotine replacement therapy (source: INPES, France)[8]

TIME TO FIRST CIGARETTE IN THE MORNING	Number of Cigarettes per day			
	<10 cigs/d	10-19 cigs/d	20-30 cig/day	> 30 cig/d
< 5 mins		Patch High Dose (0.9 mg/h) +/- oral NRT	Patch High Dose (0.9 mg/h) +/- oral NRT	2 High Dose Patches (1.8 mg/h) +/- oral NRT
< 30 mins		Patch High Dose (0.9 mg/h)	Patch High Dose (0.9 mg/h) +/- oral NRT	Patch High Dose (0.9 mg/h) +/- oral NRT
< 60 min after waking	No medication or oral NRT	Oral NRT	Patch High Dose (0.9 mg/h)	Patch High Dose (0.9 mg/h) +/- oral NRT
> 60 min after waking	No medication or oral NRT	No medication or oral NRT	Oral NRT	
Non-daily	No medication or oral NRT	No medication or oral NRT		

Dose adjustment after 24-72 hours

The availability of variable doses of oral substitution allows immediate adaptation doses of nicotine, but smokers are usually hesitant and afraid of nicotine medication although for years they take higher doses of nicotine in the form of smoked tobacco. Smokers, however, often experience for several decades titration of nicotine concentrations by modulating the number of cigarettes smoked and the intensity of consumption to adapt nicotine concentrations to satisfy their nicotine receptors.

Clinicians should be prepared to identify signs of overdose (rare) and signs of under dose (frequent) in the initial 24-72 hours following quitting.

Signs of overdose

There is no nicotine overdose when craving persists. In a patient with no desire to smoke, overdose results in the impression of having smoked too much, with nausea, tachycardia. These signs are transient and quickly stop at the end of treatment for a few hours and resume treatment at a reduced dose.

Signs of under dose

Smokers with nicotine under dosage demonstrate:

- cravings,
- extreme nervousness to their surroundings,
- food cravings that drive them to snack,
- difficulty sleeping
- often continue to smoke a few cigarettes.

It is often useful to guide smokers in regular dosage adjustments:

- by supplying information so that they can adapt the dosage themselves in most cases, or
- by asking them to call the clinician within the 24-72 hour period following quitting,
- by advising them to call quit lines or other tobacco cessation support who can help adjust the dose and provide more advice.

If the patient takes more than 8-10 oral forms or more cigarettes per day in a patch, it is better to apply a second patch to ensure a steady supply of nicotine.

4.3.1.7 Contra-indications

There are no contra-indication for nicotine replacement except in case of allergy (rare for patch users, exceptional for oral form users). In some countries pregnancy is considered to be a contra-indication. Of course, nicotine replacement therapy is not indicated for non-smokers. Precautions should be taken in the case of children under 18 or 15 years, recent severe cardiac events, and pregnancy. These precautions must be weighed according to the particularly high risk

of smoking in these conditions (50% of tobacco users are killed by a tobacco-related disease).

4.3.1.8 Adverse effects, precautions, warnings, drug interactions

The risks of nicotine medications are similar as those of nicotine in tobacco. There is no added risk due to partial or total replacement of nicotine provided by tobacco compared to that provided by substitutes. The intake of nicotine medications removes hundreds toxins contained in the tobacco smoke and constitutes an overall health benefit compared to tobacco use. The reduction of inflammation induced by tobacco cessation leads to changes in the kinetics of certain medications and it is recommend to re-evaluate treatment with theophylline, warfarin etc.

Risk of dependence to nicotine substitutes

There is a very small risk of becoming addicted to NRT. With oral NRT forms there could be a small overflow level of nicotine in the brain, which may lead to persistence of addiction in some smokers after smoking cessation. The risk of addiction is highest with tobacco, much lower with oral tobacco, lower with the electronic cigarette, even lower with oral nicotine replacement therapy and virtually absent with nicotine patches (Figure 4.7).

In subjects who use gum chronically, there is no major medical problem that the patient remains under this treatment for months or even years. After a while gums consumers often could no longer take gum and patients say they have "had enough".

By checking the timing of gum consumption, useful information arise if gum is taken instead to manage emotions in a systematic way, it means it is taken to fill a permanent deficiency. In some cases, if patches are replaced by oral substitutes they could eliminate nicotine peaks in the blood and allow complete nicotine withdrawal.

Risks of nicotine replacement therapy

Nicotine replacement therapy may have side effects, such as allergic or no allergic reactions. These phenomena are usually benign. It is sometimes difficult to know, if the side effects observed, are related to the change in smoking status (i.e. withdrawal symptoms), to the change of lifestyle or are due to the drug.

In case of allergy, it is always possible to be allergic to the nicotine replacement itself, but this risk is quite exceptional and is more theoretical than practical, however allergies do exist in relation to the patches, specifically the adhesives used. The appropriate response to such complaints depends on the severity and extent of reactions. Other side effects (see Table 4.10) are generally moderate and are not comparable with the consequences of smoking. This is why such medication is generally available without prescription.

It is always safer to take nicotine replacement therapy than tobacco.

Figure 4.7: Estimated risk of initiation of addiction and maintaining dependency as per nicotine product

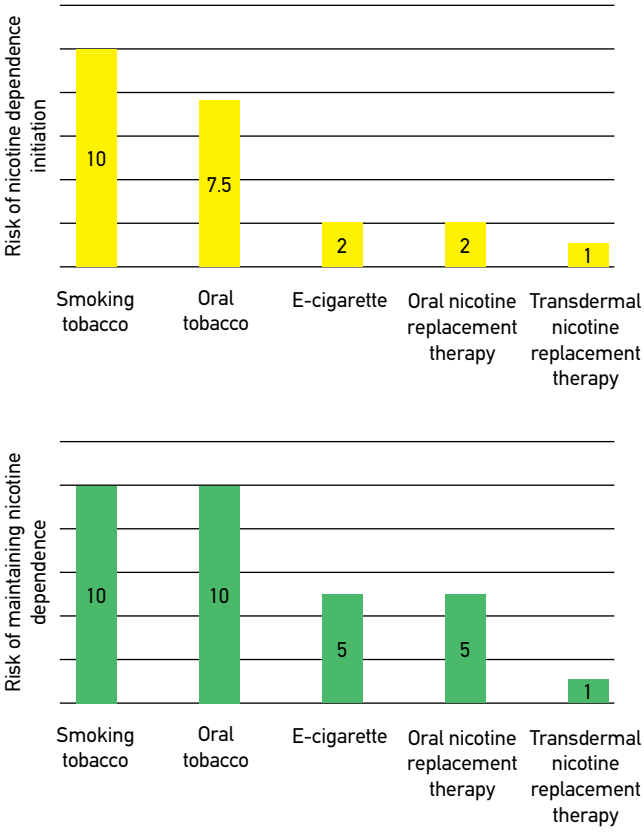


Table 4.10: Side effects of nicotine

Common side effects (more than one person in 100):
Headaches
Dizziness
Hiccoughs
Sore throat
Irritation or dryness of the mouth,
Nausea, vomiting, digestive disorders
Uncommon (more than one person in 1000):
Palpitations
Rare side effects (more than one person in 10,000):
Occurrence of cardiac arrhythmia

Adverse effects of treatment as compared to tobacco cessation related symptoms

Patients often interpret as side effects of treatment effects that are actually related to smoking cessation. The withdrawal effects most often attributed to treatment are depressive syndromes and sleep disruption.

- Many individuals who quit smoking experience signs of depression, which can range from mild to severe. The presence of depression is not related to the use of quit smoking medications, but rather due to the fact that quitting smoking may stimulate (unmask) latent depression. If a patient has a past history of depression, care should be taken in order to prevent a relapse of depression including the monitoring of changes to mood. For patients who report current depression, clinicians should initiate treatment alongside smoking cessation support as per best practice guidelines for the treatment of depression.
- Sleep disruption and changes in sleep quality is encountered by the majority of smokers who quit smoking, regardless of the use of quit smoking medications. These changes have varying degrees of severity. They require at minimum an assessment of the severity of the sleep disturbance. The occurrence of nightmares should be an immediate alert of possible depression. Other disorders may occur over a longer period (and these often disappear spontaneously). Individuals using the patch who experience nightmares should be advised to remove the patch at night.

Recommendations

- Nicotine replacement therapy is recommended as an effective pharmacotherapy for smoking cessation (level of evidence A).
- A combination of oral NRT and the NRT patch, which is titrated to approximate the daily nicotine intake of the individual when smoking will increase the success with quitting (level of evidence A).
- Extended use of NRT beyond 14 weeks has been shown to increase success with quitting (level of evidence A).

4.3.2 Treatment with bupropion SR

Bupropion SR, was the first non-nicotine therapy that proved effective in treating nicotine dependence. Bupropion SR, has been known worldwide since 1997 and in Europe since 2000. It is available only by medical prescription. This medication was used for a long time in USA for patients with schizophrenia and other illnesses. Because many patients receiving this medication quit smoking unintentionally, Linda Ferry, who was a doctor treating these patients, started to examine the efficacy of this drug in smoking cessation. A long release formulation has been studied and marketed. Because bupropion has been used as an anti-depressant in the USA since 1989;[9] its adverse pharmacological profile is very well documented with data concerning the product's safety.[10] As with any other anti- depressant, the common side effects are dry mouth, insomnia and headaches. Potential users of this medicine must be informed about its side effects.

Mechanism of action

Bupropion blocks the neuronal release of dopamine and noradrenaline and, possibly, the action of inhibiting the function of anticholinergic nicotine receptors, proved in vitro.[11] It mimics the effect of cigarette-derived nicotine by inhibiting the re-uptake of noradrenaline and dopamine and is thought to reduce nicotine withdrawal also by this mechanism. It seems that bupropion's efficacy for nicotine dependence is a property separate from

its anti-depressant action, since its positive smoking cessation action has also been proven on non-depressive patients.[12]

Bupropion acts by removing some of the nicotine abstinence symptoms, i.e. in particular depression, by reducing the severity of the withdrawal syndrome globally, which makes it recommendable as an efficient aid in the smoking cessation process. Bupropion helps patients by decreasing the appetite for smoking. Administering bupropion to smokers with severe nicotine dependence considerably reduces the depression symptoms associated with withdrawal. Bupropion doubles the abstinence ratio compared to placebos and has similar effects on both sexes.[12]

A recently published genetic analysis of the response to bupropion suggests that the success of smoking cessation using this drug is determined in part by variation in CYP2B6, the gene encoding the primary enzyme responsible for the metabolism of bupropion, rather than by genetic variation in nicotinic cholinergic receptor pathways.[13]

Clinical evidence for the efficacy of bupropion

A meta-analysis of 44 randomized studies supports the efficacy of bupropion in treating nicotine dependence and concluded that bupropion significantly increases long-term successful abstinence ratio compared to placebos (OR of 1.62; 95%, CI 1.49–1.76).[12]

In a randomized, double-blind, placebo-controlled study, 27% of the patients treated with bupropion were found abstinent after six months, compared to 16% who received placebos.[14] The long-term abstinence ratio in patients treated with bupropion was also double when it was accompanied by behavioral therapy, compared to placebo.[15] Data exists about bupropion's efficacy in smoking cessation in the sub-group of smokers with the genotype DRD2 Taq1 A2/A2 of D2 gene of the dopamine receptor: at the end of treatment, the abstinence ratio was three times higher in those who received bupropion compared to placebo.[16] Bupropion SR has also been shown to decrease craving and attenuate post-cessation weight gain among smokeless tobacco users trying to quit.[17]

Indications

Bupropion is a first-line pharmacotherapy that has proven efficient in treating tobacco use and dependence. Bupropion is recommended based solely on medical prescription to all patients motivated to stop smoking, who have no contra-indications. At the same time, it is an efficient alternative for patients who did not tolerate or have tried NRT without success, or for patients who express a preference for non-nicotine therapies.

Bupropion is recommended as an efficient smoking cessation medication, including in the following situations:

- To avoid post-abstinence weight gain: bupropion can be used on smokers concerned with putting on weight after smoking cessation. Thus, Hays et al. reported in a previous survey a better weight control associated with a higher abstinence ratio compared to placebo one year after the end of bupropion treatment course.[18]
- To prevent smoking relapses (in patients who underwent a seven-week bupropion course and stopped smoking, continuing bupropion therapy up to 52 weeks delayed smoking relapse.
- To prevent smoking relapses in alcoholic patients during recovery. In patients with chronic obstructive pulmonary disease. Although Garcia Rio et al. arrived at the hypothesis that bupropion could damage the ventilator response to hypoxia and hypercapnia with a potentially harmful effect on the evolution of COPD, none of the studies which assessed the efficacy of bupropion as a smoking cessation therapy on patients with chronic pulmonary disease could show such adverse effects.[19]

Clinical use

Bupropion is available in boxes of 28 tablets of 150 mg. In the first three days, patients should take a dose of 150 mg bupropion orally every morning, then 150 mg twice a day (at min. 8 hour interval) for the rest of the course, for a total duration of 7 to 9 or 12 weeks. Prolonging the duration of the initial cure results in more lasting tobacco abstinence. For long-term therapy, consider bupropion SR 150 mg for up to six months post quitting.[20]

Patients should begin bupropion SR treatment 1-2 weeks before they stop smoking. They must set a quit date in the second week of treatment and may start using bupropion, although they still smoke. It is considered that after one to two weeks

of treatment the serum level of Bupropion attains a constant condition and stopping smoking may be attempted. It has been proven that continuing to smoke does not significantly affect the pharmacotherapy with bupropion. According to some authors, if the patient does not succeed in stopping smoking on the date initially set, it should be recommended to delay stopping until the third or fourth week of treatment, until achieving abstinence.[20]

Prescribing instructions

Stopping smoking prior to quit date: It is recognized that some patients may lose their desire to smoke before the date set for quitting, or can spontaneously reduce the amount of tobacco used.
Dosage information: If insomnia is present, taking the evening dose earlier in the afternoon may bring some relief.
Alcohol: It is recommended not to use in combination with alcohol, or at most only a minimum quantity. If mood changes manifest themselves, consult a doctor.

Contra-indications

Contra-indications exist in the following cases:

- age under 18;
- pregnancy, breast-feeding: bupropion has not been shown to be effective for tobacco dependence treatment in pregnant smokers;
- Bupropion has not been evaluated in breast-feeding patients;
- hypersensitivity to bupropion or its inactive constituents;
- previous or current convulsive disorders, skull and brain tumors, medical history of seizures or conditions favoring seizure;
- eating disorders;
- bipolar disorders;
- withdrawal from chronic alcohol consumption, severe hepatic failure, hepatic cirrhosis;
- use of MAO inhibitors in the past two weeks, history of benzodiazepine use.

Adverse effects, precautions, warnings, drug interactions

Main adverse events

A review of clinical studies showed twice the adverse effects in patients receiving bupropion compared to placebo.[1] The adverse effects encountered most often in patients receiving bupropion are:

- insomnia,
- headache,
- dry mouth

To counteract dry mouth and headaches it is recommended to gradually ingest two to three liters of liquids a day. To avoid insomnia we recommend taking the first bupropion tablet in the morning, as early as possible, so that the second tablet is taken earlier in the afternoon, preferably at least four hours before sleep. Insomnia can be reduced also by adjusting the bupropion dose to 150 mg/day.
In a more extensive study of the French experience concerning smoking cessation treatment using bupropion in 2001-2004, the authors noted 1682 adverse reactions encountered on 698,000 patients treated with bupropion in the first three years of the product being on sale in France.[21] Of these 1682 adverse events, 28% were recorded as severe adverse reactions, with the following spectrum:

- 31.2% skin reactions (allergic, angiooedema "serum disease" type),
- 22.5% neurological reactions (especially cerebral-vascular),
- 17.2% neuropsychological reactions (especially suicidal thoughts, depression).

After careful analysis of the cases, it was proven that in 66% of neurological/psychological reactions and in almost 50% of the neurological reactions, predisposing risk factors were identified.[21]

Other adverse effects

Dizziness, high blood pressure, thoracic pain, anxiety-depression syndrome, decreasing intellectual performance, visual disturbance and, rarely, seizure, even allergic skin reactions are also described as adverse effects. The most alarming adverse effect is seizure; it occurs very rarely (1:1000) and is usually facilitated by pre-existing risk factors like brain circulation disorders, cranial-cerebral trauma, epilepsy, eating disorders, simultaneous medication which lowers the seizure threshold etc.

Rare cases of angioedema,[22] hypernatraemia, including a syndrome of inappropriate secretion of antidiuretic hormone (SIADH), are reported, and are not a rare complication of antipsychotic drug therapy.[23]

Precautions for use

In older subjects, it is recommended to adjust (reduce) the bupropion dose by half, i.e. 150 mg bupropion/day, as well as in cases associated with severe renal or hepatic failure. Drivers and patients who handle equipment requiring vigilance are advised to check the effects of bupropion before carrying out these activities, given that they could experience dizziness, impaired concentration capacity and attention.

Since high blood pressure was described by patients under treatment with bupropion, careful blood pressure monitoring is required, especially when therapeutic combinations are used, like associating bupropion and nicotine patches.

All patients using bupropion as well other medication for smoking cessation must be monitored for symptoms in the following categories: behavioral disorders, hostility, agitation, bad moods, suicidal thoughts/attempts and aberrant behavior ideation. When such manifestations occur, patients must discontinue using bupropion immediately and contact their doctor.[24] The EMEA and FDA recommend that patients should tell their health care provider about any history of psychiatric illness prior to starting this medication and those clinicians should monitor for changes in mood and behavior when prescribing this medication. For further information, consult the FDA websites for black-box warnings.[25,26]

Before prescribing bupropion, the doctor should check the following aspects that impose certain precautions for use:

- substances that may decrease the convulsive threshold: antipsychotic medication, anti-depressants, tramadolum, methylxantynes, systemic steroids, antihistamine, antibiotics like quinolones, psycho- stimulating or anorexic substances;
- history of alcoholism;
- antecedents of diabetes mellitus or skull and brain traumas.

Increased attention is also recommended in case of simultaneous use of medicines which may interact with bupropion: caution when simultaneously using drugs that induce or inhibit the enzyme 2D6 or the P 450 structures. At the same time, it is recommended to measure blood pressure, as well as blood concentrations of theophylline, tacrine, clozapine, possibly imipramine, fluvoxamine and pentazocyne, as they may increase when used simultaneously with bupropion. Concomitant administration of bupropion also determines the increase of the blood titre of some anti-depressants (imipramine, paroxetine and desipramine), some anti-psychotic medicines (risperidone, thioridazine), metoprolol, anti-arrhythmic medication like propaphenone. Caution is also recommended when using the following medications together with bupropion: cyclophosphamide, carbamazepine, valproate, levodopa and amantadine.[1]

Indications for interrupting bupropion therapy

- occurrence of convulsions;
- serum sickness symptoms: joints or muscle aches, fever;
- anaphylactic reactions or hypersensitivity: rash, skin eruptions, pains/thoracic constriction, dyspnoea, oedemas.

Cost-effectiveness of bupropion treatment

In a systematic review to compare the cost-effectiveness of first-line non-nicotine therapies (varenicline and bupropion SR) for smoking cessation, to identify differences in the models used and their conclusions of cost-effectiveness, varenicline dominated bupropion in most cost-effectiveness models.[27] However, applicability of models to clinical practice and variables which change conclusion of cost-effectiveness should be considered in the interpretation of results.[27]

Recommendation

- Bupropion SR is recommended as an effective smoking cessation pharmacotherapy (level of evidence A).

4.3.3 Treatment with varenicline

Varenicline, the newest smoking cessation pharmacological therapy, has been approved for use in Europe and worldwide since 2006. Varenicline is available by medical prescription.

4.3.3.1 Mechanism of action

The mechanism by which varenicline assists smokers in

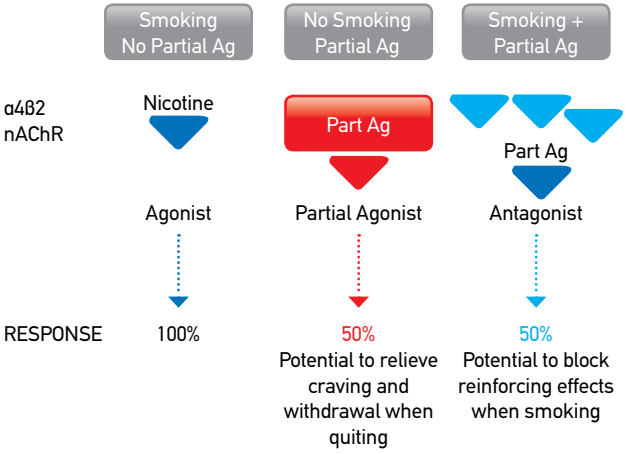
achieving abstinence must be understood within the context of the role that nicotine plays in fostering tobacco dependence. Nicotine acts on neuronal nicotinic acetylcholine receptors (nAchR) within the ventral tegmental area of the brain, causing dopamine release in the nucleus accumbens, which reinforces nicotine-seeking behavior. Activation of these receptors in the ventral tegmental area occurs when sufficient levels of nicotine are carried in the blood.[28]

The predominant neuronal nicotinic nAchR sub-types in the central nervous system are the alpha4beta2 (α4ß2) and alpha7 varieties. Of these, the former is most prevalent in the central nervous system, accounting for approximately 90% of central nervous system neuronal nAchR. This high prevalence and the high nicotine affinity of α4ß2 neuronal nicotinic acetylcholine receptors – believed to have the highest sensitivity to nicotine – suggest that the α4ß2 neuronal nicotinic acetylcholine receptor is a key bio- molecular target for both the perpetuation and treatment of nicotine addiction.[29] The α4ß2 receptor has been identified as a potential target for a smoking cessation drug, especially with a partial agonist action at this receptor sub-type.[30]

Varenicline was developed to have a high affinity for α4ß2 nAChR in the mesolimbic dopamine system31 and to act as a selective partial agonist of the α4ß2 nAChR;[28] also, it possesses a receptor-dependent mode of action, acting as a low-efficacy partial agonist to the α4ß2, α3ß2, α3ß4, and α6/ α3ß2ß3 neuronal nicotinic acetylcholine receptor and a high-efficacy full agonist to the alpha7 nAchR. As a pharmacologic agent for tobacco dependence, varenicline's partial agonism of the α4ß2 is thought to promote smoking abstinence through stimulation of dopaminergic neurons and consequent amelioration of tobacco cravings and nicotine withdrawal. Partial antagonism at the alpha4beta2 neuronal nicotinic acetylcholine receptor inhibits nicotine binding, leading to diminished reward from smoking a cigarette (See Figure 4.8).

Varenicline has been observed to diminish the desire to smoke. Compared with placebos, craving is significantly lower for participants who receive varenicline (versus placebo, P= 0.001).[24] Consistent with the proposed partial antagonist mechanism for varenicline, smoking satisfaction and psychological reward are also significantly decreased in smokers taking varenicline versus placebo.[24]

Figure 4.8: Mechanism of action of Varenicline as a partial agonist of the alpha4 beta2 nicotinic acetylcholine receptor



4.3.3.2 Clinical evidence for efficacy of varenicline

Efficacy in Healthy Adults

A meta-analysis compiled the data from 15 clinical trials including 12,233 participants receivingeither varenicline or placebo. The analysis yielded a risk ratio (RR) for continuous smoking abstinence over weeks 9–24 of 2.27 (95% CI: 2.02–2.55) in favor of varenicline 1.0 mg twice daily.[32]

A network meta-analysis completed by the Cochrane collaboration concluded varenicline was superior to single forms of NRT (OR 1.57; 95% CI 1.29 to 1.91), and to bupropion (OR 1.59; 95% CI 1.29 to 1.96) but was not more effective than combination NRT (OR 1.06; 95% CI 0.75 to 1.48).[4]

The meta-analysis also reported on three studies that compared varenicline with sustained-release bupropion. Varenicline was observed to be superior to bupropion (RR 1.59, 95% CI: 1.29–1.96) for continuous abstinence at week 52.[4]

In a pooled data analysis of phase III trials by Gonzales et al. and Jorenby et al. to explore the relative efficacy of varenicline, bupropion and placebo for smoking cessation, Nides et al. found that pooled continuous abstinence rates for weeks 9 through 12 were significantly greater for varenicline compared with

bupropion and placebo (44.0%, 29.7%, and 17.7%, respectively; both comparisons P = 0.001).[31] In similar analysis to evaluate the effects of varenicline, bupropion and placebo on craving and withdrawal symptoms among smokers, West et al. found that among all participants, cravings were significantly reduced with varenicline or bupropion compared with placebo (both P = 0.001) and with varenicline compared with bupropion (P = 0.008); that varenicline or bupropion significantly inhibited negative withdrawal syndrome compared with placebo and also that varenicline-treated patients had significantly lower pleasurable effects of smoking compared with those treated with bupropion.[33] Taken together, all these clinical data prove that varenicline is superior to placebo, and suggest that varenicline is more effective than mono therapy with NRT and bupropion for achieving abstinence from smoking in the short-term. Varenicline not only significantly attenuates the craving and withdrawal symptoms, but also significantly reduces the rewarding effect of nicotine and delays relapse to smoking.[34]

Efficacy of prolonged treatment

Longer durations of therapy using varenicline have been shown to be more effective than shorter durations on 6-12 months abstinence. In a study evaluating longer duration of therapy, participants achieving smoking abstinence at the end of treatment after 12 weeks, with open-label varenicline, were randomized to either varenicline 1 mg twice daily or placebo for an additional 12 weeks. At the end of the second treatment phase (week 24 of the study), 71% of participants receiving active treatment remained abstinent from smoking compared with 50% of participants receiving placebo (OR 2.48, 95% CI: 1.95–3.16). At 52 weeks follow-up, subjects receiving varenicline had significantly higher smoking abstinence rates compared with those receiving placebo (44% versus 37% continuous abstinence over weeks 13–52, OR 1.34, 95% CI: 1.06–1.69).[35] A secondary analysis of the data from this study suggests that, when used for relapse prevention, the additional 12-week course of varenicline is more effective in smokers who initially had difficulty in achieving smoking abstinence.[36] There is also scientific evidence that varenicline is well tolerated over the long term – over three to six months, up to one year – and that prolonging the treatment duration prevents relapses. The safety and efficacy of long-term treatment (six months) with varenicline has been also demonstrated. In a study on 377 adult smokers, participants were randomized to either varenicline (1 mg twice daily) or placebo for 52 weeks. The drug was well tolerated. The seven-day point prevalence abstinence rate at week 52 was 37% for varenicline-treated subjects v. 8% for the placebo group.[37]

Another study assessed to what degree smokers who fail to quit on the target quit date (TQD) or lapse following TQD, eventually achieve success with continued treatment. This was done by a secondary analysis of pooled data from two identical varenicline versus bupropion and placebo trials. Two successful quitting patterns were identified among smokers who achieved continuous abstinence for the last four weeks of treatment (weeks 9-12): immediate quitters (IQs) who quit on the TQD (day 8) and remained continuously abstinent for weeks 2-12 and delayed quitters (DQs) who achieved initial abstinence sometime after the TQD or may have lapsed following abstinence at week 2 and recovered by week 9 of the trial. Compared to IQs, the DQs were 'delayed' in achieving continuous abstinence to the end of treatment. These data favor recommending continuing cessation treatments without interruption for smokers motivated to remain in the quitting process despite lack of success early in treatment.[38]

Efficacy in patients with COPD

Tashkin et al., found varenicline was also proven as an efficient pharmacological therapy, well tolerated in patients with mild-moderate forms of COPD, with a continuous abstinence ratio in weeks 9-12 of 42.3% v. 8.8% placebo and up to 18.6% v. 5.6% for placebo in follow-up (weeks 9- 52). A good safety profile was found, compared to the previously known studies on varenicline (2.8% severe adverse effects in those who received varenicline compared to 4.4% in the placebo group).[39]

Efficacy in patients with heart disease

In 2010 Rigotti and Pipe et al. published their results on a trial examining efficacy of varenicline versus placebo in 714 smokers with stable cardio-vascular diseases.[40] The authors found a continuous abstinence rate higher with varenicline (47.0% versus 13.9%) in weeks 9-12, as in weeks 9-52 (19.2% v. 7.2%).

Efficacy in HIV patients

In a multi-centre pilot open label study in HIV-infected smokers, varenicline 1.0 mg was used twice daily for 12 weeks with dose titration in the first week. Adverse events (AE) and abstinence rates were comparable to those in published randomized controlled trials conducted in generally healthy HIV- negative smokers. Varenicline was safe and appears effective among HIV-infected smokers in this exploratory study, although AEs (especially nausea) were common. Close monitoring of liver enzymes and blood pressure is recommended for HIV-positive smokers taking varenicline.[41]

Efficacy in patients with psychiatric disorders

Data from the COMPASS cessation trial compared smokers with a psychiatric history to controls.[42] All patients received behavioral counseling plus varenicline with six months post-quit date follow-up. Psychiatric history was based on medical record evidence of anxiety, depression, psychotic or bipolar disorder. Similar rates of abstinence were reported in both groups. Patients with a psychiatric history were more likely to report anxiety and depression. Side effects were rated as moderate intensity or less. Overall, having a psychiatric diagnosis in this trial did not predict a worse treatment outcome or worse treatment side effects.[42]

A large multi-centre randomized controlled trial by Anthenelli et. al. conducted a head to head comparison of 12-weeks of varenicline versus placebo in a sample of stably treated smokers with current or past major depression (n=525).[43] The study assessed smoking abstinence as well as changes in mood and anxiety levels. The study found that varenicline increased smoking cessation among smokers with stably treated current or past depression without increasing depression or anxiety between 9 and 52 weeks (20.3% vs. 10.4%; OR, 2.36 [CI, 1.40 to 3.98]; $P < 0.001$). There was significant loss to follow-up reported in this study, which limits conclusions that can be drawn. This study excluded patients with untreated depression, co-occurring psychiatric illness, and those receiving mood stabilizers and anti-psycholitics.

A meta-analysis of seven studies (n=352) which compared efficacy of varenicline versus placebo among individuals with schizophrenia did not find varenicline to be superior to placebo.44 Varenicline was well tolerated among participants with schizophrenia and no increase in neuropsychiatric events was seen between groups. Due to the small sample size additional studies are required to further examine the use of varenicline in patients with schizophrenia.

The recent EAGLES study included patients with the following disorders mood, anxiety, psychosis and borderline personality disorder. No evidence of increased neurosyciatric events was documented.[45] The authors highlight however that results may not be generalisable to smokers with untreated or unstable psychiatric disorders.

A 2016 update to a meta-analysis conducted by the Cochrane Collaboration involving 14 varenicline trials found no difference between the varenicline and placebo arms in neuropsychiatric events among healthy individuals however evidence is not conclusive in people with past or current psychiatric disorders.[32]

Efficacy among smokeless tobacco users

Efficacy and safety of varenicline in helping users of smokeless tobacco (ST) to quit was assessed in 431 participants (213 varenicline; 218 placebo), as randomized and received at least one dose of the study drug.[46] Continuous abstinence rate at weeks 9-12 was higher in the varenicline group than in the placebo group (59% v. 39%). The advantage of varenicline over placebo persisted through 14 weeks of follow-up (continuous abstinence rate at weeks 9-26 was 45% v. 34%). The authors concluded that varenicline can help people to give up smokeless tobacco and has an acceptable safety profile. The response rate in the placebo group in this study was high, suggesting a population less resistant to treatment than smokers. In a pilot study to obtain preliminary data on the use of varenicline as a tobacco reduction strategy in an open-label study enrolling 20 ST users, Ebbert et al. report that varenicline may be effective in reducing ST use and achieving ST abstinence among ST users with no plans to quit but who are interested in reducing their ST use.[47]

4.3.3.3 Varenicline in combination pharmacotherapy

Heavier smokers might benefit from combination therapy with varenicline and nicotine replacement therapy because varenicline might not fully saturate nicotinic receptors during dose escalation.[24] Incompletely saturated receptors may lead to partial attenuation of

nicotine cravings. If supplemental nicotine replacement therapy can lead to more complete receptor saturation, then urges to smoke could be more completely attenuated.

This possible effect was originally evaluated in an eight-day residential treatment programme at the Mayo Clinic (Rochester, New York, USA). The first study group (n = 135) completed the residential treatment programme prior to the release of varenicline and received "usual care" consisting of nicotine patch therapy and/ or sustained-release bupropion. Short-acting forms of NRT were used ad libitum for treating acute nicotine withdrawal symptoms.[47] The second group (n = 104) completed the residential treatment programme after FDA approval of varenicline and received combination therapy with varenicline and nicotine replacement therapy. Nicotine patch therapy was the predominant form of NRT used, and it was often supplemented with short-acting forms of NRT. Nearly three-quarters of patients used more than one form of NRT. No significant differences were observed in the 30-day point prevalence smoking abstinence rates between the two groups at six months. Importantly, no increase in reported side effects in patients receiving the combination treatment was observed. Major limitations to this study were the small sample size and the uncontrolled study design.[48]

Three new randomized controlled trials have examined the efficacy.[49,50,51] Hajek et. al. found no increase in smoking abstinence among patients randomized to varenicline plus NRT versus those receiving varenicline alone, however this study is limited in its sample size (n=117).[49] In a RCT by Ramon et. al. 341 smokers who smoked 20 or more cigarettes per day were randomized to receive varenicline plus NRT patch or varenicline plus placebo patch for 12 weeks:both groups received behavioral support.[50] Overall there was a small but not statistically significant increased in abstinence in the varenicline + NRT group. Sub-analyses documented a significantly higher abstinence rate among individuals who smoked 29 or more cigarettes using the combination therapy at 24 weeks (OR 1.46; 95% CI 1.2 to 2.8). A second RCT (n=435) also comparing varenicline in alone versus varenicline in combination with NRT did find combination therapy to be associated with higher rates of smoking abstinence at 12 week follow-up (1.85; 95% CI, 1.19-2.89; P = .007) and 24 weeks (49.0% versus 32.6%; OR, 1.98; 95% CI, 1.25-3.14; P = .004).51 Authors also documented a greater incidence of nausea, sleep disturbance, depression, skin reactions, and constipation, however only skin reactions reached statistical significance.

Additional trials are required to further our understanding of the value of combination treatment with varenicline and NRT and the possibility that it should be recommended in specific sub-groups of patients. Combination treatment may be considered for use in patients who have difficulty achieving full cessation with mono-therapy, recognizing the limited evidence available at this time.

Recommendation:

- There are no contraindications to using varenicline in combination with NRT (level of evidence B)
- There may be a benefit to combing NRT and Varenicline, in particular among heavy tobacco users, however results are mixed. Additional research is required to support the efficacy of this approach as a standard practice (level of evidence C)

4.3.3.4 Varenicline and counselling

Data sustain the effectiveness of varenicline when paired with various behavioral treatment programmes as offered in a real-world setting. The extent to which varenicline is effective in association with proactive telephone counseling, delivery of health information and behavioral counseling via web-based platforms, or combination of both, was explored by Swan et al. The authors concluded that telephone counseling had greater treatment advantage for early cessation and appeared to increase medication adherence, but the absence of differences at six months suggests that any of the interventions hold promise when used in conjunction with varenicline.[52]

4.3.3.5 Indications

Varenicline is the first medication developed exclusively to assist with smoking cessation.[24] It is available only by medical prescription and is a first-line medication to treat nicotine dependence.

4.3.3.6 Clinical use

Varenicline is administered orally, regardless of food ingestion (it can be administered before and after meals) in two stages.[1]

The initial phase: boxes with tablets dosed for the first two weeks, prescribed as: 1 tablet 0.5 mg/day, in days 1-3 of treatment, then 1 tablet of 0.5 mg x 2/day in days 4 - 7 and 1 tablet of 1 mg x 2/ day in days 8-14. The continuation phase: boxes of 28 tablets of 1 mg; it is recommended to take 1 tablet of 1 mg x 2/ day, on a daily basis, between weeks 3-12.

The patient starts varenicline, then, during the first weeks of treatment, preferably between days 8 and 14, sets a date when he/she will make a quit attempt. If the smoking cessation attempt does not succeed, the course continues and the patient tries to stop on another day, until he/she is successful.

4.3.3.7 Contraindications

Contraindications of varenicline are few, namely: hypersensitivity to the active substance or its inactive components; age under 18; pregnancy and breast-feeding.

4.3.3.8 Precautions imposed by varenicline therapy

Patients with renal failure

For patients with renal failure, the dose is adjusted as follows: for patients with mild (creatinine clearance >50 and <80 ml/ min.) or moderate (creatinine clearance >30-<50 ml/min.) renal impairment no dose adjustment is necessary. For patients with severe renal impairment (creatinine clearance < 30 ml/min.) – the recommended dose is 0.5 mg twice daily.11 Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 0.5 mg twice daily. Based on insufficient evidence, treatment with Varenicline in not recommended in patients with end stage renal disease.

Vehicle drivers and heavy machinery operators

Due to US FDA reports in 2007, some safety concerns were formulated relating to varenicline use among operators of vehicles and heavy machinery, as well as in any setting in which alertness and motor control are required to avoid serious injury. In May 2008, the US Federal Motor Carrier Safety Administration and Federal Aviation Administration announced that pilots, air-traffic controllers, and truck and bus drivers were barred from taking this drug.[34] So, it is cautious to ask drivers if their current activity is influenced by the use of varenicline. Varenicline can have a minor, medium or significant influence on the capacity to drive vehicles or to use equipment (dizziness and somnolence). Patients must be advised not to drive, handle equipment or get involved in potentially risky activities until it is known for sure if this medicine does affect their capacity to perform such activities safely.

4.3.3.9 Tolerability and safety

Varenicline is generally well tolerated. The most commonly reported adverse effects, when compared to bupropion or placebo, are reported in Table 4.11.[53]

Nausea

Nausea was the most frequently reported symptom as a mild to moderate adverse event (overall incidence 24.4%-52.0%) that occurred at a higher rate in varenicline groups than in placebo groups. Most episodes of nausea began in the first week of treatment and lasted for a median duration of 12 days. Dose titration appeared to reduce the overall incidence of nausea. There was a low incidence of nausea (13.4%) in varenicline treated patients in the self-regulated flexible dosing study. In clinical trials, rates of treatment discontinuation due to nausea were generally 5% in varenicline-treated patients. In case this adverse effect does occur, the following practical information is useful for the patient to know: in general the phenomenon decreases by itself in about one week after the start of therapy; it can be avoided by administering the drug together with food and if the patient rests a little after taking it.

Insomnia

Use of varenicline at the maintenance dose of 1 mg twice a day for longer than 6 weeks is associated with adverse gastrointestinal effects. In realistic terms, for every five treated subjects, there will be an event of nausea, and for every 24 and 35 treated subjects, we

Table 4.11: Comparison of undesirable effects using varenicline, bupropion and placebo

	Varenicline	Bupropion	Placebo
Nausea	28%	9%	9%
Insomnia	14%	21%	13%
Headache	14%	11%	12%

will expect an event of constipation and flatulence respectively.[54]
Insomnia was another commonly reported adverse effect (14.0%-37.2%) associated with varenicline in clinical trials. In general, insomnia occurred during the first four weeks of treatment with varenicline and became less common as treatment continued. In one extended treatment study, the incidence of insomnia was 19.1% with varenicline and 9.5% with placebo, suggesting that insomnia may be a common symptom of nicotine withdrawal during smoking-cessation attempts.[34]

Cardiovascular

A review of randomized studies published between 2008 and 2010 resulted in new safety data concerning the use of varenicline in patients with respiratory and cardiovascular co-morbidities, as well as possible adverse psychiatric events.
A systematic review and meta-analysis by Singh et al. was published in 2011. In this highly publicized paper authors raised certain safety concerns with varenicline use, compared with placebo.[55] This Singh meta-analysis has been widely criticized in the literature based on the inappropriate analysis techniques used and conclusions drawn.
Two subsequent meta-analysis of this same data by Mills et al. concluded varenicline and other quit smoking therapies do not appear to raise the risk of serious cardiovascular disease events.[56] This meta-analysis reported risk as relative risk and used appropriate statistical methods. A second meta-analysis conducted by EMEA with mostly identical data shows no significant risk. The EMEA concluded that the benefit of using varenicline for smoking cessation remains high and does not limit use of the medication.[57]
There is no data to support an increased risk of cardiovascular events among patients using varenicline, however at this time we are unable to rule out this possibility. It is recommended that clinicians inform patients of the small potential increase in cardiovascular risk, which may be associated with varenicline use. However these risks should be weighed against the known cessation benefits of the drug.

Neuropsychiatric events

Substantial concerns regarding the neuropsychiatric safety of varenicline and buproprion have been raised and this has caused confusion within the medical community regarding the use of these medications for patients interested in quitting. Several recent well-designed trials have found no evidence to suggest an increase in neuropsychiatric events attributable to these medications. This has resulted in an update by the US FDA to the product label for varenicline noting the risk of severe neuropsychiatric events is lower then previously suspected and the benefits of using these medications outweighs the risk. We review here the history and evidence related to this issue here.
Following the availability of varenicline in global markets in 2006, several post market reports of adverse events had been reported from the use of varenicline and bupropion. This included clinical reports in the UK which followed a cohort of from 2682 patients since December 2006 and reported psychiatric effects during treatment with varenicline, including sleep disorders (1.6%), anxiety (1.2%), depression (1.0%), abnormal dreams (1.0%), mood change (0.6%), and suicidal events (n = 5).[34,58]
Based on these reports, in November 2007 the FDA issued an early alert about the safety
of varenicline, emphasizing the need to screen pre-existing psychiatric illness before using varenicline and the importance of monitoring mood or behavior changes. In May 2008, the FDA updated the warning by requiring that all patients be carefully observed and report to their physicians immediately in case of any mood or behavior changes, or worsening of pre-existing psychiatric illness, during or upon discontinuation of varenicline therapy. The FDA again updated the label for varenicline again in March 2015 to also include potential side effects on mood behavior or thinking.[59]
Since the initial report, several studies have examined the potential link between use of varenicline and neuro-psychiatric events. A publication in 2010 reviewed the incidence and relative risk of psychological disorders recorded in ten randomized, placebo-controlled studies about varenicline for smoking cessation.[58,60] Other psychological disorders than simple sleep disturbances were found in 10.7% of the subjects treated with varenicline versus 9.7% in those who received placebo, with a relative risk of 1.02. The relative risk versus placebo of adverse psychiatric events at an incidence ≥ 1 in the varenicline group

was: 0.86 for anxiety symptoms, 0.76 for physical activity changes, and 1.42 for changed mood, 1.21 for uncategorized mood disturbances and 1.70 for sleep disturbances. There were no reports of cases of suicidal behavior or pathological ideation in subjects under varenicline therapy in these ten randomized trials, but three other trials not included in this review, because of their different design, reported two cases of suicidal thoughts and one single case of suicide.

A large 2013 study by Meyer examined neuropsychiatric hospitalizations among new users of varenicline (n = 19,933) versus new users of NRT patch (n = 15,867). The study population included those with and without a history of neuropsychiatric disease. The study found no increase in the rate of neuropsychiatric hospitalizations in patients treated with varenicline compared to NRT patch at 30 and 60 days.[59,61]

Thomas et al. compared the risk of depression, self-harm, and suicide in a prospective cohort study of 119,546 patients in England.[62] The authors concluded that there is no evidence that varenicline users had greater risk of depression, suicide or self-harm compared to those prescribed nicotine.

Most recently, the EAGLES study, a large randomized double blind, placebo trial multi-centre study involving 140 centres in 16 countries examined compared the neuropsychiatric safety of bupropion, varenicline and NRT in individuals with and without a history of psychiatric illness.[45] This study had been initiated based on requirement from the US FDA to Pfizer and GlaxoSmithKline, the manufacturers of varenicline and bupropion. The study involved 8144 patients of which 4166 were included in the psychiatric cohort. For the psychiatric cohort individuals with any of four major disease categories (mood, anxiety, psychosis and borderline personality disorder) were included. Participants were randomized to receive varenicline, bupropion, NRT or placebo for 12-weeks and were followed for a total of 24 weeks. The study did not find any significant increase in neuropsychiatric events attributable to varenicline or bupropion. The study also found higher abstinence rates among participants assigned to the varenicline treatment group compared to placebo, NRT and bupropion. Likewise NRT and buproprion and NRT achieved higher abstinence rates than placebo. The authors report results may not be generalisable to smokers with untreated or unstable psychiatric disorders. The study also did not include smokers with current substance use disorders or imminent risk of suicide.

A 2016 update to a meta-analysis conducted by the Cochrane Collaboration involving 14 varenicline trials found no difference between the varenicline and placebo arms in neuropsychiatric events.[32] The RR for depression was 0.94 (95% CI 0.77 to 1.14; 36 studies; 16,189 participants, $I^2 = 0\%$), with non-significantly lower rates in the varenicline group. The RR for suicidal ideation was 0.68 (95% CI 0.43 to 1.07; 24 studies; 11,193 participants, $I^2 = 0$), with borderline non-significant lower rates in the varenicline group. Authors highlight, all five events in the varenicline group for suicidal ideation occurred in the psychiatric cohort, with none reported in the non-psychiatric group.[46,32] Authors conclude meta-analyses data "do not support a causal link between varenicline and neuropsychiatric disorders, including suicidal ideation and suicidal behavior however evidence is not conclusive in people with past or current psychiatric disorders."[32]

In December 2016, following the release of new evidence from well-designed trials both the FDA and the European Medicines Agency announced it was removing its Boxed Warning for serious mental health side effects from the varenicline and bupropion drug label.[46,63] Specifically the FDA stated: "based on a U.S. Food and Drug Administration (FDA) review of a large clinical trial that we required the drug companies to conduct, we have determined the risk of serious side effects on mood, behavior, or thinking with the stop-smoking medicines varenicline and bupropion is lower than previously suspected. The risk of these mental health side effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past. However, most people who had these side effects did not have serious consequences such as hospitalization. The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines."[46]

Thus far there is no compelling evidence that varenicline is associated with an increased risk of neuropsychiatric events. Health care professionals are advised to discuss the benefits and risk of using quit smoking medications with patients. Patients should be advised to call their health care professionals right away if they notice any side effects on mood, behaviour or thinking.[46]

Other adverse events

Other adverse effects were also reported, such as: abdominal pain, constipation, bloating and abnormal dreams, sleep disturbance, dizziness, dry mouth, increased appetite, weight gain, and headache which generally occurred at rates twice those with placebo.[64] These adverse events were mild to moderate and transient, occurring predominantly during the first four weeks of therapy. Discontinuation of varenicline due to these adverse effects occurred in 2% of participants.[34]

Drug interactions of varenicline with other medicines are not known. In turn, some effects of the interactions are evident due to stopping tobacco consumption, as the therapeutic effect of varenicline begins to act. Thereby, it is well known that smoking cessation, through enzymatic inductions implying a structure of type CYP1A2, imposes adjusting the doses of theophylline, warfarin, insulin etc.[11]

At the end of treatment, stopping varenicline can cause increased irritability, appetite for smoking, insomnia or depressive mood, in a low percentage of subjects – about 3%.[11]

Recommendation

- Varenicline is an evidenced-based first line therapy for smoking cessation (level of evidence A)

4.3.4 Treatment with clonidine

Clonidine is used primarily as an anti-hypertensive medication, but it reduces central sympathetic activity by stimulating the alpha2-adrenergic receptors. Clonidine effectively suppresses the acute symptoms of nicotine withdrawal, such as tension, irritability, anxiety, cravings, and restlessness.[65]

Clonidine is not approved for smoking cessation and represents only a second-line medication. Therefore, clinicians need to be aware of the specific warnings regarding this medication as well as its side effect profile. The US Guideline Panel chose to recommend clonidine as a second-line as opposed to first-line agent, because of the warnings associated with clonidine discontinuation, variability in dosages used to test this medication, and lack of FDA approval. So clonidine should be considered for treating tobacco use under a physician's supervision in patients unable to use first-line medications because of contra-indications or in patients who were unable to quit when using first-line medications.[1]

Efficacy

A Cochrane review of six clinical trials found clonidine, oral or transdermal, more effective than placebo, however this finding is based on a small number of trials in which there are potential sources of bias.[66] Clonidine seems to be more effective in female smokers, although women generally respond less favorably to smoking cessation treatments.[65]

Side Effects

The side effects of clonidine, especially sedation, fatigue, orthostatic hypotension, dizziness, and dry mouth, limit its widespread use. Also, it should be noted that abrupt discontinuation of clonidine can result in symptoms such as nervousness, agitation, headache and tremor, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine levels.[1]

Precautions, warnings, contra-indications, adverse effects

Clonidine has not been shown to be effective for tobacco cessation in pregnant smokers.

Clonidine has not been evaluated in breast-feeding patients.

Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be warned of a possible sedative effect of clonidine.

Most commonly reported side effects are: dry mouth (40%), drowsiness (33%), dizziness (16%), sedation (10%) and constipation (10%).

As an anti-hypertensive medication, clonidine can be expected to lower blood pressure in most patients. Therefore, clinicians should monitor blood pressure when using this medication.

Rebound hypertension: when discontinuing clonidine therapy, failure to reduce the dose gradually over a period of 2-4 days may result in a rapid increase in blood pressure, agitation, confusion, tremor.

Suggestions for clinical use

Clonidine is available in either 1 mg oral or transdermal (TD) form, on prescription only. Treatment with clonidine must be

initiated shortly before (i.e. up to 3 days) or on the quit date.
Dosage: If the patient is using transdermal clonidine, at the start of each week, he/she should place a new patch on a relatively hairless location between the neck and waist. Users should not discontinue clonidine therapy abruptly. Initial dosage is typically 0.10 mg bid. orally or 0.10 mg/day TD, increasing by 0.10 mg/day per week, if needed. Treatment duration ranges from 3 to 10 weeks.[1]

Recommendation

- Clonidine is an effective smoking cessation treatment, however prominent side effects do exist. It may be used under a physician's supervision as a second-line agent to treat tobacco dependence (level of evidence B)

4.3.5 Treatment with nortriptyline

The relationship between depressed mood and smoking behavior suggests that anti-depressant drugs may have a role in smoking cessation. Several anti-depressants, including doxepin, nortriptyline and moclobemide, have shown some effectiveness in smoking cessation. Nortriptyline is a tricyclic anti-depressant that has been shown to be as effective as bupropion and NRT in smoking cessation. The action of nortriptyline in stopping smoking is independent of its anti-depressant effect, therefore its use is not restricted to people with a history of depressive symptoms during smoking cessation.[68]

Efficacy

Meta-analysis of 6 trials using nortriptyline as the only pharmacotherapy showed a significant long-term benefit.[12] Compared to placebo, nortriptyline approximately doubles rates of smoking abstinence. This drug is not approved for smoking cessation and is recommended only as a second-line treatment.[12] Whether nortriptyline is more or less effective than bupropion, or whether using nortripytline plus NRT increases quit rates, remains unclear. This pharmacotherapy is not licensed for smoking cessation in most countries.

Adverse events

Adverse effects associated with nortriptyline, such as anticholinergic effects (dry mouth, blurred vision, constipation and urinary retention), H1-histamine receptors (sedation, drowsiness, weight gain), and alpha1-adrenergic receptors (orthostatic hypotension) may not be well tolerated in some patients.[67] Data extracted from 17 studies suggest that nortriptyline, at doses between 75 mg and 100 mg, is not significantly associated with serious adverse events when administered in patients without underlying cardiovascular disease.[70] Patients will need to be monitored closely for known adverse effects such as constipation, sedation, urinary retention and cardiac problems. When taken as an overdose, nortriptyline could be fatal. Serious adverse effects have not been a cause for concern in trials for smoking cessation, but the number of such patients exposed has been relatively small. This leads to a lack of consensus over the use of nortriptyline as a first-line or second-line therapy.[71]

Dosage

Nortriptyline should be started while the patient is still smoking, with a quit date set for 10 to 28 days later. The initial dose is 25 mg/day, increased gradually to 75-100 mg/day over 10 days to 5 weeks. The maximum dose can be continued for 8-12 weeks and tapered down at the end, to avoid withdrawal symptoms that may occur if it is stopped abruptly. There is limited evidence of any benefit of extending treatment more than three months.

Practical points for using nortriptyline:

There is insufficient evidence to recommend combining nortriptyline with any other smoking cessation medication.
People with cardiovascular disease should use nortriptyline with caution, as cardiac conductivity can/ may be affected. Tricyclic anti-depressants are contra-indicated in the immediate recovery period after myocardial infarction and in arrhythmia.
There is insufficient evidence to recommend the use of nortriptyline by pregnant women or young people under 18 who are smokers.
There is insufficient evidence to recommend using nortriptyline to prevent smoking relapse; long-term use is not recommended.
In a real life study to compare effectiveness of NRT, bupropion, nortriptyline and combination therapy and to describe factors associated with treatment success, Prado et al. sustain their point of view, in agreement with the findings from the meta-analysis of

Wagena et al.,[72] that nortriptyline is a significant treatment option, given its efficacy (comparable to those first-line options), safety and, especially, its low cost and wide availability. In their opinion, perhaps, considering the threat of a global tobacco epidemic – and even more significant impacts on the less affluent nations – the inclusion of nortriptyline in the therapeutic arsenal of smoking cessation may be a promising step towards a wider access to treatment, especially in developing countries. Based on these findings, authors propose the inclusion of nortriptyline among the list of first-line drugs for smoking cessation. However, the major limitation of this report is that it was a retrospective, uncontrolled and not randomized study and available options of treatment regimens were chosen by individual criteria on a case-by-case basis or according to the availability of medication in the public health system.[72]

Clinicians need to be aware of the side effect profile and the lack of EMEA and FDA approval for nortriptyline as a tobacco dependence treatment. This medication should be considered for treating tobacco use only under a physician's supervision and in those patients unable to use first-line medications because of contra-indications or just in patients who have been unable to quit using first- line medications.

Recommendation

- Nortriptyline is an effective smoking cessation treatment and may be used under a physician's supervision as a second-line agent to treat tobacco dependence (level of evidence A)

4.3.6 Cytisine

Cytisine is a natural alkaloid extracted from the seeds of plants such as cytisus laburnum and sophora tetraptera. Cytisine acts as similarly to varenicline, being a partial agonist of alpha4beta2 nicotinic acetylcholine receptors, responsible for reinforcing the effects of nicotine, also preventing nicotine from binding to these receptors, thus reducing the satisfaction and reward related to tobacco use, relevant negative withdrawal symptoms and cravings.[32,73,74]

Tabex® is available in oral tablet form containing 1.5 mg cytisine and has been produced and marketed by the Bulgarian company Sopharma Pharmaceuticals since September 1964.75 Tabex® was used for tobacco cessation for many decades on a national scale in the former Socialist countries, Bulgaria, Hungary, Poland, German Democratic Republic, Soviet Union being the first ever medication in human history officially approved for this purpose. However, licensing and use of cytisine in other parts of the world did not develop for decades, in part due to the lack of evidence-based, more recently GCP compliant, trials.[73,76,77]

The global search for tobacco cessation products with high availability, acceptability, efficacy and safety, combined with low cost, relevant for large scale cessation interventions within state supported programmes has recently boosted interest in cytisine. Trials consider cytisine as an alternative to nicotine-based products and anti-depressants, especially in low- and middle-income groups and in cultures where natural medicines are widely used.[77] A 25-day course of cytisine is five to fifteen times cheaper than a 25-day NRT treatment.[76]

A double-blind, randomized, placebo-controlled trial of cytisine for smoking cessation in medium- dependent workers (n=171) in Kyrgyzstan was published in 2008. At 26 weeks 10.6% of patients were abstinent in the group taking cytisine compared to 1.2% in the placebo group.[73]

In the post-Soviet Russian Federation Tabex® was officially registered for tobacco cessation in 1999 and is purchased over the counter. The first randomized controlled double blind trial on therapeutic effectiveness and safety was published in 2009 (n=196). The percentage of individuals who did not have any effect when trying to quit smoking among those who had taken Tabex® compared to the placebo group was 13% and 26% respectively. The percentage of smokers who abstained from smoking for one or more periods was 50% and 30.8% respectively. The percentage of smokers who had been abstinent for 12 weeks or longer was 50% and 37.5% respectively. No adverse effects were registered in 70% and 84% of patients in the two groups.[78]

A meta-analysis by the Cochrane collaboration identified only two trials which have tested the efficacy of cytisine as a smoking cessation therapy.[32] The pooled RR of cessation compared to control was 3.98 (95% confidence interval (CI) 2.01 to 7.87). Given these results there have been multiple calls for the increase use of this therapy.

A randomized controlled trial by Walker et al. (2014) compared cytisine to NRT. The study found a significantly higher 1-month

continuous abstinence rate in the cytisine group (Adjusted Odds Ratio 1.5; 95% CI, 1.2 to 1.9; P=0.003).[79] This differences remained significant at 6-months. No differences in 7-day point prevalence abstinence were documented at 6-months between groups. Subgroup analysis found a significantly higher 1-month abstinence rate among female participants and no significant difference (non-inferiority) among male trial participants. Adverse events including nausea, vomiting, and sleep disorders were more commonly reported in the cytisine group compared to NRT group.

The dosage regimen recommended by the manufacturer starts at 1 tablet (1.5 mg) every 2 hours (up to 6 tablets a day) over days 1 to 3. Smoking must be reduced, otherwise symptoms of nicotine overdose will develop. If there is no desired effect, the treatment is discontinued and a next attempt can be made in two to three months. With a positive response, the patient continues with a dosage of up to 5 tablets a day (1 tablet every 25 hours) from days 4 to 12. Smoking must be discontinued on the 5th day. After this up to 4 tablets a day (1 tablet every 3 hours) from days 13 to 16, then up to 3 tablets per day (1 tablet every 5 hours) from days 17 to 20, followed by 1 to 2 tablets per day (1 tablet every 6 to 8 hours) from days 21 to 25, then stop treatment.

Observing the recommended dose of cytisine a few adverse effects, similar to the intake of NRT, were registered in trials.[76,78,80] According to Periodic Safety Update authorities in Europe there are no safety signals for serious adverse reactions to cytisine based on millions of patients exposed to this product.[80]

Cytisine overdose is similar to nicotine intoxication, producing effects such as nausea, vomiting, clonic convulsions, tachycardia, pupil dilation, headache, general weakness, respiratory paralysis.[81]

Recommendation:

- Cytisine appears to increase quit rates however evidence is limited to three trials (Level of evidence B)
- There is a need for further research to examine the efficacy of this promising cessation intervention.

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4.4 Individualized therapeutic schemes

In clinical practice, we base our decision-making for medication selection and dosage on the published literature as well as on our clinical experience. It is now recognized that there are limitations to standard-dose or fixed-dose regimens with most drugs used in clinical smoking cessation. As a result, clinicians should use their skills and knowledge to individualize drug dosing for patients being treated for tobacco use and dependence.

Opportunities exist to increase smoking abstinence rates and to reduce withdrawal symptoms by using combinations of pharmacotherapy that have proved effective as mono therapies.

Certain combinations of first-line medications are more effective than mono therapy, such as: long-term (i.e. greater than 14 weeks) nicotine patch combined with nicotine gum or nicotine nasal spray, nicotine patch plus nicotine vapor inhaler, and nicotine patch plus bupropion SR.[1,2] Whether the superiority of combination therapy is because of the use of two types of delivery systems or is due to the fact that two delivery systems tend to produce higher blood nicotine levels remains unclear. Combination pharmacotherapy or higher-dose NRT appears to relieve nicotine withdrawal symptoms more effectively, especially in more dependent smokers.[1]

In real life, specialists often combine medications. For patients with more severe tobacco dependence, combination therapy and often use of three or more products simultaneously are suitable. For patients with a partial response to the initial medication, further tailoring of the medication regimen may be necessary to reach abstinence. For example, if a patient has reduced smoking using varenicline at a dose of 1 mg twice daily and has tolerated the medication, the dose may be increased to 1 mg taken three times daily. Another situation requiring creativity is a smoker who has stopped smoking using nicotine patch therapy and a short-acting NRT, but notices increased withdrawal symptoms in the early evening. Adding a 14 mg patch in the late afternoon may decrease evening withdrawal.[2,3]

In order to better address withdrawal symptoms poorly controlled during the initiation phase of the treatment with varenicline, Hurt et al. used nicotine patch therapy in a residential treatment programme for smokers treated with varenicline, because patients had to stop smoking at programme inclusion and as varenicline requires several days to reach steady-state concentrations.[5]

4.4.1 Combination of pharmacological therapies

4.4.1.1 General principles of combination pharmacotherapy

Two major types of combination pharmacotherapy have been evaluated for increasing smoking abstinence rates among cigarette smokers: (1) therapy using different NRTs and different pharmacokinetic profiles (e.g. nicotine patch and nicotine gum); or (2) therapy using two drugs that have different mechanisms of action, such as bupropion SR and NRT.

Combination therapy using two different drugs provides the opportunity to gain therapeutic synergism by using medications with distinct mechanisms of action or different therapeutic properties. For example, the combination of varenicline and bupropion SR combines the efficacy of varenicline with the ability of bupropion SR to reduce post-cessation weight gain. Also, combining different forms of NRT provides a stable baseline nicotine level from the sustained release NRT (i.e. nicotine patch) with the opportunity for intermittent increases in the nicotine level from immediate release NRT (nicotine gum, lozenge, inhaler or nasal spray) in response to withdrawal symptoms.

Combination pharmacotherapy remains controversial and underutilized. Only the combination of NRTs (i.e. more than one NRT) and the combination of bupropion SR and nicotine patch has been approved by the FDA for smoking cessation.

4.4.1.2 Combination of nicotine replacement therapy (NRT)

The two types of combination NRTs that have been described are sequential and concurrent. Sequential therapy can theoretically provide initial stable nicotine dosing to achieve abstinence (i.e. nicotine patch) and then intermittent ad-lib dosing to prevent relapse. However, little data exists to support sequential therapy. Relatively more data exists regarding the simultaneous use of multiple NRTs (i.e. concurrent therapy). This formula allows for the delivery of nicotine passively, with long-acting NRT (i.e. nicotine patch) and for the active ad lib administration of short-acting NRT (i.e. gum, lozenge, inhaler and nasal spray). Combination provides the advantages of higher treatment adherence with the nicotine patch and empowers smokers to deal with acute cravings and withdrawal symptoms through self-administration of short-acting NRT.[6]

NRT + paroxetine

In a double-blind trial Killen et al. examined the efficacy of a smoking cessation treatment that combined nicotine replacement therapy via a transdermal system with the anti-depressant paroxetine. Smokers were randomly assigned to one of the three groups: transdermal system and placebo, transdermal system and 20 mg of paroxetine, and transdermal system and 40 mg of paroxetine. Transdermal treatment was provided for eight weeks; paroxetine or placebo was provided for nine weeks. Abstinence rates for all participants at follow-up were not significantly different, but a sub-group analysis of adherent patients resulted in statistically significant differences between the paroxetine groups and the control group at week 4.[7]

Nicotine patch + gum

The patch is administered daily and it can also be used in combination with nicotine gum. Oral NRTs are short acting and can be used to provide relief from cravings as required. Short acting oral NRTs can be administered daily or intermittently.

Studies evaluating the combination of nicotine patch and nicotine gum have demonstrated that the combination is superior to mono therapy for increasing smoking abstinence rates at 12 and 24 weeks.[8,9] Outcomes of the combination therapy showed a tobacco abstinence ratio of 34% compared to only 24% in the case of 12-week mono therapy using nicotine patch, respectively 28% in the combination group compared to 15% in the 24-week nicotine patch mono therapy group.[10] Treatments that combine nicotine gum and patch and last more than three to six months should be considered for patients with a severe and/or prolonged nicotine withdrawal syndrome, for whom no other therapeutic solutions exist.[11]

Nicotine patch + nicotine spray

Combination therapy using the nicotine patch and nasal spray investigated in an open-label trial of 1384 smokers randomized to nicotine patch therapy and nasal spray or either therapy alone, was associated with significantly higher smoking abstinence rates at 6 weeks compared with either monotherapy.[12] In a placebo-controlled trial, the nicotine patch and nicotine nasal spray were superior to nicotine patch and placebo nasal spray at both short (6 weeks and 3 months) and long-term (12 months) follow-up.[13]

Nicotine patch + nicotine inhaler

Significantly higher smoking abstinence rates were observed with the nicotine patch and inhaler at 6 and 12 weeks compared to the inhaler alone, in a placebo-controlled randomized trial on 400 subjects. Patients were assigned as group 1 (n=200) receiving inhaler plus patch (delivering 15 mg of nicotine per 16 hours) for 6 weeks, then inhaler plus placebo patch for 6 weeks, then inhaler alone for 14 weeks and group 2 (n=200) receiving nicotine inhaler plus placebo patch for 12 weeks, then inhaler for 14 weeks.[14]

In general, combination NRT is well tolerated and side effects are consistent with the anticipated side effects of each agent alone.[2,3]

Nicotine patch + bupropion

Bupropion in combination with nicotine patch is more efficient than

patch only, because they have different mechanisms of acting.[7] Start with bupropion in standard doses in the first two weeks and add the nicotine patch as of the date set for quit day. Bupropion will be administered in total for 7 to 12 weeks. Optimal duration for nicotine patch treatment in combined formula is 3 to 6 months.[11]

In a four-group, double-blind, placebo-controlled study, the abstinence rate at 12 months was 35.5% for the combination therapy (nicotine patch and bupropion), compared to 30.3% for bupropion alone, 16.4% for nicotine patch alone and 15.6% for placebo.[11] Jorenby et al. randomly assigned participants to one of three groups: bupropion only, nicotine patch only, or both bupropion and nicotine patch. Participants in the control group received placebo pills and a placebo patch. The biochemically confirmed abstinence rates at 12 months were 15.6% in the placebo group, 16.4% in the nicotine patch group, 30.3% in the bupropion-only group (P<0.001), and 35.5% in the group given both (P < 0.001). Abstinence rates were higher with combination therapy than with bupropion alone, but the difference was not statistically significant.[15]

In general, literature suggests that combination therapy with bupropion SR and NRT increases short- term abstinence rates. The USPSH Guideline meta-analysis suggests that a non-significant trend exists for bupropion SR and nicotine patch to increase long-term abstinence rates (≥ 6 months) compared with nicotine patch alone [odds ratio (OR) 1.3; 95% CI: 1.0-1.8].[1] The same conclusion was made by a recent review by the Cochrane collaboration.[16]

A placebo-controlled study evaluated the association of bupropion SR (300 mg) to nicotine patch (21 mg), nicotine gum (2 mg), and cognitive behavioral therapy in 51 patients. Adding bupropion SR increased the primary outcome of smoking reduction (≥ 50%) at weeks 12 and 24 and continuous smoking abstinence at week 8.[17]

In a study involving 1700 smokers, combination therapy with bupropion SR and nicotine inhaler was observed to be superior to either agent alone.[18]

In a large effectiveness trial in primary care, bupropion SR and lozenge was observed to be superior to all mono therapies (i.e. lozenge, patch, bupropion SR).[19]

Nortriptyline + NRT

A meta-analysis of studies evaluating nortriptyline and NRT compared to NRT suggests that there is insufficient evidence of increased smoking abstinence with combination therapy (RR 1.21; 95% CI: 0.94-1.55).[16]

Varenicline + NRT

Also see section 4.3.3.3. Based on data from a pharmacokinetic study,[20] Ebbert et al.[21] put forward the hypothesis that: (1) varenicline does not completely saturate nicotinic acetylcholine receptors leading to an incomplete "reward" response and an incomplete blockade of continuing smoking reinforcement; (2) varenicline incompletely replaces the dopaminergic effect of smoking, leading to a continued craving to smoke. The authors therefore considered that some smokers may need NRT in addition to varenicline to reduce withdrawal and urges to smoke and to allow smokers to achieve complete abstinence. As they have extensive experience with combination therapy using varenicline and NRT in an eight- day residential (in-patient) treatment programme, at the Nicotine Dependence Center (NDC) in the Mayo Clinic, authors advise using NRT to provide withdrawal symptom relief, as smokers are being titrated up on varenicline. No increase in adverse effects was observed compared to smokers who were treated in the same programme, prior to the release of varenicline. However, these researchers suggest results from this study may not apply to other patient populations and should be interpreted with caution.

A clinical trial examined why smokers receiving combination medication for smoking cessation are more likely to quit smoking than are those who receive either single agent (mono therapy) or placebo. Data collected from 1504 current smokers randomized to one of six cessation pharmacotherapy conditions (placebo, nicotine patch, nicotine lozenge, bupropion nicotine patch and nicotine lozenge, and bupropion and nicotine lozenge) suggested that the combination treatments produced higher abstinence rates than the mono therapies because of greater suppression of withdrawal, craving and smoking expectations.[22]

Loh, Piper et al. answered the question whether combination pharmacotherapy should be used routinely with smokers or if some types of smokers show little or no benefit from combination pharmacotherapy versus mono therapy. They concluded: combination pharmacotherapy was generally more effective

than mono therapy, except in one group of smokers (those with low nicotine dependence) who did not show greater benefit from using combination pharmacotherapy. Use of mono therapy with these smokers might be justified considering the expense and the side effects of combined pharmacotherapy.[23]

Three new randomized controlled trials have examined the efficacy.[24-26] Hajek et. al. found no increase in smoking abstinence among patients randomized to varenicline plus NRT versus those receiving varenicline alone, however this study is limited in its sample size (n=117).[24] An RCT by Ramon et. al. 341 smokers who smoker 20 or more cigarettes per day were randomized to receive varenicline plus NRT patch or varenicline plus placebo patch for 12 weeks, both groups received behavioural support.[25] Overall there was a small but not statistically significant increased in abstinence in the varenicline + NRT group. Sub-analyses documented a significantly higher abstinence rate among individuals who smoked 29 or more cigarettes using the combination therapy at 24 weeks (OR 1.46; 95% CI 1.2 to 2.8). A second RCT (n=435) also comparing varenicline in alone versus varenicline in combination with NRT did find combination therapy to be associated with higher rates of smoking abstinence at 12 week follow-up (1.85; 95% CI, 1.19-2.89; P=.007) and 24 weeks (49.0% versus 32.6%; OR, 1.98; 95% CI, 1.25-3.14; P=.004).[26] Authors also documented a greater incidence of nausea, sleep disturbance, depression, skin reactions, and constipation, however only skin reactions reached statistical significance.

Additional trials are required to further our understanding of the value of combination treatment with varenicline and NRT and the possibility that it should be recommended in specific sub-groups of patients. Combination treatment may be considered for use in patients who have difficulty achieving full cessation with monotherapy, recognizing the limited evidence available at this time.

Varenicline + bupropion SR

Because varenicline and bupropion have different mechanisms of action, they are sometimes used in combination, particularly in smokers who have previously stopped smoking using bupropion mono therapy, but struggled during the process. A pilot study of this combination demonstrated excellent efficacy and high tolerance, suggesting that a combination of varenicline and bupropion SR may be effective for increasing smoking abstinence rates above rates observed using monotherapy.[3]

Recommendations

- Five combinations of first-line medications have been shown to be effective as smoking cessation treatments however there is insufficient evidence at present for making recommendations for all five combinations. At present only combination use of NRTs and the combination of the patch and bupropion has been approved by FDA for smoking cessation.[23] Clinicians may therefore consider using these combinations of medications with their patients who are willing to quit.
- Effective combination medications are:
  - long-term (> 14 weeks) nicotine patch and other NRT (gum, spray) (level of evidence A);
  - nicotine patch and nicotine inhaler (level of evidence B).;
  - nicotine patch and bupropion SR (level of evidence A).
- There are no contraindications to using varenicline in combination with NRT (level of evidence B).
- There may be a benefit to combing NRT and varenicline, in particular among heavy tobacco users, however results are mixed. Additional research is required to support the efficacy of this approach as a standard practice (level of evidence C).

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4.4.2 Recommendations for prolonging treatment duration

In some patients, a longer treatment duration than that usually recommended has proven beneficial.

Prolonged nicotine substitution treatment

Fears concerning the potential addiction caused by prolonged treatment with nicotine substitutes are not justified. On the contrary, prolonging the duration of such therapy may prove opportune for health, as premature relapses are often described in any smoking cessation attempt.

Studies have shown higher abstinence rates when using nicotine gum for long-term compared to short-term cure and 15% to 20% abstinence among those who used nicotine gum for

≥ 12 months.[1] Lung Health Study found that about one-third of the long-term COPD abstinent have used nicotine gum up to 12 months (and some even up to five years), without serious adverse effects reports.[2]

In an unstratified small block-randomization scheme, 568 participants were randomly assigned to 21 mg nicotine patch for 8 weeks and to placebo for 16 weeks or to extended therapy (21 mg nicotine patch for 24 weeks). Nicotine patch for 24 weeks increased biochemically confirmed point-prevalence abstinence and continuous abstinence at week 24, reduced the relapse risk and raised the likelihood of recovery to abstinence after a lapse, compared with 8 weeks of NRT patch.[3]

Nicotine gum and nicotine patch can be administered for more than six months, with good results, especially on those patients who report prolonged withdrawal syndrome.

The FDA has approved nicotine replacement therapy administered for more than six months, since it has no risks.[1] Using nicotine gum ensures better weight control after stopping smoking. There is a correlation between the dose of pharmaceutical nicotine administered and weight gain (the bigger the dose of nicotine in substitutes, the lower the weight gain).[1]

Few persons can really become addicted to nicotine substitution products. But, indeed, some former smokers may continue to use them for up to one year or even longer, because they are afraid of failing and returning to smoking.[1] A total of 402 participants completed a 12-week treatment programme that included group counselling, NRT and bupropion. Participants, independent of smoking status, were then assigned randomly to: (1) standard treatment (ST; no further treatment); (2) extended NRT (E-NRT; 40 weeks of nicotine gum availability); (3) extended cognitive behavioral therapy (E-CBT; 11 cognitive behavioral sessions over a 40-week period); or (4) E-CBT plus E-NRT (E-combined; 11 cognitive behavioral sessions plus 40 weeks of nicotine gum availability). The authors agreed on the benefits of extended treatments that can produce high and stable abstinence rates.[4]

Prolonged treatment with varenicline

A longer than 12-week period of treatment with varenicline is safe, well tolerated and ensures a higher long-term abstinence rate, considerably reducing relapsing risk.

Varenicline can be administered as an efficient medication to treat nicotine dependence, for 24 weeks, with good tolerance, especially on those patients whose appetite for smoking returns after the first 12 weeks of treatment. Varenicline is the first drug that has proven to have a significant long-term effect against relapsing. According to Tonstad et al., 70.6% of the varenicline group quit smoking in weeks 13-24, compared to 49.8% in the placebo group; respectively 44% v. 37.1% subjects were abstinent in weeks 25-52.[5]

Prolonged treatment with bupropion

The duration of treatment with bupropion can be prolonged over the 7-9 week standard cure, with a good efficiency on both abstinence rates at the end of treatment and in follow-up, but also on relapse prevention. In a randomized, placebo-controlled study, in which 300 mg bupropion was administered for seven weeks in 784 healthy smokers, followed by a 45-week additional cure of bupropion v. placebo, a good abstinence ratio was found after 52 weeks in the bupropion group (55.1%) v. 42.3% in the placebo group. This proportion remained the same during follow-up, at 78 weeks (47.7% in the bupropion group v. 37.7% in the placebo group, p=0.034), but it became insignificant at the 104-week end of study visit (41.6% for bupropion group v. 40.0% for placebo group). Relapses occurred on average at 156 days for the bupropion group versus 65 days for the placebo group (p=0.021), a fact that is undeniably in favor of longer bupropion treatment courses.[6]

Cox et al. randomized abstinent smokers treated with bupropion for seven weeks to either continued bupropion for one year or to placebo.[7] Bupropion produced a higher abstinence rate at the end of treatment when compared to placebo, but no differences at one-year follow-up. Killen et al. treated smokers for 12 weeks with an open-label bupropion, nicotine patch and weekly relapse prevention training.[8] All participants were then offered four relapse prevention sessions and continued on either active or placebo bupropion for another 14 weeks. There were no differences in abstinence rates between conditions at 1 year.

When appropriate, pharmacological treatment could be prolonged for periods longer than is usually recommended. It is recognized that the greatest effects on abstinence rates are due to long-term nicotine patch therapy and ad libitum other NRT.[1]

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4.5 Available evidence on other interventions to support tobacco cessation

Numerous approaches exist to support tobacco cessation with yet unproven effectiveness based on vaccines, drugs and non-pharmaceutical factors. Interventions subject to scientific research, which have so far not yielded positive conclusive evidence for at least 6 months follow-up from the beginning of treatment, include the following:

Vaccines

Three anti-nicotine vaccines are currently under clinical evaluation.1Review of available five phase I/II clinical trials using vaccines against nicotine found an increase in quit rates only in small groups of smokers with particularly high antibody titers. A conclusion was drawn that shortcomings may exist in underlying animal models of addiction and there is a need to better understand the processes contributing to addiction.[2]

A second review by the Cochrane collaboration concluded there is no evidence to support the use of vaccine to support smoking cessation. Further research is required.[3]

Silver Acetate

A review of randomized trials of silver acetate marketed for smoking cessation found lack of effect.[4]

Nicobrevin

A review of randomized long-term trials to assess effects of Nicobrevin, a proprietary product marketed as an aid to smoking cessation, did not yield any evidence that Nicobrevin can aid smoking cessation.[5]

Lobeline

Review of trials of Lobeline, a partial nicotine agonist, used in commercially available preparations to support smoking cessation did not find any positive evidence that Lobeline can aid long-term smoking cessation.[6]

Anxiolitics

A review of the effectiveness of anxiolytic pharmacotherapy with drugs such as diazepam, doxepin, meprobamate, ondansetron, and beta-blockers metoprolol, oxprenolol and propanolol in aiding long- term smoking cessation did not find consistent evidence of any positive effect, although a possible effect was not excluded.[7]

Opiod Antagonists

A review of available evidence on the efficacy of opioid antagonists, including naloxone and naltrexone in promoting long-term smoking cessation did not produce any definite results and suggested the need for new and more extensive trials.[8]

Mecamylamine

A review of trials using nicotine antagonist mecamylamine, also in combination with NRT showed the need to confirm available evidence in more extensive studies.[9]

Gabapentin

In a preliminary proof-of-concept study evaluating gabapentin for the treatment of tobacco dependence, gabapentin administered at the usual dosage was not found to increase rates of tobacco use.[10]

CB1 Receptor Antagonists

A review of three trials to determine whether selective CB1 receptor antagonists (currently rimonabant and taranabant) increase the number of people stopping smoking, and to assess their effects on weight change depending on cessation success, found some positive evidence, however development of these drugs was discontinued by the manufacturers in 2008.[11]

Glucose Tablets

In a randomized trial of glucose tablets to aid smoking cessation, which aimed to assess whether glucose tablets improve six-month continuous abstinence rates compared with low-calorie placebo tablets, no significant effect of glucose tablets over sweet tasting tablets was detected. However, researchers claimed that the possibility of an effect as an adjunct to NRT or bupropion deserves studying.[12]

Non-pharmaceutical interventions

Partner-based interventions

A review of available 57 articles on partner involvement as a means to attain long-term effect in tobacco use cessation did not reach any definite conclusions and recommended more research.[13]

Financial Incentives

A review of 17 studies of competitions, material or financial incentives to reinforce smoking cessation did not find definite evidence on enhancing long-term cessation rates.[14] Authors conclude that Incentives appear to boost cessation rates while they are in place with mixed results doucmneted on long-term cessation. Incentive-based interventions tested among pregnant smokers improved cessation rates at the end-of-pregnancy and post-partum period.

Exercise-based Interventions

A review of trials of exercise interventions for smoking cessation found that only one of the 20 trials reviewed showed positive impact of exercise in a year-long follow up. Other reviewed trials had shortcomings, so more research of exercise interventions was recommended.[15]

Hypnotherapy

A review of 11 randomized controlled trials of efficacy of hypnotherapy promoted as a method for aiding smoking cessation found conflicting results and did not provide evidence that hypnotherapy could be as effective as counseling treatment.[16]

Acupuncture, Laser, electro-stimulation

A review of 38 reports of randomized trials on the effectiveness of acupuncture and related techniques of acupressure, laser therapy and electro stimulation promoted as treatments for smoking cessation did not find consistent evidence of effectiveness of these interventions for smoking cessation, however no firm conclusions were drawn and further research using frequent or continuous stimulation was recommended.[17]

Aversive Stimulation

A review of 25 trials to determine the efficacy of rapid smoking and other aversive methods of smoking cessation and to ascertain possible dose-response effects depending on the level of aversive stimulation did not find sufficient evidence to determine the efficacy of rapid smoking, or whether there is a dose-response to aversive stimulation.[18]

Recommendations:

- The efficacy of non-conventional therapies, such as hypnosis, acupuncture, phytotherapy, homeotherapy, has not been demonstrated properly and such therapies are not recommended by experts.

- As the safety of such procedures is generally good, if a patient requests such a non- conventional therapy, the health professional may discourage it, but it is advisable not to prohibit it, due to the danger that the smoker may renounce conventional medicine.
- A combination of conventional and non-conventional medicine is in most cases better than using non-conventional medicine alone.

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E-cigarettes

E-cigarettes or "e-cigarettes" are battery operated devices that heat and emit vapor from a liquid solution that typically contains glycerin and propylene glycol, flavors, and additives.[1] The disposable cartridges which contain the liquid used in e-cigarettes are available in both nicotine free and nicotine containing forms. These products are commercially available and may be advertised as both as an alternative to cigarettes as well as a smoking cessation product.

There are however concerns that the e-cigarette has now become a tobacco initiation product, a product for consumption in non-smoking areas. With disposable cartridges, e-cigarette have become more economical than regular cigarettes per nicotine puff absorbed and experimentation with e-cigarettes by young people is becoming more and more common throughout Europe.[2]

Efficacy

A systematic review by the Cochrane collaboration examined available evidence regarding the efficacy of e-cigarettes in smoking abstinence or smoking reduction.[3] The review identified

a total of 24 studies including two RCTs and 21 cohort studies. Only two published RCTs of e-cigarettes exist, both of which used early electronic cigarette models with low nicotine content, and these studies suffer from several methodological limitations. Participants using an e-cigarette were more likely to have abstained from smoking for at least six months compared with participants using placebo EC (RR 2.29, 95% CI 1.05 to 4.96; placebo 4% versus e-cigarettes 9%.[3] Bullen et al. conducted a three arm comparison of e-cigarette (nicotine containing), e-cigarette (no nicotine), and NRT patch. The study found no significant difference between e-cigarette (nicotine containing) and NRT patch, and both were superior to e-cigarette (no nicotine).[4]

In terms of smoking reduction, the very limited available evidence suggests people were able to reduce cigarette consumption by at least half with nicotine containing e-cigarettes compared with placebo e-cigarettes (RR 1.31, 95% CI 1.02 to 1.68, 2 studies; placebo: 27% versus EC: 36%) and compared with patch (RR 1.41, 95% CI 1.20 to 1.67, 1 study; patch: 44% versus EC: 61%).[3] Similar finding have been reported from cohort studies. Polosa et al. tested the Category e-cigarette in Italy among smokers unwilling to quit, reporting substantial reductions in the number of cigarettes smoked per day and sustained abstinence rates of 22.5% and 12.5% after 6 months of e-cigarette use.[5] Again these studies suffer from methodological limitations.

Laboratory studies have also found that e-cigarettes are effective in curbing cigarette cravings in smokers.[6,7]

There is an urgent need for clinical trials to determine the efficacy, if any, of e- cigarettes in promoting smoking abstinence.

Safety

Emissions of total suspended particulate matter (TSP) derived from e-cigarettes are around 60 mcg/m^3, 10-15 times lower than those of conventional cigarettes.8 For each of the different fractions of PM, ($PM^{1,2.5,7,10}$), there is a lower density (ranging from 6 to 21 times) for e-cigarettes compared to conventional cigarettes, but the levels still slightly exceed WHO outdoor air quality guideline values.[1]

The smoke-like vapor produced by ethylene glycol or glycerol is an irritant when exposure is repeated, but has not been found to be a severe toxin in short- term use.[9] Recent research has examined the toxicity of the flavorings used in e-cigarette liquids. Lerner et. al. reported that exposure to e-cigarette aerosols/ juices incurs measurable oxidative and inflammatory responses in lung cells and tissues that could lead to unrealized health consequences.[10]

Three recent systematic reviews have reported on the safety of e-electronic cigarettes.[3,11,12] Farsalinos and Polosa reviewed laboratory and clinical evidence regarding potential risk of e-cigarette use compared to continued cigarette use and concluded e-cigarettes are less harmful compared to the significant risk of continued smoking.[11] Pisinger and Dossing reported on a review of 76 studies which reported on health consequences of e-cigarette use. The authors concluded that due to the relatively few studies and methodological issues of existing studies as well as the inconsistencies and of results among published studies, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of ECs.[12] Authors noted despite the lack of evidence, that e-cigarettes should not be considered harmless.

The lack of reliable studies had led most national authorities to prohibit the promotion of this product as a smoking cessation product.

Recommendations:

- There is insufficient evidence to appropriately estimate the health risks associated with use of e-cigarettes (level of evidence B).
- There is insufficient evidence on the efficacy of e-cigarettes as a cessation aid to support their use as a cessation aid (level of evidence B).
- There is no evidence of frequent or severe adverse effects, but there is likewise no evidence of efficacy for smoking cessation, so in view of the absence of studies health professionals should not recommended this product (level of evidence B).
- There is an urgent need for clinical trials to determine the safety and efficacy, if any, of e-cigarettes in promoting smoking abstinence.

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4.6 Recommendations for the smoking reduction approach

Smoking reduction is proposed as a second-line option for smokers who are unwilling or unable to stop smoking completely. Smoking reduction should be viewed as an intermediary step towards later cessation for smokers who cannot or will not stop smoking. The goal for all tobacco users remains complete smoking cessation.

The benefits of the reduction in smoking approach is two-fold:

- reducing smoking and thus at least some of the risks involved in smoking;
- increase patient's confidence in his/her ability to stop completely and increases the number of attempts in the year.

There was concern that the proposed reduction of smoking for some smokers would decrease the quit rate. There is no data to support this concern; the opposite effect has even been observed. A review by the Cochrane Collaboration found no difference in terms of likelihood of cessation between abrupt quitting and reducing cigarette consumption before the quit date, and concluded patients can be given a choice to quit with either of these ways.[1] Patients not willing to stop, but who were proposed to reduce smoking, are more likely to be abstinent at one year than those who were not proposed to reduce smoking, but were offered a complete stop as the only solution.[3,4]

Smoking reduction was defined as a 50% decrease in initial cigarette use, but without complete abstinence.[1]

Limited data (from small studies, on selected populations and for short follow-up periods) suggest that a substantial smoking reduction would reduce several cardiovascular risk factors and would ameliorate respiratory symptoms. Smoking reduction is associated with a 25% decrease in tobacco bio-markers and pulmonary cancer incidence and with a low, almost insignificant, increase in the birth weight of babies born to smoking mothers.[2] Remarkable benefits on the pulmonary function do not seem to occur if smoking is reduced.[5]

Smoking reduction represents a therapeutic alternative for smokers not yet ready to quit smoking completely. The smoking cessation ratio in a study group treated with nicotine gum was double versus placebo after three months and tripled at 12-month follow-up.[2] Concomitant nicotine gum use with reduced continuing smoking was well tolerated with a significant decrease of the carbon monoxide biomarker.[2] The ROSCAP study concerning smoking reduction in cardiac patients was

a controlled randomized trial which assessed efficacy of the smoking reduction strategy on diminishing the harmful effects of tobacco exposure. Those who managed to reduce smoking were especially men, with a more intense tobacco consumption compared to the control group.[6]

4.6.1 Smoking reduction with nicotine replacement

Smoking reduction with nicotine replacement therapy is only recommended in a dependent smoker, i.e. a smoker in whom the large number of nicotinic receptors and their desensitization is an important factor in consumption among those with a Fagerström score greater than 3, or even greater than 6.[4] Reduce smoking should be proposed systematically to highly dependent smokers with a score of 7 or more in the Fagerström test, having a tobacco-related disease and not ready to quit smoking.

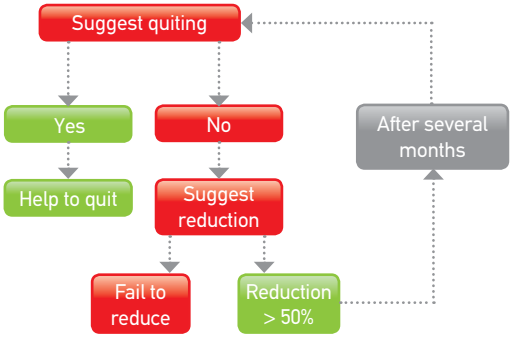
A meta-analysis of seven randomized, controlled trials involving 2767 smokers, who were initially unwilling to quit, showed that the abstinence rate six months after the initiation of treatment was significantly higher among smokers who were randomly assigned to NRT (nicotine gum, inhaler or patch) for six months or more, while trying to reduce their smoking, than among those in the control group: 9% v. 5%.[7]

Nicotine replacement therapy is used as a substitution as the number of cigarettes smoked per day is reduced and so the harmful effects of tobacco products (other than nicotine) are potentially reduced. More nicotine is delivered in a more progressive way, so with less maintenance of addiction. Pharmaceutical nicotine will increase gradually until a reduction of at least 50% of the number of cigarettes smoked, and may be increased to bring about quitting (Figure 4.9).

4.6.2 Smoking reduction with varenicline

A recent study by Ebbert et al. reported on a randomized double blind controlled trial which examined the use of varenicline among smokers who were not willing or able to quit smoking within the next 30 days but were willing to reduce smoking and quit in the next 3 months.[8] The study found that the use of varenicline significantly increased rates of smoking abstinence at the end of treatment and at the end of follow-up compared to placebo (at 12-months: 27.0% for the varenicline group vs 9.9% for the placebo group; RD, 17.1% [95% CI, 13.3%-20.9%]; RR, 2.7 [95% CI, 2.1-3.5]).

Figure 4.9: 'Reduce to quit' smoking strategy



Recommendations

- Smoking reduction increases the probability of a future smoking cessation attempt (level of evidence A).
- The use of NRT is recommended as part of a 'reduce to quit' approach among smokers who reported higher rates of nicotine dependence (level of evidence A).
- The use of varencline as part of a 'reduce to quit' approach has been shown to be effective in one trial (level of evidence B).

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4.7 Treatment recommendations to prevent relapse to smoking

Relapse defined as the resumption of substance use after a period of abstinence is a frustrating but unavoidable part of recovery from the smoking process. Referring to relapse as long-term treatment failure in a general sense, Piasecki shows it is a common and quick finding among quitters, as the vast majority of smokers enrolling in smoking cessation trials report a history of past quit attempts, as most have already failed at least once while using a pharmacological cessation aid[1,2] and as many lapses occur within the first 24 hours following the quit day.

Behavioural strategies

Three major strategies are common to current relapse prevention programmes: (1) cognitive- behavioral strategies to avoid relapse when cravings occur and to learn from any lapse event; (2) social support strategies focusing on the smoker's need for emotional support from family members/ close friends; (3) lifestyle change strategies centered on helping smokers develop new social identities as drug-free individuals.[1,2]

At the present time evidence lacks to support the use of any specific behavioral interventions to help prevent relapse prevention among individuals who have successfully quit.[3] The specific individual or group interventions did not prevent relapse, regardless of their duration or contact time, even after eight weeks of phone counseling.[2,3]

Interventions focused on identifying and resolving tempting situations offer the most promise in terms of effective behavioral strategies for preventing relapse.[3]

In order to design effective interventions to reduce relapse in vulnerable categories of smokers, such as postpartum women or incarcerated people, identification of specific relapsing factors can increase the efficacy of combined motivational interview and cognitive-behavioral therapy.[5,6]

Use of medications

Extended treatment with varenicline appears to be effective in preventing relapse following an initial period of abstinence or an acute treatment episode, however evidence is limited to one study.[3] Hayek et al. in 2009 found prolonged varenicline administration in preventing relapse, especially in those patients who achieve abstinence later on, during the standard 12-week varenicline cure.[7] Patients were randomized in two groups: three months supplemental varenicline treatment v. three months supplementing with placebo. The authors report a higher risk of relapse in patients who stopped smoking only in the 11th week of treatment, compared to those who stopped as of the first week. Abstinence ratio in the 52nd week was 5.7% for the late abstinent people and 54.9% for the early ones. From this viewpoint it can be concluded that a repeated 12-week course of varenicline in smokers who do not succeed to quit at the week 1 or week 2 set quit day, will prove beneficial, as observed in this study on 1208 patients, who were still abstinent in the 12th week of varenicline therapy.[7]

There is no strong evidence that extended use of bupropion is thought not to benefit relapse rates.[3] A small number of studies have found extended use of NRT to be effective in preventing relapse however additional research is required.[3]

Japuntich et al. examined the effects of five types of pharmacotherapy for smoking cessation (bupropion, nicotine lozenge, nicotine patch, bupropion and lozenge, patch and lozenge) over eight weeks following a quit attempt.[8] Authors used the approach described by Shiffman et al. to examine the effect of smoking cessation medications on three smoking cessation "milestones": initial abstinence, lapse and the lapse-relapse transition. In sum, these researchers hypothesized that, compared to placebo: (1) bupropion will increase initial abstinence

rates; (2) the nicotine lozenge will reduce lapse risk; (3) bupropion and nicotine patch will reduce relapse risk following a lapse; and (4) combination pharmacotherapy (bupropion and lozenge, patch and lozenge) will produce beneficial effects relative to the mono therapies at each of the milestones. This research found that smoking cessation medications are quite effective at promoting initial abstinence and reducing lapse risk, but the evidence is weaker that they prevent a transition from lapse to relapse. Combination of pharmacotherapy tended to be superior to the mono therapies in boosting attainment of initial abstinence and in lapse prevention. The nicotine patch and lozenge was superior to bupropion and lozenge in producing initial abstinence.

Bupropion, NRT and varenicline appear cost-effective at preventing relapse by smokers during quit attempts or who have recently become abstinent. More widespread use of these effective relapse prevention treatments could add a substantial health gain, at an acceptable cost, for health care providers.[9]

Knowledge of the degree of relapse risk might help clinicians provide individuals with optimal treatments by identifying those in need of more aggressive interventions. Such interventions might include either higher doses or longer durations of pharmacotherapy, or more frequent or more intense psycho-social interventions. Thus, Bolt et al. developed the WI-PREPARE seven-item questionnaire to provide researchers and clinicians with a tool to measure relapse proneness that is effective in predicting both short- and long-term relapse among smokers interested in quitting.[10]

Recommendations:

- At present there is insufficient evidence to support the use of any specific behavioral intervention for helping successful quitters to avoid relapse (level of evidence B).
- Extended treatment with varenicline may prevent relapse (level of evidence B),
- Extended treatment with bupropion is unlikely to have a clinically important effect (level of evidence B).
- There is some initial evidence that extended use of NRT may prevent relapse, however additional studies of extended treatment with nicotine replacement are needed (level of evidence B).

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4.8 Treatment recommendations in special situations and population groups at risk

The interventions found to be effective in current smoking cessation guidelines are recommended for all individuals who use tobacco, except when medication use is contra-indicated, such as during pregnancy and for adolescents. There are also specific considerations for certain populations at risk, when insufficient evidence is available or when medication has not been shown to be effective (e.g. smokeless tobacco users, moderate smokers, etc.). Particular situations and groups at risk are examined in the following sub-chapters.

4.8.1. Treatment recommendations for pregnant women

Tobacco abstinence is essential for pregnant women. A Danish cohort has shown that smoking during pregnancy doubles the risk of still birth and death during the first year of life.[1] The in uterus hypoxia related to smoking is associated with a low body weight at birth, but in many women cravings are very high during pregnancy.[2]

The best choice is to stop smoking before pregnancy using all available support.

For pregnant woman who are unable to quit smoking, ensuring access to the best psychological support and medication, this is the best choice during pregnancy. A reduction to a few cigarettes per day cannot be an acceptable goal. Only total tobacco abstinence before the end of the first term is an acceptable target.

There is good evidence that psychosocial interventions are effective in increasing rates of smoking abstinence among pregnant women (RR 1.44, 95% confidence interval (CI) 1.19 to 1.73; 30 studies).[3] There was unclear evidence regarding the efficacy of social support interventions provided by peers in supporting cessation (five studies; average RR 1.42, 95% CI 0.98 to 2.07).[3] There is promising evidence that incentive-based interventions are effective is supporting cessation however more research is required.[3]

No convincing study reports any specific side effects of nicotine replacement therapy as being more severe than the effects of smoking.[4] While there is compelling experimental and clinical evidence that nicotine harms the developing fetus,4 there is no evidence that the use of NRT in pregnancy has either positive or negative impacts on birth outcomes.[4]

Eight studies have examined the efficacy of NRT during pregnancy. Evidence suggests NRT may increase cessation outcmes in late pregnancy, however studies had several methodological limitations and in general low rates of adherence to NRT treatment were reported. As such high quality evidence is lacking that NRT aids smoking cessation in pregnancy.A UK randomized trial where more than 80% of pregnant women did not receive treatment after one month did not show any difference in cessation except during the first month of treatment.[5]

The risk to fetus when compared to continued smoking is sufficiently less than using NRT.

Oral nicotine may be used to reduce the overall risk compared to 24-hour patch.

Varenicline and bupropion are not indicated in pregnant women and are not recommended.

Recommendations:

- All pregnant women should have their smoking status assessed throughout their pregnancy and offered support with quitting (level of evidence A).
- Intensive behavioural / psychosocial intervention are recommended for all pregnant women who smoke (level of evidence A).
- NRT is the only medication that has been tested among pregnant women. There is mixed evidence to support the use of NRT as an effective strategy to support cessation at the present time, however the risk to fetus when compared to continued smoking is sufficiently less than using NRT.

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4.8.2. Treatment recommendations for young people under 18

Nicotine addiction is rapidly developed at young ages.[1] As tobacco use often begins in pre-adolescence, doctors should intervene to

support smoking prevention as a priority in this age group.

An overview of the literature in this field shows a wide range of approaches, but also their limited effectiveness.[1] Smoking interventions for adolescents have included pharmacotherapy, behavioral approach (such as school and community-based programmes) and tobacco control policies; these interventions have had mixed results. It appears that the most significant therapeutic effect in teenagers was observed for self-monitoring and coping skills, motivational strategies (reducing ambivalence to change) and addressing social influences that affect smoking behavior.

The Center for Disease Control (CDC) in the USA recommends as most efficient those interventions which are multi-component and which combine school support-based programmes with local community involvement.[2]

When smoking cessation counseling is delivered to young people, it must be taken into account that in most cases they underestimate their own nicotine dependence. Teenagers who smoke either occasionally or daily believe that they can easily quit smoking at any time. In fact, only about 4% of the smokers aged 12-19 succeed in quitting smoking every year, with a failure ratio higher than adult smokers.[3] Statistics also show that teenagers are very interested in quitting smoking: 82% of those aged between 11 and 19 years think about quitting and 77% have undertaken serious attempts to quit in the past year.[3] Teenagers' attempts are rarely planned: most teenagers choose to quit smoking without any qualified help, but research has demonstrated that young people who participate in smoking cessation programmes have twice as high a chance of successfully quitting.[4]

Counseling and smoking cessation therapies recommended to people under the age of 18

Despite the high prevalence and significant health implications of adolescent smoking, little work has been done to develop smoking cessation programmes targeting this age group. This area of research has almost exclusively focused on psycho-social treatments, as shown in one meta-analysis which found a quit rate of 12% three months following treatment, compared with 7% among control groups.[5] One psycho-social intervention that has proven encouraging, but only with regard to the preliminary results, is contingency management (CM), which is a behavioral treatment based on operant conditioning, in which desired behaviors (such as smoking abstinence) are directly reinforced with rewards (e.g. vouchers, cash). Evidence suggests that CM, alone or when combined with cognitive- behavioral therapy (CBT), may be efficient in encouraging adolescents to quit smoking. One study (n=28) demonstrated particularly encouraging results, with 53% of participants receiving CM and CBT achieving abstinence at the end of one-month treatment, compared with 0% of those receiving only CBT.[6] Based on these pilot findings, a recent larger-scale study (n=110) investigated a three- week, twice-daily CM intervention, alone or combined with motivational therapy, among non-treatment seeking college student smokers.[7] Participants receiving CM (with monetary rewards, based on carbon monoxide levels in the first week and on smoking abstinence in the second and third weeks) demonstrated significantly lower carbon monoxide levels and a greater abstinence (55% v. 18% of readings) during treatment, than those not receiving CM.

A meta-analysis which examined the efficacy of counseling in young people showed that this method doubles long-term abstinence rates compared to the common approach (brief advice, self-help materials, and referral to smoking cessation centers) or compared to the absence of any intervention.8 In general, teenagers can be approached using various treatment formats: either in individual sessions (face-to-face), by combining individual sessions with phone counseling/phone or Internet messages, or by group sessions. Counseling of teenagers must be confidential and must respect their privacy, and must preferably not be in the presence of parents or teachers.

Peer format sessions proved very effective: this method provides counseling together with the young smoker's colleague or best friend, even though such partners are not smokers. If the teenager comes from a family with smokers or is passively exposed to smoking, it is also recommended to provide counseling to the parents.

Research has shown that counseling interventions for parents provided within pediatric services or in relation to hospitalized children, increased pro-quitting interest, the number of cessation attempts, as well as the smoking cessation rate in the respective

parents. Moreover, informing parents about the risks of exposing their children to passive smoking can reduce exposure, as well as smoking rates among parents.[1,4]

Programmes designed specifically for teens

These ones include: school-based tobacco cessation programmes,[9] media campaigns for effective prevention messages,10 interactive smoking cessation programmes such as the European project *Adolescent Smoking Cessation*,[11] video lessons such as the Dutch programme *I do not smoke*, contests with prizes and incentives, such as *Quit and Win for Teenagers*,[11] *N-O-T (Not on Tobacco)* which is the American Lung Association's voluntary smoking cessation programme for high school students.[12]

Telephone counseling

Tobacco quit lines are more appealing to adolescents due to the fact that they are easy to access and are semi-anonymous, they can be individualized to the caller within a structured protocol and can include proactive follow-up, so the counselor, not the caller, takes the initiative to call back after initial contact has been established. For example, in the California Smokers' Helpline protocol, counselors work to help adolescents view quitting rather than smoking as an adult behavior. Also, they approach topics specific to this age category, such as: identity formation, sense of invulnerability, dependence on family, identification with peers and desire for autonomy.[13]

In a study comprising 1058 high school pupils, such phone counseling methods were used weekly, obtaining a very good adherence to the treatment protocol in the study population (90%). In a similar study that provided cognitive-behavioral counseling and motivational interview by phone, one-year follow-up of the 2151 high school pupils proactively identified found 21.8% abstinent at 6 months in the intervention group v. 17.7% in the control group.[1]

Pharmacotherapy for teenagers

Despite clear evidence of nicotine withdrawal and craving in adolescents, limited research has focused on pharmacological agents in adolescent smoking cessation.[14,15,16] Although there are seven FDA-approved first-line medications for adult smoking cessation, there is not enough evidence to recommend any of these for the treatment of adolescent smokers. Moreover, the majority of European countries forbid by law prescribing medication for quitting smoking to this category of individuals. Tests of medications in adolescent smokers have been limited to nicotine replacement therapy and bupropion.

The very few studies published on this topic found either an insignificantly different abstinence rate for nicotine patch therapy v. placebo at 12-week follow-up from quit day, or did not find any differences between efficacy of nicotine gum versus nicotine patch versus placebo at six-month follow-up. In all these study groups, young people received, besides study drug/placebo, a minimum of six counseling sessions.[4,8]

A non-controlled, open-label trial of nicotine patch, combined with minimal behavioral treatment (n=101), demonstrated point prevalence abstinence rates of 11% at the end of treatment and 5% at six-month follow-up.[17] Another controlled study of both groups receiving CBT and CM (n=100) supported the safety of patch in adolescents, but revealed no differences between patch and placebo (28% versus 24% point prevalence abstinence at the end of treatment, respectively).[18] In a randomized NRT trial involving 120 adolescent daily smokers, Killen et al. found at the end of treatment, and again at three-month follow up, that 20.6% of those assigned to patch were confirmed abstinent, compared with 8.7% in the gum group and 5% in the placebo group.[19] Moolchan et al. compared patch, gum and placebo among adolescent smokers also receiving group-based CBT for smoking cessation (n=120). Continuous abstinence following a two-week grace period was achieved by 18%, 7% and 3% in the three groups, respectively.[20] A recent pilot study (n=40) revealed poor treatment adherence and no difference in cessation outcomes between nicotine nasal spray and placebo.[21]

In light of the modest effect of NRT, some investigators have focused on bupropion SR for adolescent smoking cessation. A research group conducted an open-label trial of bupropion SR, combined with brief individual counselling in adolescent smokers (n=16) and found 31% abstinence after four weeks of treatment.[22] Killen et al. compared combined treatment with bupropion SR 150 mg daily and nicotine patch to nicotine patch alone(n=211), both treatments provided together with a group skills training intervention. They found only 8% abstinence at

26-week follow-up for the combined therapy versus 7% for the nicotine patch alone.[23]

In a large-scale randomized trial (n=312), Muramoto et al. compared bupropion SR 300 mg/day, bupropion SR 150 mg/day, and placebo treatment, added to brief weekly individual counseling.[24] The bupropion SR 300 mg/day group (but not the 150 mg/day group) demonstrated superior point prevalence abstinence, compared to placebo, at treatment conclusion (15% versus 6%) and at 26-week follow-up (14% versus 10%). In another study, 134 treatment-seeking adolescent smokers were randomized to receive bupropion SR and/or contingency management (CM), each alone or in combination with the other, in a 2x2 six-week controlled trial. Authors found abstinence rates of 27% for combined bupropion SR and CM, 8% for bupropion SR and non-CM, 10% for placebo and CM, and 9% for placebo and non-CM, at 30% treatment completers.[25]

Consistent with recent reviews and US guidelines, there is currently insufficient evidence to recommend the use of pharmacotherapy for smoking cessation in adolescents. According to the clinical practice guidelines, referral to appropriate psycho-social intervention (e.g. school- or community-based, group or individual counseling) is the most appropriate front-line treatment for adolescent smokers. Although these interventions produce relatively low overall quit rates, they do significantly increase the odds of quitting over no treatment. While pharmacotherapy may be considered, they should be prescribed only with close monitoring and after careful consideration of the adolescent's smoking rate, history of failed quit attempts, and current motivation to quit smoking. The inconclusive results from adolescent smoking cessation pharmacotherapy trials suggest the limits of prescribing such medication in adolescents.[19]

Recommendations

- Doctors are recommended to question all young patients under the age of 18 about tobacco consumption and to transmit clear messages about the importance of abstaining from smoking (level of evidence C).
- Counseling proved to be an effective smoking cessation method for teenagers (level of evidence B).
- Passive smoking is harmful to children and teenagers. Smoking cessation counseling provided within pediatric services proved efficient in increasing tobacco abstinence ratios in smoking parents. For this reason, in order to protect children against passive smoking, we recommend clinicians to evaluate parents' smoking and to provide them with advice and assistance for quitting tobacco consumption (level of evidence B).

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4.8.3. Treatment recommendations for smokers with respiratory, cardiovascular, psychiatric, cancer and other comorbidities

Tobacco users with co-morbid medical conditions such as cancer, cardiac disease, COPD, diabetes, and asthma are important to target for tobacco use treatments, given the role that smoking plays in producing or exacerbating these conditions. Using chronic disease management programmes to integrate tobacco dependence interventions into treatment may be an effective and efficient way to deliver tobacco use interventions to these populations.[1] Cessation treatment proved to be efficient in smokers with a wide variety of co-morbidities, even if some difficulties arise and precautions are imposed.

Cardiovascular disease

In a systematic review, Critchley and Capewell found that quitting smoking is associated with a substantial 36% reduction in risk of all-cause mortality among patients with coronary heart disease (CHD), regardless of differences between the studies in terms of index cardiac events, age, sex, country and time period.[2] Smoking cessation treatment for patients with cardiovascular diseases differs from those for other patients in that patients are often forced to quit smoking after an unexpected cardiovascular event that suddenly occurs and to continue abstinence for life. Since the onset of cardiovascular disease is the most significant reason that motivates smokers to quit smoking, physicians must provide appropriate cessation programmes for patients with cardiovascular diseases.[3]

Special considerations should be made for smokers with cardiovascular disease because (1) as evidence shows, they should be strongly recommended to quit smoking; (2) they should discontinue smoking during the acute phase of cardiovascular disease and continue abstinence thereafter; and (3) they are contra-indicated for nicotine replacement therapy during the acute phase of cardiovascular disease only (first 48 hours post event).[1] Medication effects are substantially increased when coupled with behavioral interventions delivered as counseling by a doctor or other health care provider, with stop-smoking groups and also with telephone quit lines.

All patients with any risk factors for cardiovascular disease should be instructed to quit smoking. Varenicline and/or nicotine replacement therapy should be considered. Apart from the recommended precautions for nicotine substitute use in smokers with acute cardiovascular diseases, current evidence suggests that nicotine replacement has shown no adverse effect on

outcomes in patients with cardiac disease.[3] Varenicline seems to be reasonably safe in patients with stable CHD without a history of depression or psychiatric disease. Specific data about use of varenicline for smoking cessation in cardiovascular disease patients were quoted in section 4.3.3.9 Finally, interventions combining multiple strategies (pharmacological and psycho-social) may have better long-term efficacy, especially for those patients who do not respond to the drug alone.[4]

Respiratory disease

Being exposed directly to tobacco smoke, the respiratory organs are the most affected by tobacco. This is why smoking cessation must be strongly encouraged in patients with COPD, lung cancer, asthma, respiratory infections, interstitial and sleep respiratory disorders.

COPD

Smoking cessation is the most important therapeutic intervention for COPD smoking patients. COPD patients who smoke have a particularly high level of nicotine dependence, which requires structured smoking cessation programmes that comprise drug interventions as well as non- drug interventions. A 2016 review by the Cochrane Cochrane on smoking cessation in COPD patients and current literature indicates that the smoking cessation concept to include medication and psycho-social support is effective for COPD patients (level of evidence A).[5]

The psycho-social intervention consists of a structured smoking cessation programme over several hours by approaching cognitive aspects and subjective or objective respiratory findings, such as the lung function.[6] Some studies analyzed whether using special vocabulary like "smoker's lung" or contingent reinforcement with lottery tickets for reduced breath carbon monoxide or performing lung function tests has a stronger impact on the efficacy of counseling. No significant differences were found when these more intensive interventions were compared with the usual advice; however, they did show a trend in favor of the intensive intervention.

The best way of increasing self-efficacy and self-esteem in these patients is to offer them continued assistance. The Clinical COPD Questionnaire (CCQ) is a valuable tool indicating the health-related quality-of-life gains attributable to smoking cessation among COPD patients.[7] Every smoker suffering from COPD should be repeatedly advised to quit smoking by his/her physician. One visit per month is recommended, but also intensive behavioral interventions in individual or group format.[8]

In an open, randomized study examining four different NRT regimens used in a daily routine for COPD patients in a lung disease clinic, the average 12-month success rate for the three considered active treatments was only 5.6%.[9] Tonnesen et al. evaluated the efficacy of nicotine sublingual tablets and two levels of behavioral support for smoking cessation in COPD patients.[10] They found that abstinence rates were significantly superior in the sublingual nicotine group v. placebo, even though there was no significant difference between the effects of low v. high behavioral support. Analysis of 7372 COPD patients showed that smoking cessation counseling (SCC) in combination with NRT had the greatest effect on prolonged abstinence rates v. usual care, v. SCC alone and v. SCC combined with an anti-depressant.[11]

A combination of different forms of NRT can be used as valid strategies to help COPD patients quit. The combination of two types of NRT with different types of delivery is highly recommended. Increasing the length of time that NRT is used to up to six or twelve months can help more smokers to quit than using NRT for the usual time. NRT can be used to help in the progressive reduction of the number of cigarettes smoked as a gateway to quitting permanently. COPD smokers are usually unmotivated to quit. Using this approach can help to increase own motivation and build up self-efficacy in quitting.[8]

In three clinical trials that analyzed the efficacy of bupropion for treatment of smokers with COPD, it was found that bupropion was significantly more effective than placebo for achieving continuous abstinence at six-month follow-up (16% v. 9%),[12] that bupropion was more effective than placebo for achieving continuous abstinence at six-month follow-up (27.9% v. 14.6%)[13] and that bupropion and nortriptyline seem to be equally effective, but bupropion appears to be more cost-effective compared with placebo and nortriptyline.[14] Bupropion combined with counseling was significantly more effective in achieving prolonged abstinence than a placebo by 18.9% (95% CI 3.6-26.4%). Annual spirometry with a brief smoking cessation intervention, followed

by a personal letter from a doctor, had a significantly higher three-year abstinence rate among COPD smokers, compared to smokers with normal lung function.[15]

The efficacy and safety of varenicline for treating COPD smokers was evaluated in two studies: a multi-centre, double-blind study on 504 patients with mild to moderate COPD and without known psychiatric disorders and another open study on 472 smokers with severe or very severe COPD who received treatment for smoking cessation. In the first study, the continuous abstinence rate (CAR) for weeks 9 to 12 was significantly higher for patients in the varenicline group (42.3%) than for those in the placebo group (8.8%), respectively 18.6% v. 5.6% through weeks 9 to 52.[16] In the second study, as the treatment programme consisted of a combination of behavioral therapy and drug treatment (NRT, bupropion or varenicline), the CAR from 9 to 24 weeks for NRT, bupropion and varenicline was 38.2%, 60.0% and 61.0% respectively. Varenicline was more effective than nicotine patch: 61% v. 44.1%.[17]

Hoogendoorn et al. analyzed the effectiveness of continued assistance in smokers with COPD and concluded that despite the high costs for this aggressive smoking cessation programme, beneficial economic effects are likely to be obtained in the long run.[18]

Recommendations

- NRT or varenicline should be used for smoking cessation in all smokers with COPD, regardless of disease severity and number of cigarettes smoked (level of evidence B).
- NRT, varenicline and bupropion SR are effective and well tolerated in smokers with COPD patients (level of evidence A).

Asthma

As cigarette smoking is an important predictor of asthma severity and poor asthma control, in a dose- dependent manner, tobacco cessation becomes crucial in the case of asthmatic smokers.[19] Asthma smokers show more severe asthmatic symptoms, a greater need for rescue medication, greater corticosteroid resistance and poorer health-status indices than never-smokers. According to a study that evaluated the effect of smoking cessation on lung function and quality of life in patients with asthma during corticosteroid treatment, continuing smoking resulted in a greater decrease in lung function in long-term asthmatic smokers.[20]

Two treatment strategies are recommended when looking ahead to better outcomes for people with asthma who smoke:

- to look for drugs to target the altered inflammatory mechanism (theophylline appears to increase the effect of low-dose ICS and to improve symptoms and FEV1; fluticasone/salmeterol combination confers greater improvements in airway hyper-responsiveness and airway caliber, compared to double the dose of fluticasone; leukotriene receptor antagonists have demonstrated preferential airflow improvements);
- to provide evidence-based quit smoking support (there is limited evidence to help us decide on the most effective asthma-specific stop-smoking programmes; behavioral techniques and telephone counseling proved efficient; evidence about risk of NRT spray must be considered).[21]

Recommendation

- Flag smokers with asthma as high-risk patients and discuss with them quitting smoking at every opportunity. Providing written asthma self-management plans and educational leaflets ensures stop smoking as a treatment for asthma is included.[22,23]

Tuberculosis

Smokers have a higher risk of being infected with tuberculosis bacilli and once infected they develop tuberculosis disease more often than non-smokers. TB is spread more easily, pulmonary TB, sputum positive and cavity lesions are more frequent and also risks of TB relapses and death due to TB are higher in smokers with TB. Since smoking is known to increase the risk of TB infection and disease, never or quitting smoking helps better control of TB in a community. As smoking significantly reduces the effectiveness of TB treatment, the integration of smoking cessation into TB treatment programmes is highly advocated to reduce the dual global burden of smoking and TB.[24]

The International Union Against Tuberculosis recommends the ABC approach to quit smoking (Ask- about smoking status, Brief

Advice, Cessation support) for smoking TB patients. These three easy steps can be delivered by any health professional treating TB smokers and data must be noted in the patient's treatment record.[25]

In a multi-centered non-randomized controlled study involving 120 TB patients who were current smokers at the time of TB diagnosis in Malaysia, patients were assigned to either of the two groups: the usual TB-DOT plus smoking cessation intervention SCI (SCIDOTS group) or the usual TB-DOTS only (DOTS group). On comparison, participants who received the integrated intervention had a better HR QoL – found as a significantly greater increase in EQ-5D utility score during six-month follow-up – than those who received just the usual TB care. The Euro QoL five-dimension questionnaire (EQ- 5D) was developed to assess TB patients' self-evaluations of the impact of the disease and of the associated treatments on their physical, mental and social well-being and functioning.[26]

Cancer

Tobacco cessation is a significant challenge in this complex patient population.[27] When treating tobacco dependence in patients with lung cancer, one should consider the following:

- **Motivation:** Evidence suggests that the majority of lung cancer patients are motivated to stop smoking. Yet, although a diagnosis of lung cancer is assumed to be a strong motivator, lung cancer patients who smoke are at various stages of readiness to quit.
- **Stigma and self-blame:** There is empirical evidence to indicate that lung cancer patients experience significant levels of perceived stigma whether they are current smokers or not.
- **Mood management:** As a result of a lung cancer diagnosis, patients often experience increased psychological distress, increased feelings of burden, stress and stigmatization.
- **Smoke-free homes:** Considerable evidence suggests that having a smoke-free home may be associated with increased successful quitting.[28]

Patients with cancer may have higher levels of nicotine dependence, higher levels of co-morbidity, or more difficulty in quitting, as well as poorer health and physical functioning, and more stress and emotional distress. This suggests the need for more intense or tailored programmes that combine behavioral interventions with pharmacologic cessation.[28] Counseling, medication and motivational counseling are efficient in this category of patients. Combination pharmacotherapy has also been found to be effective with highly dependent smokers.[28] A nurse-managed smoking cessation programme for 145 patients with head and neck or lung cancer showed favorable long-term success rates (40% abstinence at six months). The programme was most intensive in the first month and consisted of physician's advice, nurse management intervention and different products (nicotine lozenges, bupropion and combinations of products) and lasted a total of one year, in order to support the patient through several (annual) risk situations, such as birthdays, stress situations and holidays.[29]

Psychiatric disorders, drug consumers

Psychiatric disorders are more frequent in smokers and these patients may experience a difficult quitting process. Smoking behavior is more often encountered in alcohol and drug users. These categories of smokers do more rarely ask for smoking cessation therapy. Treating their tobacco dependence is a complex process, within the context of a psychiatric diagnostic and specific medication. Compared to smokers with no history of psychiatric disorders, smokers who have ever had a mood disorder or an anxiety disorder (including those who had one in the past year) were all less likely to be abstinent at eight weeks post quit. Having had a diagnosis of an anxiety disorder was also related to a decreased likelihood of maintaining abstinence at six months post quit. These findings may offer a basis for treatment tailoring in smokers with psychiatric comorbidities.[30]

Importantly, treating tobacco dependence in patients with stable psychiatric conditions does not worsen mental state and may in-fact improve mood.[31-33]

A meta-analysis by the Cochrane collaboration examined interventions to support smoking cessation among individuals with current or past depression.[34] The review included 49 trials and found evidence that adding a psycho-social mood management component to standard smoking cessation intervention was effective in increasing long term among smokers with current

or past depression. The review found evidence that the addition of bupropion was effective in increasing long-term abstinence rates in smokers with a history of depression.[34] Pharmacological treatment was delivered in association with intensive counseling. There was no evidence of an effect among individuals with current depression. There was also insufficient evidence examining the use of other anti-depressant medications or NRT in this population of tobacco users.[34]

For treating smokers who suffer severe mental disorders like major depression, schizophrenia and psychosis, it is recommended to increase and prolong the treatment period, to implement joint psychological cognitive behavioral techniques and to use any drug treatment that helps to control/ reduce relapse to smoking or to baseline psychiatric symptoms.[35]

In schizophrenic patients, smoking status should be included in the clinical assessment and NRT should be provided to smokers.[36] Although a high relapsing risk has been described in these patients, medication for tobacco dependence is effective. A meta-analysis from the Cochrane collaboration reported on smoking cessation among adults with schizophrenia found good evidence to support the use of bupropion to increase smoking abstinence.[37] Varenicline can attenuate abstinence-induced adverse events and appears to be well-tolerated in smokers with schizophrenia.[38] Both varenicline and combination pharmacotherapy were effective and did not increase psychological distress for up to six months in smokers with comorbidities, however additional research is required to rule out possible adverse events (see section 4.3.3.9).[39] Prescribers should closely monitor patients due to the possibility that the drug may cause psychiatric instability.[40]

Patients treated with atypical anti-psychotics could respond better to bupropion SR than those under standard anti-psychotics.[21] In an open label study of a group of 412 smokers (111 being diagnosed with psychiatric illnesses) varenicline was equally effective and was not associated with a higher incidence or severity of adverse drug reactions among patients with psychiatric comorbidity.[21]

Counseling and pharmacotherapy are effective in smokers treated simultaneously for illicit drug addiction, although there is little evidence on how nicotine addiction therapy influences drug addiction recovery. Current studies demonstrate the efficacy of a brief voucher-based contingency management intervention in promoting initial smoking abstinence among opioid-maintained patients.[41] A randomized, open-label trial compared treatment as usual (TAU) combined with nicotine patch plus cognitive behavioral group counseling for smoking cessation (n=153) to TAU alone (n=72) for patients enrolled in treatment programmes for drug or alcohol dependence, who were also interested in quitting smoking. This report is a secondary analysis evaluating the effect of depressive symptoms (n=70) or the history of depression (n=110) on smoking cessation outcomes. A significant association was seen between measures of depression and difficult to quit cigarettes. These data suggest evaluation and treatment of depressive symptoms may play an important role in improving smoking cessation outcomes in this category of patients.[42]

Recommendations:

- Treating tobacco dependence is effective in patients with severe mental illness. Treatments that work in the general population work also for those with severe mental illness and appear almost equally effective.
- For treating smokers who suffer severe mental disorders like major depression, schizophrenia and psychosis, it is recommended to increase and prolong the treatment period.
- Close monitoring of patients with mental health illness who are prescribed pharmacotherapy is recommended due to the possibility that the drug may cause psychiatric instability.

HIV infected patients

HIV-positive individuals are more likely to smoke than the general population.[43] Today, HIV- positive individuals live longer due to treatment advances, making the issue of cigarette smoking in this population a significant health concern. Higher mortality rates and lower quality of life are reported by HIV-positive smokers than HIV-positive non-smokers. In addition, HIV-positive smokers appear to be at greater risk for developing invasive pneumococcal diseases and other infections compared with non-HIV infected individuals. Relative to non-smoking HIV-positive individuals, smoking among HIV- positive persons is

associated with increased risk of several opportunistic infections and spontaneous pneumothorax. Data suggest that HIV-positive smokers underestimate the effects of smoking on their health, and some state that they will not live long enough for the health effects of smoking to matter. In addition, some HIV-positive smokers report that smoking is an effective way to cope with the stress of their illness.[1]

A 2016 review by the Cochrane Collaboration examined smoking cessation interventions for individuals living with HIV and AIDs.[43] The review identified 12 studies, most of which examined interventions involving both pharmacotherapy and counseling. Among the controlled trials evaluated there was no strong evidence of the intervention being more effective than the control group compartor. There was low quality evidence that intensive interventions were superior to controls in achieving short term abstience.[43] No long-term randomized clinical trial analyzed efficacy of interventions in this group of patients. More studies are needed.

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4.8.4 Recommendations to approach post-smoking cessation weight gain

Most smokers who quit gain weight variably, below 5 kg, but 10% of them may gain over 15 kg weight. However, weight gain (WG) consecutive to smoking cessation is a minor threat on health, compared to the risks of continuing smoking.[1] The tendency to gain weight is higher in women than men, in black people, regardless of their gender, in subjects older than 55 and in heavy smokers.

Teenagers, if pre-occupied with body weight, start to smoke more frequently.[5] This is why there is a need to promote healthy methods of maintaining weight and to dispel the notion of tobacco use as a weight control method for adolescent smokers. Adolescents should be made aware that there are other ways to lose weight that are more effective and healthier, and such messages should be included in educational curricula, especially when discussing quitting smoking.[2]

Data provided by Levine et al. showed weight-concerned women receiving the combination of CONCERNS (cognitive behavioral therapy CBT for smoking-related weight concerns and bupropion SR) were most likely to sustain abstinence at six months (34%

v. 21% in standard CBT and bupropion v. 11.5% in CONCERNS and placebo). This effect was not related to differences in post-cessation WG or changes in weight concerns.[3]

Nicotine replacement therapy and bupropion are efficient in limiting the weight gain described after smoking cessation. In two smoking cessation studies with varenicline compared to bupropion and placebo, the weight gain in the 12-week varenicline treatment group was lower (under 3 kg).[1]

The weight gain is produced by raising calorie supply and decreasing the metabolism ratio. The available data about involvement of metabolic mechanisms suggest that smokers will gain weight during a quit attempt, even though they do not raise the calorie supply.[5] The patient must be informed and prepared about the possibility of gaining weight and must be offered support for weight control, by encouraging him/her to adopt a healthy life style, to practice moderate physical exercise, to consume healthy food rich in fruits and vegetables, to sleep well and to limit alcohol use. A 45-minute exercise programme, three times a week, increases long-term smoking abstinence in women and limits overweight, if also combined with a cognitive-behavioral programme. Weight gain is minimal if smoking abstinence is associated to increasing physical activity.[4]

Personalized weight management support may be effective and may not reduce abstinence, but there are too few data to be sure about this. One study showed a very low-calorie diet increased abstinence but did not prevent WG in the longer term. Cognitive behavioral therapy to accept WG did not limit post cessation WG and may not promote abstinence in the long term. Exercise interventions significantly reduced weight in the long term, but not in the short term. More studies are needed to clarify whether this is an effect of treatment or a chance finding. Bupropion, fluoxetine, NRT and varenicline reduce post-cessation WG while using the medication. Although this effect was not maintained one year after stopping smoking, the evidence is insufficient to exclude a modest long-term effect. The data are not sufficient to make strong clinical recommendations for effective programmes to prevent weight gain after cessation.[5]

Nicotine replacement – in particular 4 mg nicotine gum and 4 mg nicotine lozenge – appears to be effective in delaying post-cessation weight gain. Moreover, it seems there is a dose-response relation between gum use and weight suppression (i.e. the greater the gum use, the less weight gain occurs). Bupropion SR also appears to be effective in delaying post-cessation weight gain. However, once either nicotine gum or bupropion SR therapy is stopped, the quitting smoker gains on average an amount of weight that is about the same as if he/she had not used these medications.

Recommendation

- In those smokers concerned with a possible weight gain after stopping smoking; it is recommended to use varenicline, bupropion or nicotine gum as medication to limit possible post abstinence overweight (level of evidence B).
- Monitoring caloric intake and increasing caloric expenditure is recommended to manage weight gain.

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PART TWO | Chapter 5

Research and Scientific Recommendations for Evaluating Smoking Cessation

"Effective smoking cessation strategies should increase quit rates and counter patient relapse"

5.0 Research and Scientific Recommendations for Evaluating Smoking Cessation

5.1 Criteria for clinical research in smoking cessation

Smoking cessation treatment is now integrated into many health care systems and a significant research effort is under way to improve current success rates. Until recently, results from randomized clinical trials have been reported in many different ways, leading to problems of interpretation. West et al. proposed six standard criteria comprising the Russell Standards (RS).[1] These criteria are applicable to cessation trials where participants have a defined target quit date and there is face-to-face contact with researchers or with clinical staff. These criteria are: (1) follow-up for six months (RS6) or 12 months (RS12) from the target quit date or from the end of a pre-defined grace period; (2) self-report of smoking abstinence over the whole follow-up period allowing up to five cigarettes/day in total; (3) biochemical verification of abstinence at least at the six- or 12-month follow-up point; (4) use of an "intention-to-treat" approach in which data from all randomized smokers are included in the analysis unless they have died or moved to an untraceable address (participants who are included in the analysis are counted as smokers if their smoking status at the final follow-up visit cannot be determined); (5) follow-up of the "protocol violators" and using their true smoking status in the analysis; and (6) collecting follow-up data blind to smokers' allocation to trial group.

Summary of Criteria for assessment of tobacco abstinence for scientific work:[1]

- ***Duration of abstinence:*** *it is appreciated as an abstinence affirmation criterion a timeframe of minimum 6 months since the date set for and the actual achievement of smoking cessation.*
- ***Definition of abstinence:*** *the patient reporting a consumption of < 7cigarettes in the six months since he/she stopped smoking, together with a negative result of the carbon monoxide test in exhaled air. A distinction should be made between abstinence at the moment (peak abstinence) determined at the moment of the medical visit and continuous abstinence, appreciated through serial visits throughout 6-12 month follow-up.*
- **Bio-chemical validation of abstinence:** it is recommended to determine the carbon monoxide (CO) concentration in the exhaled air at each visit; this is mandatory in the end-of-treatment visit.
- ***Intention-to-Treat Analysis****: the abstinence ratio is determined considering all the subjects who received treatment, carried out the complete treatment and attended all follow-up visits. Those patients lost in follow-up (by changing home address, phone number etc.) will be considered as still active smokers, being kept in the smoking cessation central database.*
- ***Protocol Violators:*** *abstinence is confirmed according to criteria 1-4, only if the patients followed the correct treatment – in standard doses, did not add other therapies to the therapeutic scheme by their own, and attended all follow-up visits, with biochemical validation of the smoking status.*
- ***Blinding:*** *Data collection should be done through double-blind methods, when possible.*

5.2 Cost-effectiveness of tobacco dependence therapies

Tobacco control aims to ensure that people can breathe smoke-free, healthy air by banning smoking in indoor public places. Smoking cessation, one of the major components of tobacco control, reduces many health problems by helping smokers to quit. There is a wide range of research demonstrating the effectiveness of smoking cessation interventions. There is also sufficient literature on the cost-effectiveness of smoking cessation based on surveys carried out in many countries. Earlier studies evaluated bupropion and nicotine replacement therapies. One earlier study on the cost-effectiveness of smoking cessation interventions revealed that, compared with other preventive

interventions, smoking cessation was extremely cost-effective.[2] The study was designed for primary care physicians to screen all adult smokers and motivate them to quit during routine visits. Only counselling and NRT were used for the cessation intervention. The average cost was calculated to be USD 3779 per quitter, USD 2587 per life-year saved and USD 1915 for every QALY saved.

Compared to routine strategies for preventing myocardial infarction, smoking cessation intervention was found to be more cost-effective. More than 10,000 GBP per year of life saved is required for the primary prevention of myocardial infarction with drugs such as simvastatin or pravastatin, whereas a smoking cessation intervention, including brief advice and NRT, would cost only several hundred to one thousand GBP.[3,4]

A study done at primary health care settings in Switzerland in 2003 revealed that both bupropion and nicotine patch were cost-effective. The study was performed on two cohorts of heavy smokers; one group received only counselling from a GP, the second group received additional pharmacotherapy. At the end of the study, bupropion and the patch were found as the most cost-effective treatments, followed by, in descending order, spray, inhaler and lastly gum.[5] After the introduction of varenicline, this drug was also evaluated and found to be cost-effective.

The cost of smoking was calculated to be USD 193 billion in the US annually, including USD 97 billion due to lost productivity and USD 96 billion in smoking-related health care expenses.[6] The direct cost of smoking to the UK NHS was GBP 5.2 billion,[7] and the EU Member States' total direct and indirect costs were estimated as being between € 97.7 billion and € 130.3 billion per annum.[8]

In a workplace-based smoking cessation intervention, twelve months cost-saving was calculated as USD 541 for varenicline, USD 151 for bupropion and USD 82 for brief counseling.[9,10]

A meta-analysis carried out in the USA concluded that smoking cessation counseling with supportive contact after discharge is potentially cost-effective and may reduce the incidence of smoking and its associated adverse health events and social costs.[11] Using the data from a meta-analysis of randomized trials, the investigators developed a hypothetical US cohort of smokers hospitalized with acute myocardial infarction and evaluated the cost-effectiveness of smoking cessation counselling coupled with follow-up supportive contact. Its cost-effectiveness was USD 540 per quitting patient in programme costs, USD 4350 per life-year saved and USD 5050 per QALY saved, when all health care costs are considered.[11]

Smoking is the most important risk factor for the development and also for the clinical course of COPD. Therefore, smoking cessation is particularly important for this group. Two studies performed in the Netherlands showed that smoking cessation was cost-effective among patients with COPD. In a systematic review of nine randomized controlled trials on smoking cessation intervention in COPD patients, it was found that average 12-month continuous abstinence rates were estimated to be 1.4% for usual care, 2.6% for minimal counselling, 6.0% for intensive counselling and 12.3% for pharmacotherapy. Compared with usual care, the costs per quality-adjusted life year (QALY) gained for minimal counselling; intensive counselling and pharmacotherapy were € 16,900, € 8200 and € 2400 respectively.[12] The other study was designed to determine the cost-effectiveness of a high-intensity smoking cessation programme (Smoke Stop Therapy; SST) versus a medium-intensity treatment (Minimal Intervention Strategy for lung patients [LMIS]) for chronic obstructive pulmonary disease outpatients. At the end of the study, it was found that the health care cost of SST including the costs of the smoking cessation programme was € 581, versus € 595 in the LMIS. The SST is also associated with a lower average number of exacerbations (0.38 versus 0.60) and hospitalisation days (0.39 versus 1) per patient and a higher number of quitters (20 versus 9) at lower total costs. This leads to a dominance of the SST compared with the LMIS.[13]

In a study carried out in Massachusetts, USA, it was found that comprehensive smoking cessation services result in substantial savings for Medicaid programmes. Comprehensive smoking cessation services including pharmacotherapy, counseling and outreach cost about USD 183 per programme participant in 2010, and estimated savings were USD 571 per participant. This finding indicates that every USD 1 cost in the programme was associated with USD 3.12 in medical savings.[14,15]

In a recent economic evaluation Cantor et. al. (2015) found training for physicians and pharmacists in smoking cessation

to be a highly cost-effective method of supporting cessation in community.[16]

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5.3 Recommendations about implementation of smoking cessation guidelines

A good guideline is really only useful if it is disseminated and implemented in the target population, in accordance with best practice standards.

The most reliable example in Europe to illustrate this applies to the NHS Stop Smoking Services in the UK. By developing a NICE guidance implementation algorithm, smoking cessation guidelines were transformed into a valuable tool for all categories of professionals involved in assisting smokers. Thus, guidance can help national organizations to meet worldwide recognized scientific and national governments' standards for public health, determine national and local organizations within the public sector to meet government indicators and targets to improve health, reduce health inequalities and promote well-being within communities.[1]

Guidelines should be implemented to apply to services delivered within primary and secondary care, pharmacies, local authorities and workplaces, but also to apply to training bodies and health policy- makers.

In order to achieve this goal, the implementation process needs a project leadership structure and a step-by-step approach to do the followings:

- ensure that all relevant groups are aware of the guidelines and are provided access to websites, print-outs etc.;
- working with the relevant specialists groups to compare their current activity with the recommendations contained in the guidelines;[1]
- identify which organizations/hospital etc. will need to change

current way of working in order to align with guidelines and build partnerships with existing networks (such as regional tobacco control networks);
- identify key areas to help implementation, such as local referral pathways to cessation centers, increasing the number of practitioners receiving training and focus on hard-to-reach communities;
- assess how much it will cost to implement the guidelines;
- build an action plan for guideline implementation by working together with local actors and specialists.

To ensure effective implementation, all relevant commissioning, public health, local authority and local priority-setting organizations and representatives should sign up to the action plan, e.g. via a local area agreement. Implementation of the guidance should be reviewed and monitored and results fed back to the most pertinent trust board. Also, it is very important to share experience about guideline implementation with other organizations within various professional or scientific events.[2]

In an experimental study that tested the effectiveness of dissemination interventions to improve implementation of smoking cessation guidelines in maternal and children's health clinics, Manfredi et al. reported post-dissemination improvements over baseline in the sub-population of smokers reporting receipt of provider advice, self-help booklets, videos, posters and an adjunct intervention. Nevertheless, the most significant increases were noticed in the proportion of smokers receiving both booklet and an adjunct intervention.[3]

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PART THREE | Chapter 6

European Standards For Accreditation Of Tobacco Cessation Services and Training in Tobacco Cessation

"Training health care professionals is at the cornerstone of treating tobacco use and dependence"

6.0 European Standards For Accreditation Of Tobacco Cessation Services and Training in Tobacco Cessation

This chapter describes standards for training all health professionals and standards for tobacco cessation services (targeted professional groups to deliver smoking cessation interventions, general standards for training in smoking cessation treatments, authorized training bodies and their responsibility towards cessation, training format and evaluation).

A systematic review and meta-analysis of smoking cessation-training interventions for health professionals conducted by the Cochrane Collaboration provided evidence that training was associated with positive changes to clinical practice.[1]

It is widely recognized that good governance is required in the health care sector. The general public, patients' and third party payers want to have more objective assessments of health service quality. Countries have taken different approaches to maintaining quality and improving standards. In some countries, professional organizations and provider associations try to exercise quality control over members to improve standards for care, often without input from government or society. In other countries, the state exercises rigid control over the health sector, leaving almost no scope for professional judgment – resulting in defensive medicine and unnecessary referrals to higher levels of care. The challenge is to balance the roles of health professionals, government policymakers, members of the public, and other stakeholders in enhancing the quality of, and setting the standards for, the health sector.

A review of available literature identified multiple sources of directives, guidance and evidence, which could be translated into explicit statements of requirements for health services in Europe (See Figure 6.1).

Independent reviews in the USA and Australia have emphasized

Figure 6.1: Overview of European Practice Standards for Health Services

Council of Europe	
Recommendation (1997) 5	Protection of medical data
Safe Medication Practices (P-SPPH/SAFE) 2006	Safe medication practices
Resolution ResAP (2003) 3	Nutritional care in hospitals
Recommendation (2000) 5	Patient participation
Recommendation Rec (2006)7	Patient safety
WHO	
WHO-HEN-OBS 2009	Physicians' skills
Standards for health promotion in hospitals 2004	Health promotion
Checklist to reduce morbidity and mortality in a global population	Surgical safety
A performance assessment framework for hospitals: PATH	Performance indicators
EC directives	
Directive 2005/36/EC	Professional qualifications
Directive 1995/46/EC	Processing of personal data

Continued

Figure 6.1 Continued

Directive 2011/24/EU	Patients' rights in crossborder healthcare
EC research	
Development of pan – European standards and criteria for the inspection of (EU-Blood-Inspection)	Blood establishments
European quality system indicators and methodology on organ donation (ODEQUS project)	Organ donation
Antibiotic Resistance and Prescribing in European Children (APREC)	Antibiotic use
Developing Rational Use of Medicines in Europe (DRUM Europe)	Use of medicines
PROSAFE – Promoting patient safety and quality improvement in critical care	Critical care
Defining best practices in palliative care in Europe (PPP)	Palliative care
International Programme for Resource Use in Critical Care (IPOC) – a methodology and initial results of cost and provision in four European countries.	Critical care
Improving patient safety of hospital care through day surgery (DAYSAFE)	Day surgery
European Union (EU) Care and Management of Services for Older People in Europe Network (CARMEN)	Services for Older People
Best Practice in Access, Quality and Appropriateness of Health Services for Immigrants in Europe (EUGATE)	Minority populations
NGOs	
European Resuscitation Council guidelines 2010	Resuscitation
Union Européene des Médecines Spécialistes (UEMS)	Quality of medical practice
UEMS Bastle Declaration	Continuing professional Developemnt
European charter of Patients' rights www.activecitizenship.net	Patients' rights
EACH Charter for children	Patients' rights
International Association of Gerontology: The Old Person's Charter of Standards	Patients' rights
European Society of Radiology (ESR). Risk management in radiology, 2004	Radiology
European Hospital and Healthcare Federation (HOPE), October 2010	Chronic diseases
CEN	
EN ISO 22870:2006 (POCT) – Rrequirements for quality and competence (ISO 22870:2006)	Chiropractic
EN 16224:2012 Healthcare provision by chiropractors	Point-of-care testing
WS0668001 Health care services – Quality criteria for health checks	Health checks
00414001 Osteopathic healthcare provision	Osteopathy
CEN/TC 403 Aesthetic surgery services	Aesthetic surgery

Continued

Figure 6.1 Continued

ISO 9001 interpretation for health services	Quality management systems
National Standards Authority of Ireland: Health Services Application of ISO 9002 in a hospital environment	
SGS Yarsley International (SGS) in UK: BS EN ISO 9000: Guidance notes for its application to hospitals	
Swedish Standards Institute, Guide (CEN/TS 15224)	
DNV National Integrated Accreditation for Healthcare Organizations – Interpretive Guidelines	
CEN/TC 362 Healthcare services – Quality management systems	

the need for active collaboration between public and private agencies in order to reconcile the conflict between top-down regulation and bottom-up development. A partnership between the public sector and any accreditation agency is essential for accreditation to succeed.[2,3]

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6.1 Recommendations for criteria of standard smoking cessation expertise training

Discussions concerning assistance for smokers to quit must be a mandatory chapter of medical curricula. Training of all categories of professionals involved in this area must be done through training courses given by authorized experts in the field. In a review published by Nancy Rigotti et al. in 2008, the authors report on a scan of smoking cessation training activities in multiple countries.[1] Data collected highlighted the wide variety of approaches and formats of existing training activities as well as multitude of funding sources supporting these training activities. This scan was particularly valuable in drawing attention to the need for standards in specialized training for the treatment of tobacco dependence internationally.

The target population for smoking cessation training includes all smoking cessation service advisers and co-coordinators: doctors, nurses, midwives, pharmacists, dentists, psychologists or quit line counselors and others who advise people on how to quit smoking.

All European authorized bodies responsible for the education and training of healthcare workers who advise people to quit smoking should take action in order to:

- Train all frontline healthcare staff to offer brief advice on smoking cessation in accordance with best available guidance and to make referrals, where necessary and possible, to available publicly funded smoking cessation services;
- Ensure that training on how to support people to quit smoking is part of the core curriculum for healthcare undergraduates and postgraduates;

- Ensure and maintain availability of training and continuing professional development;
- Train all stop smoking service practitioners by using a programme that complies with the best available standards for training in smoking cessation treatments;
- Provide additional, specialized training for those working with specific groups, e.g. people with mental health problems, hospitalized patients and pregnant women who smoke;
- Encourage and train healthcare professionals to ask patients about all forms of tobacco use and advise them of the dangers of exposure to second-hand smoke.

Such authorized training bodies vary across Europe from accredited universities to other governmental or recognized national training structures.

The training standard for smoking cessation covers two main areas: knowledge and skills. The standard applies to the content of the programmes and the intended learning outcomes of trainings.

The UK NHS training standards focus (See Table 6.1) on the minimum elements and modules for delivering smoking cessation interventions at three different levels (brief opportunistic, intensive one-to-one and groups). The training standard provides guidance to trainers over what should be included in the training of smoking cessation advisers. The training format is different for each level, in general the brief opportunistic advice should correspond to curricula for medical university graduates, while intensive one-to-one and groups are based on medicine/psychology/nursing university postgraduates.

Table 6.1: NHS tobacco cessation training assessment standards

1. Evidence of attendance of the training course;
2. Continuous assessment of course work (formative assessment);
3. Testing of key knowledge and skills upon completion of the course;
4. In-service assessment of skills and knowledge, through observation;
5. Provision of evidence of learning and of application to practice through a portfolio of continuing professional development.

The term *minimum content requirements* refers to those elements of the programme that are considered essential to achieve the standard. Each objective is marked K or S to indicate whether it is knowledge or skills-based. This distinction is important because they require different forms of assessment. The former can be assessed by means of written tests at the end of a course, while the latter is more difficult and may require a practical test or observation of practice following the course.

6.2 Recommendations to develop smoking cessation curricula for medical university graduates in Europe

Rationale

Tobacco use is one of the most important public health problems, killing more than 6 million people globally, and this number is set to increase to 8 million at 2030.[2] In Europe alone tobacco kills some 500,000 people every year. Research has shown that half of current smokers will die due to tobacco- related health issues, many of whom will die prematurely.[2] Besides this death toll, tobacco use harms the environment and has an important economic burden. Therefore, there is an urgent need to control tobacco use and reduce the number of smokers. One of the approaches to this end is to help smokers to quit. Many countries implement successful tobacco control programmes, including treatment of patients, and have reduced tobacco use and death toll due to tobacco use.[2]

Content of training programme

- tobacco epidemic in Europe and globally;
- factors initiating tobacco use;
- pharmacological basis of tobacco dependence;
- health hazards due to tobacco use;
- other (e.g. environmental, economic etc.) consequences of tobacco use;

- approaches for tobacco control;
- physician's role in tobacco control;
- tobacco control legislation.

Training methods

Training is theoretical during the first years of medical school, and more practical exercises are done during clinical studies (years 4 to 6). The duration of the theoretical training is 10-12 hours (minimum), integrated in the curriculum of first three years (pre-clinical period) of medical studies. Class lectures, small group discussions, panel discussions or case examples are used for theoretical training. The aim of class training is to increase awareness among students to develop an awareness of tobacco- related issues (See Table 6.2). During the clinical training period, more case studies can be discussed to develop an "anti-smoking" attitude and behaviour. It should be stressed that all physicians should inquire as to the smoking behaviour of all patients (including the smoking behaviour of parents of juvenile patients) and they should advise and help smokers to quit. Therefore, some case studies and treatment of tobacco dependence are discussed during the clinical phase.

Cognitive field

B1: Know (recall, count, define), e.g. knowledge of prevalence of tobacco use, factors effecting prevalence; list the health effects of tobacco use by organs and systems.

Table 6.2: Details of the programme

GENERAL AIMS	TARGETS	Period and Level (*)		
		Preclinical	Clinical	Internship
Information on tobacco use prevalence and factors for initiation	Basic epidemiological properties of tobacco use (person, place, time trends etc.)	B2		
Information on health hazards of tobacco use	Composition of tobacco smoking and effects on health	B1		
	Effects of smoking on respiratory system	B1	B2	
	Effects of smoking on cardiovascular system	B1	B2	
	Effects of smoking on cancer and hematopoietic system	B1		
	Effects of smoking on urogenital system	B1		
	Effects of smoking on pregnancy and children	B1		
Tobacco dependence and its importance for individuals and population	Neurobiological basis of tobacco dependence	B1	B2	
	Cognitive and behavioural aspects of tobacco dependence	B1	B2	
Environmental effects of tobacco use	Indoor air quality and pollutants	B1		
	Environmental pollution, fire hazards	B1		
Social and economic effects of tobacco use	Effects on individuals	B2		
	Effects on community	B2		
Legislation on tobacco control	International level (FCTC Framework Convention on Tobacco Control)	B2		
	National level (national legislation)	B2		

Continued

Table 6.2 Continued

Tobacco control concept and its strategies	MPOWER strategies	B2		
	Relevant national legislation(s), i.e. National Tobacco Control Programme	B2		
Physician's role for tobacco control and relevant behaviour	Non-smoking behaviour as a role model	B2	B2 D2	B3 D3
	Help smokers to quit, implementing 5A and 5R principles	B1	B3 D3	B3 D3
	Evidence-based methods of quitting		B2	
	Cessation in clinical practice			B3
	Prevention of relapse	B2	B3	B3
	Advocacy and leadership for tobacco control		D3	B3
	Beware of and combat tobacco industry manipulations		B3	D3
	Smoking cessation in specific population: surgery, COPD, cardiac, psychiatric disorders			D3
	Role of media in tobacco control	B2		
	Governmental and non-governmental institutions in tobacco control	B2		
Tobacco control in daily life and work with relevant institutions	Governmental and non-governmental institutions in tobacco control	B2		

B2: Understand, implement, analyze, evaluate, e.g. biological and psychological mechanisms of health effects of tobacco use, explain environmental effects and economic burden of tobacco use.
B3: Using knowledge of B2 in implementing in real situations (on patients) (taking history, evaluating and deciding), e.g. implement 5As, offer help to smoker, give information on different treatment options.

Perceptive field

D1: Awareness, e.g. know marketing methods of tobacco industry.
D2: Attitude, e.g. consider the marketing methods of the tobacco industry and the importance of counteracting them.
D3: Behaviour, e.g. make a plan to counteract the marketing methods of the tobacco industry and implement plan.

Evaluation

The effect of the programme is evaluated through pre- and post-tests. A pre-test is given to students before the programme begins (i.e. first year), and a post-test before graduation from school (i.e. final year). The pre- and post-tests comprise multiple-choice questions specific to the targets of the training programme. In addition, written and oral feed-back from students and teachers is given after each course. The students' names are not recorded; group performance is evaluated.

6.3 Recommendations to develop smoking cessation curricula for medical university postgraduates in Europe – Certificate Programme

Rationale

Tobacco use is one of the most important public health problems,

killing more than 6 million people globally, and this number is set to increase to 8 million at 2030.[2] In Europe alone tobacco kills 500,000 people every year. Research has shown that half of current smokers will die due to tobacco-related health issues, many of whom will die prematurely.[2] Besides this death toll, tobacco use harms the environment and has an important economic burden. Therefore, there is great need to control tobacco use to reduce the number of smokers. One of the approaches to this end is to help smokers to quit.

Many countries implement successful tobacco control programmes, including treatment of patients, and have reduced tobacco use and death toll due to tobacco use.[2]

Aims of training programme

The aim of the training programme is to teach prevention, diagnosis and treatment of tobacco dependence to the participants. By the end of the training, the participants are expected to be able to operate a smoking cessation centre. To achieve this aim, the following topics are discussed within the scope of the programme:

- tobacco epidemic,
- factors initiating tobacco use;
- pharmacological basis of tobacco dependence;
- health hazards of tobacco use;
- other (i.e. environmental, economic etc.) consequences of tobacco use;
- approaches for tobacco control;
- physician's role in tobacco control;
- tobacco control legislation (international and national);
- tobacco control services in the country;
- establishing and operating a smoking cessation centre.

Training methods

The programme is conducted in two parts: distance learning and face-to-face learning. The teaching material is available on the web page, and participants are able to access the web page using their password for a defined number of days. They are expected to complete the reading materials and take an examination upon completion. Those who pass the examination receive a two-day face-to- face training. This programme is organized by the Ministry of Health or authorized universities. The maximum number of participants is 25.

Details of the face-to-face training programme:

- pre-test, participants' expectations, programme training targets;
- epidemiology of tobacco use, national figures and trends;
- tobacco use among special groups: children and youth, women, pregnant women, patients with morbidities, health personnel;
- tobacco dependence, mechanisms, measuring the level of dependency: Fagerström Test for Nicotine Dependence (FTND), European Medical Association Smoking and Health (EMASH) criteria;
- approaches to intervening with smokers: 5As and 5Rs;
- resistant/problem cases, heavy smokers, light smokers, smokers with co-morbidities etc.;
- psychosocial support;
- pharmacological treatment, including first line pharmacotherapies;
- legislation: tobacco control legislation, legislation for tobacco

Figure 6.2: An example of a training program on smoking cessation for health professionals in Turkey

The programme was conducted by the Turkish Thoracic Society with financial support from the International Pfizer Foundation (Tobacco Control and Policy Micro-Grants). The standardized "modular" training programme was prepared by the members of Tobacco Control Working Group of the Turkish Thoracic Society. Then a group of 40 chest physicians were trained as trainers, forming the central training team. The training programme was made accessible to all members of the Society via electronic media. A total of 765 participants completed the e-training module. The aim of this e-course was to integrate the first two As (Ask and Advise) of the 5A principles into their daily clinical practice. At the end of each module, participants answered the questions on the main points of the module. After completing the e-training course, participants wishing to improve their practice attended a face-to-face training lasting one day (in fact all 765 participants attended the face-to-fact training). These training programmes were conducted by the members of the central training team in 18 provinces of Turkey. At the end of theses field training programmes, participants developed their capacity to deal with smokers and help them quit by implementing scientific methods of smoking cessation. All participants rated the programme as very good and good with regard to both the content and the relevance of the course.

control centers (physical capacity, manpower etc.;
- case studies role play etc.;
- visit to cessation centre;
- post-test and evaluation of training,, participants' recommendations for future programmes.

Evaluation

Success is evaluated by means of pre- and post-tests and successful participants receive certification from the Ministry of Health or other governing body. Verbal feedback is also given. Certified physicians are entitled to set up and operate a smoking cessation centre.

Training programme for chest physicians

The ERS had published a monograph on smoking cessation in patients with COPD in 2007 and a new version will be soon available.[2,3] Figure 6.2 reports on the Turkish experience in the field.

References

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6.4 Recommendations to develop smoking cessation curricula for other categories of professionals involved in delivering smoking cessation in Europe: psychologists, nurses, health policy-makers

Besides doctors, all categories of personnel working in tobacco cessation centres or involved in assisting smokers need to have basic knowledge and skills about treating tobacco use and dependence. This is vital to ensure best practices for quitting tobacco. A basic smoking cessation training module is thus recommended for: nurses, midwives, psychologists, facilitators, social workers and pharmacists or any other category of staff assisting smokers to quit, depending on the regulations in force in each country.

Curricula should comprise minimum teaching content about tobacco-related disorders, the neurobiology of nicotine addiction, tobacco dependence (to address physiological and psychosocial factors), smoking and quitting processes, types of cessation interventions, assessment of smokers and evidence-based tobacco use therapies.

Training needs to be supported by governmental systems, which ensure that health professionals have access to it. This is an issue for national health authorities' commissioners and managers, who should fund smoking cessation training as a core health care activity. In order to better understand these needs and better design such programmes, we strongly advise that a minimum smoking cessation training module should also be offered to professionals in positions of authority. By acquiring elementary notions about tobacco-related morbidity and mortality and also about the cost-effectiveness of tobacco prevention and cessation therapy, health policy-makers will become more aware of the magnitude of the problem and will set priorities accordingly in order to improve the situation.

Training level 2 is suitable for all health professionals. Training level 1 is designed for those wishing to become tobacco cessation specialists.

Recommendations

- Smoking and smoking cessation should be part of the core curriculum of the basic training for all health professionals working with smokers.
- Training should be a core part of a smoking cessation program for all health authorities. Protected time and funding should be built into this programme (level of evidence B).
- Smoking cessation should be funded and prioritized within existing training budgets (level of evidence B).

References

1. West R., McNeill A., and M. Raw. Smoking cessation clinical guidelines for health professionals: an update. Thorax 2000;55;987-999.

6.5 Training standards for tobacco cessation clinicians

Background

Tobacco cessation is often a complex treatment, and there are many different training methods for cessation skills. Although tobacco dependence has many characteristics in common wherever in the world it is described, the environment and culture surrounding the user may differ substantially. Health care systems may also differ, both regarding their resources and their priorities. In the following section, we refer to cigarette users, as smoking tobacco is the most prevalent tobacco product used. Cessation of other tobacco products is much less well researched, but the methods used for smoking cessation are usually applied when dependent users of other tobacco products require assistance with quitting. Tobacco cessation does not necessarily have to be part of the health care service, but the training scheme proposed here is targeted at health professionals.

Smoking cessation skills should be trained in clinicians who are able to devote time and resources to smoking cessation, including follow-up time of at least six months.

Content of training

Training is offered over three days:

1. Basic certificate (2 days) In order to qualify, presence is mandatory for the first two days of the course. Content: 50% theory, 50% practice (behavioural-cognitive therapy motivational interviewing and practice of tobacco cessation).
2. Advanced certificate (1 day follow-up) In order to qualify for the advanced certificate, the following is required in addition to the basic certificate:
   - one day (3rd day) of follow-up three to six months after basic training (cf. above);
   - a written test of knowledge, about 30 minutes, staring on day 3;
   - 3 patient cases, written clinical reports, observing a template;
   - 3 supervised sessions in group or individual counseling (live or by telephone).

The advanced certificate is awarded when all parts are successfully completed, i.e. 2+1 days of training, the written test, three written patient cessation records (of which at least one is followed up for 2 months) plus three supervised cases (group or individual, live or by telephone). The advanced certificate must show that the training has been performed observing national standards for cessation training (cf. below). A special logotype can be issued to prove that the training has followed the national standard (including a detailed description). A certificate of the basic training, if appropriate, should preferably be less elaborate and should be clearly distinct from the advanced certificate.

Mandatory content of training curriculum

Content of basic training (days 1 and 2)

T=theory and P= practice

- **T** Introduction: An overview of the major health consequences of tobacco use, costs, dependence, and an overview of the different aspects of tobacco prevention and tobacco use.
- **T** Risk of tobacco use in more detail and benefits of stopping.
- **T** Methods for tobacco cessation (Cochrane Library, www.treatobacco.net), methods for evaluation of outcome.
- **P** Methods for counselling and training sessions.
- **P** Tobacco cessation in practice, individual counselling procedures, relapse prevention, follow-up and training sessions.
- **T** Tobacco dependence, withdrawal, pharmacotherapy.
- **T** Methods for different settings/groups, materials and other resources.
- **T** Optional content, such as: legislation, tobacco advertising and/or global issues.

Content of follow up (day 3)

Compulsory items:

1. Knowledge test: 0.5 h, 10 questions, 5 multiple choice + 5 essay questions.
2. Group treatment: Discussion with questions and answers for 2.5 h on planning, the role of the group leader, structure of the meetings, issues of recruitment and composition of the group, documentation.
3. Individual treatment: Exchange of experiences/discussion in small groups from patient cases and from case studies

provided by the students (2 h).

Optional discussions:

4. Issues of the day (1 h), i.e. new regional survey results, water pipe smoking, other tobacco products, new legislation, ETS(environmental tobacco smoke), pharmacological therapy, youth/schools, gender, global issues, and new material.

Evaluation of training

The participants should be given an opportunity to evaluate (a) the two first days of the training and then (b) all three days to cover the whole course.

I. Training modules that should be part of the evaluation of days 1 and 2.

Questions about:

1. Background, setting/profession.
2. Content of theoretical part.
3. Content of practical part.

II. Training modules that should be part of the evaluation of day 3.

Questions about:

- Content of theoretical part, day 3
- Content of practical part, day 3
- Coaching between days 1-2, and day 3 – organization and content.
- Training as a whole
- How many patients have you treated since the basic training (days 1 and 2)?

Material to use in the training:

- Set of questions for the knowledge test
- Templates for responding to home lessons and for recording of patients
- Written patient cases to use in discussions
- Information (presentation) on pharmaceuticals
- Information (presentation) on how to follow up and evaluate reactivation.

Clinicians who want to reactivate dated skills should be offered day 3 of the above plus coaching and should be asked to present three written patient cases, which can qualify them for award of the advanced certificate.

Authorization to conduct training courses for tobacco cessation

A national board of experts should be established with the authority to evaluate proposals for courses. A detailed programme and a description of the competencies of the teachers and instructors must be examined by the national board. After any necessary adjustments a new course can be approved.

6.6 Quality standards in tobacco dependence treatment

Definition

A Tobacco Dependence Treatment Specialist (TDTS)1 is a professional who possesses the skills, knowledge and training to provide effective, evidence-based interventions for tobacco dependence treatment, across a range of intensities. The TDTS may have various professional affiliations and may work in a variety of settings including, but not limited to, hospitals, community health centres, health maintenance organizations (HMOs), medical and dental practices, educational settings, social service agencies, public health organizations, tobacco treatment centres, telephone quitlines, drug abuse treatment programmes and mental health centres. The TDTS may engage not only in providing treatment, but also in educating others (health care professionals, administrators, scientists, smokers and non-smokers) about tobacco dependence treatments.

Role and responsibilities of the Tobacco Dependence Treatment Specialist

Tobacco dependence – knowledge and education

Provide clear and accurate information about tobacco use, strategies for quitting, and the scope of the health impact on the population, the causes and consequences of tobacco consumption.

1. Describe the prevalence and patterns of tobacco use, dependence and cessation in the country and region in which

the treatment is provided, and how such rates vary across demographic, economic and cultural sub-groups.
2. Explain the role of treatment for tobacco use and dependence within a comprehensive tobacco control programme.
3. Utilize the findings of national reports, research studies and guidelines on tobacco dependence treatment.
4. Explain the societal and environmental factors that promote and inhibit the spread of tobacco use and dependence.
5. Explain the health consequences of tobacco use, but also the benefits of quitting and the basic mechanisms of the more common tobacco-induced disorders.
6. Describe how tobacco dependence develops and be able to explain the biological, psychological and social causes of tobacco dependence.
7. Summarize and be able to apply valid and reliable diagnostic criteria for tobacco dependence.
8. Describe the chronic relapsing nature of tobacco dependence, including typical relapse patterns and predisposing factors.
9. Provide information that is gender, age and culturally sensitive and appropriate to learning style and abilities.
10. Identify evidence-based treatment strategies and the pros and cons for each strategy.
11. Be able to debate alternative therapies such as harm reduction, hypnosis, acupuncture, cigarette tapering.
12. Demonstrate ability to access information on the above topics.

Counselling skills

Demonstrate effective application of counselling theories and strategies to establish a collaborative relationship and to facilitate client involvement in treatment and commitment to change.

1. Demonstrate effective counseling skills, such as active listening and empathy that facilitate the treatment process.
2. Demonstrate establishing a warm, confidential and non-judgmental counseling environment.
3. Describe and demonstrate use of an evidence-based method for brief interventions for treating tobacco use and dependence, as identified in current guidelines.
4. Describe the use of models of behavior change including motivational interviewing, behavioral- cognitive therapy and supportive counseling.
5. Demonstrate the effective use of clinically sound strategies to enhance motivation and encourage commitment to change.
6. Demonstrate competences in at least one of the empirically supported counseling modalities such as individual, group and telephone counseling.

Assessment interview

Conduct an assessment interview to obtain comprehensive and accurate data needed for treatment planning.

1. Demonstrate the ability to conduct an intake assessment interview including:
   (a) tobacco use history;
   (b) validated measures of motivation to quit;
   (c) validated measures for assessing tobacco use and dependence;
   (d) current challenges and barriers to attaining permanent abstinence;
   (e) current strengths to support abstinence;
   (f) prior quit attempts including treatment experiences, successes and barriers;
   (g) availability of social support systems;
   (h) preferences for treatment;
   (i) cultural factors influencing making a quit attempt.
2. Demonstrate the ability to gather basic medical history information and conduct a brief screening for psychiatric and substance abuse issues.
3. Describe when to consult with primary medical care providers and make appropriate referrals before treatment planning is implemented.
4. Describe the existing objective measures of tobacco use such as CO monitoring and cotinine level assessments.

Treatment planning

1. Demonstrate the ability to develop an individualized treatment plan using evidence-based treatment strategies.
2. In collaboration with the patient, identify specific and measurable treatment objectives.
3. Plan individualized treatments that account for patient assessment factors identified during the intake assessment

and history gathering.

4. Collaboratively develop a treatment plan that uses evidence-based strategies to assist the patient in moving toward a quit attempt and/or continued abstinence from tobacco.
5. Describe a plan for follow-up to address potential issues including negative outcomes.
6. Demonstrate the process to make referrals to other health care providers or to recommend additional care.

Pharmacotherapy

Provide clear and accurate information about pharmacotherapy options available and their therapeutic use.

1. Describe the benefits of combining pharmacotherapy and counseling.
2. Provide information on correct use, efficacy, adverse events, contra-indications, known side effects and exclusions for all tobacco dependence medications approved by national regulatory agencies.
3. Identify information relevant to a client's current and past medical, psychiatric and smoking history (including past treatments) that may impact pharmacotherapy decisions.
4. Provide appropriate patient education for therapeutic choices and dosing for a wide range of patient situations.
5. Communicate the symptoms, duration, incidence and magnitude of nicotine withdrawal.
6. Describe the use of combinations of medications and higher dose medications to enhance the probability of abstinence.
7. Identify second-line medications and be able to find information about them as needed.
8. Identify possible adverse reactions and complications related to the use of pharmacotherapy for tobacco dependence, making timely referrals to medical professionals/services.
9. Demonstrate ability to address concerns about minor and/or temporary side effects of these pharmacotherapies.
10. Demonstrate ability to collaborate with other healthcare providers to co-ordinate the appropriate use of medications, especially in the presence of medical or psychiatric comorbidities.
11. Provide information about alternative therapies based upon recognized reviews of effectiveness.

Relapse prevention

Offer methods to reduce relapse and provide on-going support for tobacco-dependent persons.

1. Identify personal risk factors and incorporate into the treatment plan.
2. Describe strategies and coping skills that can reduce relapse risk.
3. Provide guidance in modifying the treatment plan to reduce the risk of relapse throughout the course of treatment.
4. Describe a plan for continued aftercare following initial treatment.
5. Describe how to make referrals to additional resources to reduce risk of relapse.
6. Implement treatment strategies for someone who has lapsed or relapsed.

Approaching difficult/special categories of smokers

Demonstrate competence in working with various population sub-groups and with those categories of smokers having special health problems.

1. Provide culturally competent counseling.
2. Describe specific treatment indications for special population groups (i.e. pregnant women, adolescents, young adults, elderly, hospitalized patients, those with comorbid psychiatric, chronic respiratory, etc. conditions).
3. Demonstrate an ability to respond to high-risk client situations.
4. Make effective treatment recommendations for non-cigarette tobacco users.
5. Describe recommendations for those exposed to environmental tobacco smoke pollution.

Documentation and evaluation

Describe and use methods for tracking individual progress, record-keeping, programme documentation, outcome measurement and reporting.

1. Maintain accurate records utilizing accepted coding practices that are appropriate to the setting in which services are provided.
2. Develop and implement a protocol for tracking client follow-up and progress.

3. Describe standardized methods of measuring recognized outcomes of tobacco dependence treatment for individuals and programmes.

Professional resources

Utilize resources available for client support and for professional education or consultation.

1. Describe resources (web-based, community, quitlines) available for continued support for tobacco abstinence of patients.
2. Identify community resources to refer any concomitant medical, psychiatric or psycho-social conditions.
3. Name and use peer-reviewed journals, professional societies, websites and newsletters related to tobacco dependence treatment and/or research.
4. Describe how patients can explore reimbursement for treatments.

Law and ethics

Consistently use a code of ethics and adhere to government regulations specific to the health care or work site setting.

1. Describe and use a code of ethics established by your professional discipline for tobacco dependence treatment specialists, if available.
2. Describe the implications and utilize the regulations that apply to the tobacco treatment setting (confidentiality, privacy, work site specific regulations).

Professional development

Assume responsibility for continued professional development and contributing to the development of others.

1. Maintain professional standards as required by professional license or certification.
2. Utilize the literature and other formal sources of information/ inquiry to keep up to date in tobacco dependence treatment knowledge and skills.
3. Describe the implications of current research to the practice of tobacco dependence treatment.
4. Disseminate knowledge and findings about tobacco treatment with others through formal and informal channels.

References

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6.7 Requirements for accreditation of specialized tobacco cessation service

Tobacco cessation service (TCS)[1] is defined as any place where a health professional practices to treat tobacco dependence as the goal or as one of the goals of the service.

According to the e.SCCAN estimate there are 2500 tobacco cessation services in Europe.[2] All these services state that tobacco cessation is one of the goals of the heath service. Tobacco cessation services have a role to do the followings:

- treat tobacco dependence cases and focus or more difficult cases;
- educate/train health professionals about tobacco cessation;
- research/evaluate tobacco cessation interventions;
- disseminate good practices in smoking cessation among health professionals and the general population and eliminate bad practices;
- promote health.

6.7.1 Three levels of tobacco cessation services[2]

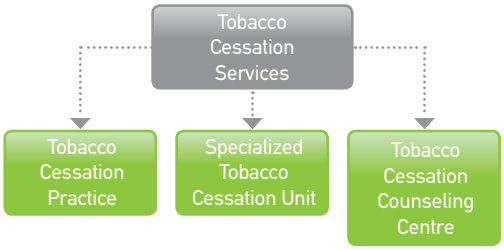
The definition of tobacco cessation services covers three sub-groups:

- tobacco cessation units;
- tobacco cessation specialist's practices;
- tobacco cessation counseling centres.

Specialized tobacco cessation units (STCU)

STCU is a centre dedicated to smoking cessation with a minimum of one doctor and two health professionals, one being a tobacco cessation specialist, with full availability of medication prescription and behavioral support, CO monitoring testing facilities for all patients, standard medical record keeping, standard procedures for follow-up and evaluation of the activity.

Figure 6.3: The three levels of tobacco cessation services (adapted from e.SCCAN)[2]



Tobacco cessation specialist's practice (TCSP)

TCSP is a medical practice dedicated in part or full time to tobacco dependence treatment with the ability to prescribe medication, but without the full range of options offered by a tobacco cessation clinic.

Tobacco cessation counselling centre (TCCC)

TCCC is a centre dedicated to tobacco dependence treatment, where the presence of a tobacco cessation specialist is required, but not the presence of a medical doctor. It usually has the presence of a psychologist, nurse or other health professional acting as counselors. Prescription of medication is not provided, but advice on pharmacological support is available.

See Figure 6.3.

Like all other places where tobacco cessation is performed, such as GP practices, pharmacies etc., TCS have to follow best practice guidelines for tobacco dependence treatment. In order to obtain accreditation as a specialized tobacco cessation service, it is compulsory to meet the requirements detailed below.

6.7.2 Accreditation of specialized tobacco cessation units

Centers accredited as specialized tobacco cessation units are strongly advised to have optimum human and material resources.[3] These units must demonstrate criteria of excellence in relation to healthcare, teaching and research.

Human resources

- According to scientific evidence a team of more than one health professional increases cessation success rates.[3]
- A multi-disciplinary team including doctors, nurses, psychologists, dieticians is optimal to cover the needs of most tobacco users during cessation.
  - A tobacco (smoking) cessation specialist is needed in each tobacco cessation service. According to WHO, a tobacco cessation specialist is someone who is trained and paid to deliver skilled support to smokers who need help to quit smoking, over and above brief punctual advice; the personnel involved needs not to be medically trained.
  - Medical doctors may cover all tasks in the tobacco cessation service.
  - Non-medical health professionals may provide behavioral support and tobacco cessation training in a medical team or in a non-medical unit.
  - Non-health professionals trained in tobacco dependence may play a specific role under supervision.
  - Specialized health professionals such as midwives in maternity wards, anesthetists in surgery, psychiatrics for tobacco users with mental disease, may play a specific role in specific populations.
- Staff has to be sufficient to ensure a first visit not later than three weeks after a request for tobacco dependence treatment has been received.
- The centre is staffed by a multi-disciplinary team of health care professionals specialized in tobacco dependence treatment. Such professionals are defined as healthcare workers highly qualified in this field and expert in their capacity to prevent, diagnose and treat smoking/tobacco dependence, which work full time and are paid for these activities.
- It is necessary for the healthcare professionals who operate this specialized smoking cessation units to be able to accredit adequate training in the prevention, diagnosis and treatment of smoking/ tobacco dependence.
- Ideally, the centre should also have administrative personnel to attend to and channel patient calls and to maintain the corresponding patient records and conduct the relevant administrative functions.
- The availability of these resources must be adequately

documented. Certification will be requested from some competent authority demonstrating the existence of a multidisciplinary team with the specified characteristics and working full time in the centre. Likewise, certification is required of adequate training in the prevention, diagnosis and treatment of smoking.

Material resources

- Proprietary rooms available on a full time basis: consulting room, exploration room, administrative office, waiting room and meeting room.
- Computer supported databases and files for specific documentation on smoking and tobacco consumption.
- Specific smoking/tobacco consumption clinical records.
- Clinical intervention protocols.
- Self-help material.
- Proprietary office material.
- Audio-visual projection material.
- Clinical material: stethoscope, blood pressure recorded, device to measure CO in exhaled air, spirometry, electrocardiography, patient height and body weight measuring systems (including calculation of body mass index, BMI). Samples or display of medication.
- Possibility of measuring nicotine or cotinine in body fluids.
- Dedicated contact phone number of the service.

The availability of these resources must be adequately documented.

Table 6.3: Questionnaires for tobacco cessation services

Self-assessment questionnaires mandatory:
- Profile of tobacco use,
- Tobacco dependence test: Fagerström test.
Self-assessment questionnaires recommended:
- Mood assessment questionnaire (HAD or other),
- Questionnaire on motivation to quit and/or perceived barriers.
Non self-administered questionnaire:
- Questionnaire such as the Beck Depression Inventory (BDI).

Certification is requested from the competent authority demonstrating the availability for own use of clinical material and computer- supported databases and files for specific documentation on smoking/tobacco consumption. The possibility of measuring nicotine and cotinine in body fluids must also be documented.
Presentation of a specific smoking clinical record is required, together with specific questionnaires, clinical intervention protocols and self-help materials.

Categories of tobacco users that should be referred to tobacco cessation services

High-risk tobacco users

The main role of tobacco cessation services is to ensure a high standard of treatment for high-risk tobacco users, such as pregnant women, smokers with planned elective surgery, smokers with underlying psychological, cardiovascular, respiratory diseases and cancer patients, tobacco users with other addictions (alcohol and other drugs), socially disadvantaged smokers and smokers who have a history of unsuccessful aided quit attempts.

All tobacco users

All tobacco users who need assistance in their quitting process could be referred to tobacco cessation services by health professionals, quit lines or social services or can access these services on their own.

Specific public

Tobacco cessation services may be specialized for one target group, such as pregnant women, adolescents or tobacco users addicted to other substances. In these cases the specificity of that tobacco cessation service has to be clearly stated.

Healthcare activities

Accreditation as a specialized smoking cessation unit is based mainly on quality health care criteria. The criteria defining quality in the prevention, diagnosis and treatment of smoking/tobacco dependence are as follows:
Healthcare is to be provided in three formats:

- Individualized,

- Group,
- Telephone-based.

The centers must have individualized, group and telephone-based management protocols. These protocols must contemplate a minimum of visits in the course of the follow-up, which should extend for at least 12 months after quit-date.

- In the case of individualized visits, the patients are seen at least six times, and each visit lasts no less than 15 minutes. The first visit will last no less than 30 minutes.
- In the case of group consultations, patients will be seen over the course of a 5 to 9 group sessions with a duration of between 45 and 90 minutes.
- Telephone-based consultations should be conducted in those cases where the patient has difficulties to visit the centre, in those cases where only less intensive intervention is required, or in those cases where point and direct intervention is needed.

The healthcare activity is to be carried out by a multidisciplinary team of physicians, nurses and psychologists. All of them are to be qualified experts in the prevention, diagnosis and treatment of smoking.

The healthcare activities of these units should not be confined to the actual centre; in effect, the professionals of the unit should be willing and capable to address and resolve the consultations made by other healthcare professionals treating tobacco users with specific difficulties.

Presentation is required of the necessary documentation demonstrating the existence of healthcare protocols that satisfy the commented characteristics. Documentation is to be presented, issued by the competent authorities, disclosing the following data: number of new patients seen per year (minimum required number = 300), number of check-ups carried out per year (minimum required number = 1000), number of CO measurements performed per year (minimum required number = 1000), number of determinations of nicotine and/or cotinine in body fluids made per year (minimum required number = 100), number of spirometric explorations made per year, and number of ECG studies made per year.

Table 6.4: Example of organization of smoking cessation visits

First visit:
- should be face-to-face and/or could take place in the frame of a group visit;
- is the occasion to access the tobacco user, record tobacco use and to educate on tobacco products, health consequences of tobacco use and on cessation;
- should be extensive: 30-60 minutes.
Follow-up visits:
- number of follow-up visits lie usually between 5 and 9 visits, e.g. at weeks 2, 4, 8, 12, 26 but other schemes are also possible, e.g. an additional visit at W1 or a visit after 1 year;
- duration is generally 15-30 minutes;
- may be improved by telephone support, Internet support and testing as well as non-lanned visits;
- have to be adapted in duration and support to the individual situation and needs

Tobacco cessation services respect international and national best practice guidelines for tobacco cessation. Tobacco cessation services respect general good practice in all procedures, respect the rights of patients and commit to data protection rules.

Likewise, documentation is to be presented, issued by the competent authorities, attesting co- ordination of activities of the centre with other centers or departments in aspects related to smoking prevention and treatment.

The tobacco cessation service should disseminate good practice of tobacco dependence treatment and tobacco prevention to other health services and to the public at large.

Teaching activities

- It is strongly recommended for the health professionals at specialized smoking cessation units to have sufficient qualification and accreditation to conduct teaching activities related with the prevention, diagnosis and treatment of smoking in faculties of medicine, psychiatry and health sciences, as well as in nursing schools.

- These units should also be able to meet training requirements of other healthcare departments. The professionals belonging to the unit should be able to impart training courses for the prevention and control of smoking, targeted to other healthcare professionals with less training in these areas.
- The specialized smoking cessation units must be prepared to accept the responsibility of providing training in the prevention, diagnosis and treatment of smoking for residents in training in the specialties of respiratory medicine, family and community care medicine, preventive medicine and public health, or other clinical-surgical specialties, and also for residents in psychology.

Presentation is required of the necessary documentation demonstrating that some of the healthcare professionals working full time in the centre have the academic qualifications needed to teach undergraduates. Honorary collaborating lecturers, private university lecturers, contracted lecturers, associated professors, assistant university professors and university rectors will be especially valued in this respect.

The tobacco cessation service should disseminate good practice of tobacco dependence treatment and tobacco prevention to other health services and to the public at large.

The presentation of documentation issued by the competent authorities, indicating that the centre routinely undertakes teaching activities for ongoing training of healthcare professionals in aspects related to the prevention, diagnosis and treatment of smoking will likewise be particularly valued. The number of courses, conferences and other teaching meetings held by the members of the centre in the last two years must be specified. At least four ongoing training activities must have been carried out each year in order to obtain accreditation as a specialized smoking cessation unit.

Certification from the teaching commission of a healthcare centre or hospital confirming that the residents in training in medicine or psychology rotate through the unit will be particularly valued.

Research activities

The specialized tobacco cessation unit must show adequate research activity in the form of epidemiological and clinical research or basic research studies.

Tobacco cessation services have to assess their activity and provide data. Data provided will inform possible research projects and improve the practice of tobacco dependence diagnosis, prevention and treatment.

Tobacco cessation services may participate in academic research. With the support of an accredited body, tobacco cessation services may participate in management or academic research.

Tobacco cessation services should report on their activities annually, specifically ensuring that:

- The number of new patients and follow-up visits are recorded;
- The six-month checked tobacco cessation status is recorded for all patients who visit the tobacco cessation service;
- Standardized computer records for tobacco cessation recording are used.

For Gold Level accreditation, the necessary documentation demonstrating the research activity of the unit in the past five years must be presented. The following documentation must be submitted: scientific publications (at least three in national or international journals), communications at international congresses (at least three), and communications at national congresses (at least six).

Role of tobacco cessation services in health promotion

TCSs have to promote healthy lifestyles without tobacco among the general public, among tobacco users with or without associated disease. They should do so for patients who attend the service and within the community.

Recommendation:

When implementing the standardized European accreditation system based on common ENSP - Quality Standards we should be aware and we should respect the diversity of the 53 Member States in the WHO European Region4 with different structures and organizations in their health and educational systems.

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Table 6.5: Smoking Cessation Self Audit evaluation

Tobacco Cessation service Self audit		No implementation (0)	Some implementation (0)	Half implementation (0)	Near totally implementation (0)	Yes fully (0)	Non applicable (NA)	Observations
1. The tobacco cessation service states clearly that the service is dedicated to caring for tobacco users and conducting tobacco cessation								**GOAL**
1.01	Word "tobacco" (or equivalent) is present on print document of TCS and on the building entrance	0	1	2	3	4	NA	
1.02	Word "tobacco" (or equivalent) is present on internet presentation of service	0	1	2	3	4	NA	
1.03	A specific phone number exists to reach a tobacco cessation health professional staff of the TCS	0	1	2	3	4	NA	
1.04	If roster of TCS exists at regional or national level, TCS is on the list	0	1	2	3	4	NA	
2. Tobacco cessation service makes best effort to have sufficient human and materiel resources to accomplish his mission								RESOURCE
2.01	Staff time is sufficient to insure less 3 weeks delay for a first visit	0	1	2	3	4	NA	
2.02	All staff is well trained in smoking cessation	0	1	2	3	4	NA	
2.03	At least half of the staff is certified as tobacco cessation specialist	0	1	2	3	4	NA	
2.04	Prescription is fully available	0	1	2	3	4	NA	
2.05	There is a quiet room >10m2 for consultation	0	1	2	3	4	NA	
2.06	There is one CO tester/600 visit a year	0	1	2	3	4	NA	
2.07	There is computer in consultation room	0	1	2	3	4	NA	
2.08	Self-evaluation questionnaires such as Fagerstrom Nicotine Dependence test	0	1	2	3	4	NA	
2.09	There is available medication or display or medication to show to smoker	0	1	2	3	4	NA	
3. TCS receives all smokers, but cares for the more severe case. If service decides to receive only specific population, e.g. pregnant women, this decision is clearly indicated.								PUBLIC

Continued

Table 6.5 Continued

3.01	>50% of new patients have comorbidity, co-addiction, pregnancy or low incomes	0	1	2	3	4	NA	
3.02	Specificity of population who may access to the TCS are clearly stated (NB: 4 if no restriction to access)	0	1	2	3	4	NA	
4. Tobacco cessation service respect best practice and validated guidelines related to smoking cessation.								BEST PRACTICE
4.01	Recommendations of good practice are listed and applied	0	1	2	3	4	NA	
4.02	First visit time duration is at least ½ hour	0	1	2	3	4	NA	
4.03	TCS disseminate good practice of cessation for health professionals who are not tobacco cessation specialists	0	1	2	3	4	NA	
5. Tobacco cessation service participates in the education and training of health professional on smoking cessation								EDUCATION
5.01	TCS participate in the education of medical doctors on tobacco dependence evaluation and tobacco cessation	0	1	2	3	4	NA	
5.02	TCS participate in the education and training of non-medical health professionals on tobacco cessation	0	1	2	3	4	NA	
6. Tobacco cessation service record and provide data local and/ or national evaluation of smoking cessation								RESEARCH
6.01	TCS record and provide data local and/ or national evaluation of smoking cessation	0	1	2	3	4	NA	
6.02	TCS participates in academic research on tobacco dependence	0	1	2	3	4	NA	
7. Tobacco cessation service conduct on routine base actions of health promotion in connection with the community								HEALTH PROMOTION
7.01	TCS conduct this year or past year action in health promotion	0	1	2	3	4	NA	
8. Tobacco cessation service asses his activity and proceed to continuous improvement according to feedback of assessment								EVALUATION
8.01	6 month abstinence is recorded and assessed	0	1	2	3	4	NA	
8.02	Statistic of result of smoking cessation are available	0	1	2	3	4	NA	
TOTAL /100								
CENTER				**DATE**			**TOTAL**	

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