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Smoking cessation in the management of Chronic Obstructive Pulmonary Disease (COPD): narrative review and recommendations

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Abstract

Background. The percentage of smokers who develop COPD (Chronic Obstructive Pulmonary Disease) peaks at 40-50% in most recent publications.

Summary. Tobacco smoke remains the main cause of COPD, though smoking-related limitation of the flow is rather subjective. For patients who keep on smoking, general practitioners (GPs) and pulmonologists should be able to offer smoking cessation programs as an important part of COPD treatment. This narrative article aims to provide the scientific basis to help healthcare professionals develop this therapy; with this aim in mind, the authors have analyzed the most recent literature.

Key messages. Only 3% of smokers who try to quit without availing themselves of any support succeed. Effective smoking cessation methods are counselling and pharmacotherapy, which, combined together, are credited with a 24% success rate. Although there are no therapeutic novelties with strong scientific evidence for smoking cessation, it is however advisable to keep the literature updated to new devices and new digital therapies.

Key words
- COPD
- smoking cessation
- counseling

INTRODUCTION

Tobacco smoking is one of the most serious, frequently avoidable, non-infectious cause of death in the world. According to data released by the World Health Organization (WHO), there are 1.3 billion smokers in the world and more than 8 million deaths from smoking-related diseases every year [1]. About 50% of cigarettes smokers die prematurely; the loss of lifespan due to tobacco-related diseases compared to non-smokers is about ten years. This appears to be caused by a failure to implement effective primary and secondary tobacco prevention programs [2, 3]. Smoking is an addictive condition with a high risk of causing other diseases [4]. This narrative review aims to provide the scientific basis to help healthcare professionals develop effective tobacco quitting therapies. The most recent literature on the subject was analyzed to find possible treatment options available; while this study mainly focuses on smoking cessation therapies in patients with Chronic Obstructive Pulmonary Disease (COPD), its findings remain valid at a much more general level.

THE ROLE OF TOBACCO SMOKING IN THE GENESIS AND EVOLUTION OF COPD

COPD is the fourth cause of death in the world and is likely to become the third by 2030 [5]. Besides being

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an obstructive bronchial disease characterized by a partial or total irreversibility of bronchial obstruction and a progressive fatal pulmonary deterioration [6], it is also recognized to be a systemic inflammatory disease with pulmonary and extrapulmonary symptoms, including an increased risk of developing lung cancer [7]. COPD has a marked effect on the patients' quality of life and affects up to 50% of smokers [8]. Tobacco smoking remains the leading cause of COPD, although susceptibility to smoking-related flow restriction is rather individual, due to the interaction between environmental factors and the host [9, 10]. In fact, some genetic studies highlight that variants and the upregulation of nicotinic receptors are involved in addiction, COPD and/or lung cancer [11]. Bronchopulmonary damage is caused by oxidative stress, release of inflammatory cytokines, increased protease activity due to the imbalance between proteases/antiproteases and the expression of autoantibodies [12]. All these factors together can lead to chronic bronchitis with alteration of mucociliary clearance and possible progressive evolution towards COPD and pulmonary emphysema; the latter may represent risk factors for lung cancer [13, 14]. A recent meta-analysis [15] confirmed that smokers have a 4.01 times greater risk of developing COPD (RR 4.01; 95% CI, 3.18-5.05). Exposure to passive smoking in adults for an average of 1 hour a day carries a 1.44-fold risk of developing COPD compared to non-exposed people. The percentage of smokers who develop COPD is high: it ranges from 15-20% in the seminal studies of Fletcher and Peto [16] (considered an underestimation [17]) to 40-50% in the most recent publications [18-20]. An early decline in forced expiratory volume (FEV 1) is recorded in adolescent smokers, while the maximum level of respiratory function appears to be partly determined by exposure to smoking in prenatal life and after birth [21]. The risk of COPD is dose-dependent, hat is, related to the duration of tobacco use and the cumulative dose. The lowest FEV 1 value is observed among smokers with exacerbations. A recent study shows that each new exacerbation corresponds to an additional loss of 23 ml/year in addition to the expected 87 ml/year [22]. For this reason, it is advisable to keep the respiratory function under control in smokers for an early detection of alterations that may evolve into COPD [23].

BENEFITS OF SMOKING CESSATION IN COPD PATIENTS

Early smoking cessation brings many benefits: it prevents the onset of the disease, limits its evolution [24], and reduces morbidity and mortality from associated illnesses such as cardiovascular or bronchial diseases and cancer [25]. Smoking cessation should be offered to all patients with chronic bronchitis and COPD regardless of the stage of the disease and the patient's motivations to quit [26]. Indeed, as it happens in France, smokers should be advised to undergo COPD screening in smoking clinics, so that the doctor who diagnoses COPD may be aware from the start that the patient is a chronic smoker [27]. These "challenging" smokers [28] generally have a strong nicotinic dependence, a rather high daily consumption of tobacco and important anxious-depressive traits, the latter also being responsible for flare-ups and difficulties in quitting [29]. Conversely, some studies have showed that smoking cessation is also effective in reducing stress, anxiety and depression in COPD smokers [30]. Complete smoking cessation is necessary, as simply reducing tobacco intake is not enough to limit the decline in respiratory function [31]. Former smokers have fewer lower respiratory tract infections and COPD exacerbations [32], while active smokers show a greater clinical and functional decline [33]. Hospitalizations for COPD can be reduced in those who quit smoking [34], including patients with severe COPD, as demonstrated by a 2008 systematic review [35]. Smoking cessation also has a positive therapeutic impact, since cigarette smoking alters the therapeutic response to medications used to treat respiratory diseases [36] through the induction of liver isoenzymes, pharmacodynamic interactions and reduced sensitivity to corticosteroids. Finally, the cost-effectiveness ratio of smoking cessation is associated with high-intensity cessation interventions [37], also through savings from the reduction of exacerbations and hospitalizations of COPD patients.

TOBACCO AND CANNABIS

Tobacco has long been considered a gateway to cannabis consumption [38] and it is now common in anti-smoking centres to come across smokers who also use cannabis. It is good practice to identify this associated consumption, especially because many young adults believe that smoking cannabis involves little or no health risks, while it is known that as far as consequences on respiratory function are concerned, a single joint equates 2.5-3 tobacco cigarettes [39, 40]. The prevalence of COPD and related risk factors in people on opioid agonist treatment (OAT) is also a fact, because they appear to develop COPD at a lower age than the general population [41]. These kinds of smokers must be told from the start to quit both addictive substances, namely nicotine in tobacco and delta-9-transtetrahydrocannabinol (Δ9-THC, mainly) in cannabis. THC is absorbed by the respiratory tract mucosa, with a bioavailability of approximately 20% and a maximum blood concentration reached in approximately 10 minutes. Furthermore, cannabis is inhaled differently from tobacco: the volume of the puffs is greater with cannabis and the inhalation is quicker and deeper, sometimes followed by a Valsava maneuver to achieve an even greater absorption of THC. To implement a successful de-addiction therapy, it is useful to know that the THC pulmonary retention time is longer than nicotine, whose plasma elimination half-life is about 2 hours: THC in fact, being lipophilic, binds to body fat, in particular in the brain, with a plasma half-life between 25 to 35 hours or even much longer in case of regular consumption [39]. As in the case of tobacco cigarettes, cannabis smoke contains many carcinogenic components, and/or components which alter the respiratory epithelium. Confirmed respiratory effects in chronic cannabis smokers include symptoms of chronic bronchitis with a cumulative effect on COPD due to tobacco, the occurrence of emphysema, with an increased risk of bullous emphysema and pneumothorax, and an increased risk of recurrence after pleu-

ral symphysis. Further, recent prospective studies have shown a negative impact on lung function, with damage to the airways, alteration of carbon monoxide diffusion lung (DLCO) and accelerated decline in forced expiratory volume in the first second (FEV1) [42]. Anti-smoking centers operators should ascertain the dual use of cannabis and tobacco, and advise quitting by offering their help after a careful evaluation of both consumption and its causes. The management of cannabis and tobacco smokers requires psychotherapeutic support; furthermore, if previous medications to help quit cannabis have not been effective, nicotine replacement therapy can limit withdrawal syndrome and cravings, and may improve smokers' adherence to care and monitoring. In a systematic review of the literature it was found that cannabis and tobacco users had greater difficulty quitting cannabis than simple cannabis users, and had more frequent psychosocial disorders, such as anxiety and depression [43]. This greater difficulty is also linked to the fact that, predominantly, these patients intend to stop smoking tobacco while maintaining a reduced use of cannabis, thus underestimating their addiction.

Smokers who also use cannabis can be supported by means of the following strategies:

- inform the patient and evaluate the damage caused by consumption, so that the patient may become aware of the addiction, including that from THC. Inform the patient of the risks associated with use and the advantages of abstinence, offering to help him/her stop [44]. It is necessary to evaluate the level of addiction by using the cannabis abuse screening test (CAST) [45] for cannabis and the Fagerström test (FTND) for nicotine, quantifying the severity of the addiction according to the Diagnostic and Statistical Manual of Mental Disorders 5-Cannabis use Disorders (DSM-5-SUD) items. The psychopathological reasons for consuming cannabis and nicotine and the existence of anxious-depressive disorders must be sought through clinical tests (HAD tests) [46], as well as situations of social precariousness, use of other substances, psychoactive or legal problems. Patients who experience serious difficulties due to cannabis addiction are included in specialist drug addiction consultations. However, anti-smoking centres may also manage occasional cannabis smokers, proposing them to stop both substances at the same time, as they share a common route of administration, neurobiological interactions, and social rituals. The therapy then proceeds in a similar way to tobacco cessation;
- *psychotherapeutic support*: this support, with its various facets (cognitive-behavioral therapies, including psychodynamic and family therapies) allows to create a therapeutic alliance, strengthen motivation to quit, generate adherence to therapeutic monitoring, and facilitate learning about craving and prevention of relapse after cessation [47, 48]. Remote support tools (internet, telephone lines), when available, allow for the provision of further assistance [44];
- *pharmacological support*: this mainly involves nicotine replacement therapy (NRT), in transdermal and oral forms; this approach also allows to limit withdrawal syndrome and cravings when simultaneously trying cessation of nicotine and cannabis. Bupropion is not recommended due to the sleep disturbances it can generate [49] in those patients who, according to the clinical experience of this manuscript's Authors, usually consume cannabis only in the evening for "relaxing" purposes. Varenicline is currently in a test phase for this indication [50]. A recent Cochrane Review, based on 21 studies [51], assessed the benefit of current pharmacological strategies to combat cannabis addiction, and concluded that, given the state of the art, no valid recommendations could be deduced. Some molecules (serotonin reuptake inhibitors, buspirone, atomoxetine, antiepileptics) may, however, find some use. Cannabinoid agonists, although promising, are still in the testing phase, as are gabapentin and N-acetylcysteine. The role of e-cigarettes in helping to stop this dual use is still poorly understood. On the other hand, synthetic cannabinoids mixed with nicotine-containing liquids have been reported to cause severe, sometimes fatal pneumonia [52]. It is necessary to further develop research into pharmacological therapies with integrated preventive measures aimed at reducing the use of these psychoactive substances, ever more widely diffused (as in the case of cannabis) with their undergoing legalization (a legislative process already completed in many countries).

COPD AND SMOKING IN PATIENTS WITH COVID-19

Most studies highlight the importance of anti-smoking therapy in patients with COPD and COVID-19. An interesting meta-analysis based on 15 studies including 2,547 confirmed COVID-19 cases [53] showed that although the prevalence of COPD in COVID-19 cases was low, COVID-19 infection was associated with higher severity and mortality rates in presence of COPD. Compared with former smokers and people who never smoked, smokers were at a higher risk of serious complications and showed a higher mortality rate. Similarly, in the 2020 work by Gallus *et al.* [54], tobacco smoking resulted one of the most important avoidable risk factors. In Italy, an observational, longitudinal, and multicenter study on patients with a diagnosis of COVID-19 confirmed by molecular swab in 24 hospitals and 2 community centers showed that smokers are twice as likely to die from COVID-19 as people who never smoked [55, 56].

SMOKING AND THE WILL TO QUIT

Smoking is not a simple "vice" or "habit": it is fully recognized as an *addictive pathology* by the WHO International Classification of Diseases (ICD-10) and by the American Psychiatric Association (APA) Diagnostic and Statistical Manual of Mental Disorders [57]. Nicotine is a neuro-psychotropic substance that triggers neurochemical alterations, modifies the plasticity of some brain areas and receptor structures, and induces behavioral changes in memory, emotions, and learning, like other psychotropic substances. As clearly demonstrated by Nobel Prize winner Dr Eric Kandel [58], nicotine acts as a "gateway" for other drugs. Unfortunately, the idea of treating smokers is not very wide-

spread because people think that it is enough for them to simply *want* to quit; however, with "do-it-by-yourself" systems only 1-3% of the cases result a "spontaneous cure" [59]. When asked, two thirds of all smokers say they would like to quit, and 20% say they would like to drop tobacco within the following 30 days [60]. Smokers with COPD should be informed of the benefits of smoking cessation therapy, which should be prescribed as an integral part of their treatment following the indications of evidence-based medicine (EBM) and smoking cessation guidelines [61-65].

HOW TO HELP THE SMOKER PATIENT

Smoking cessation: available treatments

The main recommendation in all the guidelines for the treatment of smoking [62-64] is the use of effective pharmacological therapies and counseling on tobacco addiction for all tobacco smokers. Smoking cessation is the most effective strategy to slow down the progression of COPD and to reduce mortality in approximately 50% of smoking COPD patients [66].

As yet, there is no gold standard, intended as a single effective smoking cessation technique; however, there are some common key-points in all the methodologies that are gaining solid scientific validation:

a) individual or group counseling;
b) pharmacological treatments – consisting of nicotine substitutes (nicotine replacement therapy, NRT), bupropion, varenicline and cytisine – are effective and safe therapeutic supports, especially in combination with counseling [59].

Addiction to smoked tobacco is characterized by a *physical* addiction to nicotine and by a *socio-environmentally* conditioned behavior. The best treatment for tobacco addiction must then integrate both counseling and pharmacotherapy in a multidisciplinary approach, as recommended by the United States smoking cessation clinical practice guidelines [67], by the European Network for Smoking Prevention and Cessation (ENSP) [62] and, in Italy, by the recent Italian guidelines published by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) [63]. The importance of therapeutic education (TE) of smokers with COPD has also recently been evaluated: it aims to strengthen smokers' understanding of their disease and bring out new skills to improve their quality of life hrough sessions based on group dynamics and which exploit the knowledge acquired by the patient on the disease, treatments, respiratory physiotherapy and nutrition. TE, when included in a multidisciplinary management aimed to complement and strengthen smoking cessation follow-up, appears to increase the chances of a successful cessation [68].

Non-pharmacological therapy

Non-pharmacological therapy lays essentially in counseling, in all its forms (individual, group, telephone, short, intensive). The United States Preventive Services Task Force provides a "Grade A" recommendation for physician-provided brief smoking cessation interventions. Counseling by non-medical health professionals, including nurses, oral health professionals, and pharmacists, also increases cessation rates [69]. In clinical counseling, a "consultant" helps patients by providing them with accurate information and psychological support, thus creating a process of empathy. Several studies [67, 69, 70] show that:

a) individual, group and telephone consultations are effective, and their effectiveness increases with treatment intensity;
b) the longer the first interview, the higher the probability of smoking cessation;
c) effectiveness increases when the counseling is intensive and prolonged over time;
d) effectiveness also increases when different kinds of professionals are involved.

Most smokers try to quit smoking without help, by reducing the number of cigarettes or, more drastically, by abstaining from smoking overnight [71].

In addition to counseling, it is worth mentioning further strategies aimed at smoking cessation in the context of non-pharmacological therapies, since they have been proposed with positive results in patients with COPD:

- *monetary incentives*: monetary incentives rewarding the outcome (quit smoking) or the involvement (participation in the treatment) have already shown to be moderately effective [72]. They can be given through different methods, for example through incremental vouchers linked to the reduction of exhaled carbon monoxide and urinary cotinine during the program. Although the results of a randomized pilot study [73] supported the potential effectiveness of such an incentive, further efforts are needed in research activities aimed at increasing the sample size and evaluating long-term abstinence following this intervention;
- *physical activity*: several studies have shown that physical activity can help reduce symptoms of depression in patients with lung problems, and it is known that major depressive disorder (MDD) can have a negative effect on withdrawal during and after cessation treatment smoking [74, 75]. Physical activity was inversely associated with MDD even after controlling for potential confounding variables, such as lung function [76]. Furthermore, secondary analyses showed that physical activity was inversely related to depression in a dose-response manner. Several randomized controlled trials that included physical activity to reduce tobacco craving in smoking cessation have demonstrated the effectiveness of this strategy [77].

Brief advice

This type of help can be provided in the first place by the GP or by a specialist with first-level training, and successively by smoking cessation therapists in anti-smoking centres. The minimal clinical intervention technique (very brief advising and counseling) recommended by the main guidelines of non-European and European National Entities (including the most recent ISS Italian guidelines [63]), is known as the "5As: Ask, Advise, Assess, Assist, Arrange". It is The National Cancer Institute's (NCI) gold standard for short termination advice [78]. In this technique, the first 2 As (Ask and Advice) are part of a rapid approach (Mini-

mal or Brief Advice), that is the minimum advising that all clinicians should deliver during a medical examination of a smoker (Ask: ask all patients if they smoke or have ever smoked, and always report the data in their medical record. Advice: recommend quitting if they are smokers or compliment them if they are former smokers or if they have never smoked. Follow up those who have stopped smoking for at least one year).

The next three As (Assess, Assist, Arrange) are part of a possible therapy. In particular, the third A (Assess) assumes significance only in view of treatment continuation [79-81]. Assess: consists in identifying smokers who are motivated to quit and those who are not, also using questions such as "can I help you quit smoking?" but without ever trying to overcome a determined refusal; in the latter case, the clinician should inform the smoker on the possible advantages in terms of health and relational aspects, and offer the willingness to help in the future. It should be remembered that such patients may respond to brief motivational interventions that are based on principles of motivational interviewing (MI), a directive, patient-centered counseling intervention. There is evidence that MI is effective in increasing future quitting attempts. The four general principles that underlie MI are: (1) express empathy, (2) develop discrepancy, (3) roll with resistance, and (4) support self-efficacy.

Assist: if the smoker accepts to be helped, he/she must be motivated by way of creating a relationship based on empathy and cooperation so that it is up the smoker to bring out the benefits but also the difficulties encountered, and to find his/her own motivations and resources for quitting. Information and recommendations must be provided to overcome any reported problems, and the patient must be continually encouraged to reach the goal. Obviously, in a motivated patient it is best to provide advice on a precise cessation date, and on the use of pharmacological therapy to be shared with other professionals for better compliance.

Arrange: plan a follow-up, i.e., a schedule of visits aimed at checking progress and pharmacological therapy, strengthening motivation and considering possible relapses as events from which to gain experience, and not as failures.

The 5As can be assimilated to an "individual treatment": behavioral support + medication [82]. *Figure 1* is an adaptation from Fiore *et al*. [67] and graphically synthesizes the 5As approach.

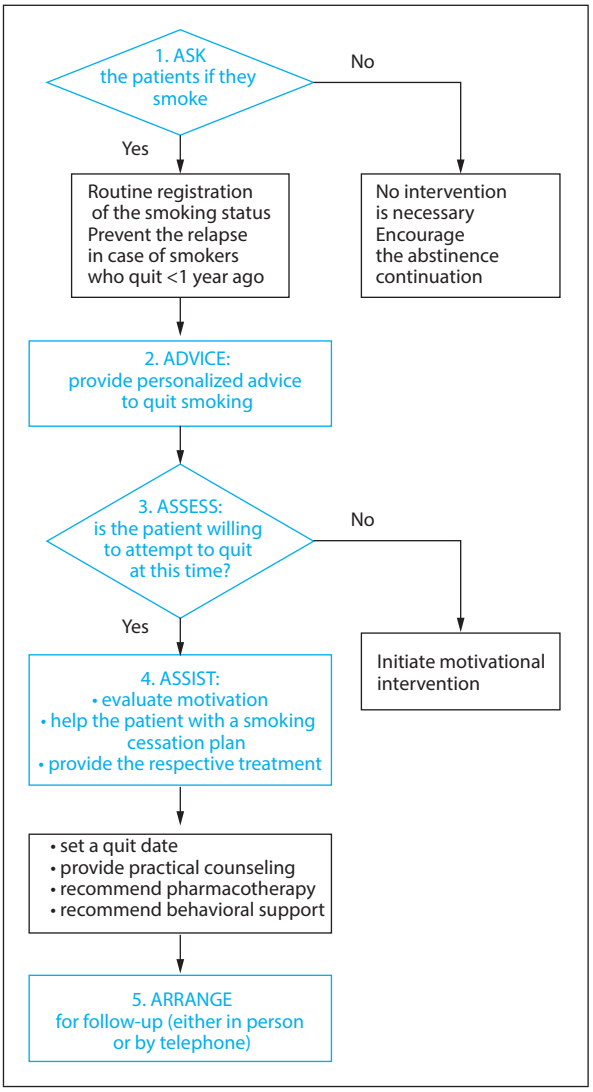

Figure 1
"Patient" journey: addressing healthy individuals and those at risk of developing CVD/DM, progressing to individuals diagnosed with CVD/DM at risk of disease progress and multimorbidity. This encompasses both individual and population levels, within different settings.
CVD: cardiovascular disease; DM: diabetes mellitus.

Intensive smoking cessation counseling, alone or in combination with other therapies

Clinical Practice Guidelines recommend intensive smoking cessation counseling, individually or in groups, in clinical, behavioral, or community settings for smoking cessation treatment [63, 67]. A systematic review of 49 randomized trials with approximately 19,000 participants concluded that intensive counseling alone (without pharmacological support), provided by a cessation counsellor, was more effective than minimal contact (i.e., brief advice and self-help materials) and performed best when combined with smoking cessation medications [70]. It should be noted that, in patients with COPD, combining respiratory rehabilitation with a cognitive-behavioral and pharmacological therapy for smoking cessation proved to be more effective than in smoking patients with COPD who did not have a rehabilitation program [83]. Furthermore, as confirmed by Sundblad *et al.* [84], hospitalization for respiratory rehabilitation is a particularly apt moment for smoking cessation interventions in COPD patients.

Telephone counseling [69] and AI technologies on smartphones (App, Internet, SMS, social networks) [85] have also proved to be a support for smoking cessation although further randomized controlled trials are needed. According to the ISS Italian guidelines [63] it is well worth developing applications for mobile devices to be promoted through media campaigns at national level in the National Health Service. At a European lev-

el, some digital tools to stop smoking are already available, developed within media campaigns that are repeated annually in England [86], the Netherlands [87, 88] and France [89] and which have already involved a large number of patients. As a research priority, the ISS Italian guidelines [63] suggest implementing such media campaigns associated with digital systems, and recommend future studies relying on process indicators such as the number of people accessing the applications for the first time or the frequency of weekly or monthly access, and outcome indicators such as self-reported measures of nicotine consumption and withdrawal. Monitoring could also serve to understand any parts of the application that could be improved.

New digital therapy Apps for smokers with COPD were found to be so popular in an Austrian survey that it was suggested to add "Apps" as the sixth A. Mobile apps combined with psychopharmacological therapy seem to be effective in achieving smoking cessation. In addition, the easy integration of these tools in primary healthcare can improve knowledge about possible treatments and integrate smoking cessation into routine care [90]. An interesting 2019 review of quit-smoking Apps available on the UK market [91] examined the use of *gamification* (the use of game elements in a non-game context) to increase patients' engagement and motivation. The review showed that only a few of the 140 quit-smoking Apps had a high level of gamification, thus welcoming further exploration into its use.

As for telemedicine, the results are still too recent and controversial for a long-term evaluation. However, telemedicine may be a strategic added value in the care of COPD, by reducing the burden of both in-patient and out-patient healthcare [92] as demonstrated by the COVID-19.

Among other possible anti-smoking therapies based on alternative medicine are acupuncture and hypnosis. The few reliable studies report controversial results. For example, Wang *et al.* [93] conducted a randomized controlled trial which concluded that acupuncture is a possible smoking cessation treatment. But in the same issue of the Journal, an editorial by Braillon and Ernst [94] criticized the validity of the same study and the conclusions drawn by its authors for the overly small size of the sample (195 patients), the double blind with nicotine performed with reduced concentrations of transdermal therapeutic system, the high drop-out rate (35%), and the non-independence of the study.

PHARMACOLOGICAL THERAPY

Tobacco smoke determines a state of psychological and pharmacological addiction [57] known as *nicotine disorder*. Chemical dependence can be measured by the nicotinic addiction assessment test (Fagerström test) which scores the degree of addiction as mild, medium, strong, or very strong, thus enabling the grading of the pharmacological therapy [95]. There are three pharmacological mechanisms which can facilitate smoking cessation: (i) reduce nicotine withdrawal symptoms; (ii) reduce nicotine's rewarding effects; and (iii) provide an alternative source of nicotine [69]. As indicated by the guidelines for smoking cessation [63, 64; 67-69], there are three safe and effective "first-line" drugs capable of increasing abstinence rates, including long-term abstinence, from tobacco smoke: nicotine replacement therapy, bupropion SR and varenicline. A new entry, but not yet officially included in the first-line treatment, is cytisine [96].

Nicotine replacement therapy (NRT)

NRT is undoubtedly the most used approach in smoking cessation: it reduces withdrawal symptoms (dysphoric or depressed mood, insomnia, irritability, frustration, anger, anxiety, difficulty in concentrating, hyperactivity, irritability, increased appetite and weight) and decreases the desire to smoke. To avoid overdoses, patients should not smoke while treated with NRT. In fact, although a selection of articles up to April 2018 report that there is "moderate certainty" that use of NRT before quitting can improve quit rates compared with its use after the quit date, the authors of a major 2019 review conclude that more research is needed to ensure the robustness of this claim [92]. The results of the above-mentioned review by Lindson *et al.* [97] are especially valuable: aiming to evaluate the effects of different NRT regimens on smoking cessation, they excluded trials that did not assess smoking cessation as an outcome; they also excluded studies that followed participants for less than six months, in line with the standard methods of the Cochrane Tobacco Addiction Group [98]. For each study included, they used the strictest available criteria to define abstinence: in studies with a biochemical validation of cessation, only participants meeting the criteria for biochemically confirmed abstinence were considered abstinent; sustained cessation was preferred over point prevalence; and the participants lost to follow-up were considered continuing smokers [99]. Different formulations of NRT (nicotine gum, nicotine inhaler, nicotine tablets, nicotine patches and nicotine nasal and oral sprays) can be combined. The combination of a short-term acting NRT (gum, lozenges, sprays or inhalers) with a long-term acting NRT (nicotine patches) produces higher cessation rates than using a single formulation and is recommended as a first-line treatment. NRT products are marketed in different dosages, with higher doses for more dependent smokers [97]. Each route of administration differs in the kinetics, the time to reach nicotine blood peak, and effectiveness. Over the past three decades, several meta-analyses have been published evaluating the safety and effectiveness of NRT (patches, chewing gum, tablets, inhalers, or nasal sprays) [100, 101]. Nicotine patches provide 2 to 3 times greater discontinuation rates than the placebo [102]. The paper by Hartmann-Boyce *et al.* [102] also found that the risk ratio of abstinence for any form of NRT compared to the control was 1.55 (95% CI: 1.49-1.61); the pooled risk ratios for each type were 1.49 (95% CI: 1.40-1.60; 56 trials; 22,581 participants) for nicotine gum; 1.64 (95% CI: 1.53-1.75; 51 trials; 25,754 participants) for nicotine patches; 1.52 (95% CI: 1.32-1.74; 8 trials; 4,439 participants) for oral tablets/lozenges; 1.90 (95% CI: 1.36-2.67; 4 trials; 976 participants) for nicotine inhalators; 2.02 (95% CI: 1.49-2.73; 4 trials; 887 participants) for nicotine nasal sprays.

The Fagerström test on the degree of nicotinic addiction should guide the initial transdermal nicotinic dosage [103], using high-dose patches (from 20 to 30 mg depending on the Fagerström test) for 3 months. High-quality evidence showed that individual counseling was more effective than minimal contact monitoring (brief counseling, usual care, or self-help materials) when pharmacotherapy was not provided (RR 1.57, 95% CI: 1.40-1.77; 27 studies; 11,100 participants) [70].

Gums generally need 30 minutes to reach nicotine plasma peak; one gum is administered every hour up to a maximum of 12 per day. To obtain maximum effectiveness, the gum should be chewed slowly and, after 5-10 chews, should be kept in the mouth without chewing and then chewed again to allow it to release all the nicotine available. Each piece of gum, in 2 and 4 mg dosages, should be chewed for about 20-30 minutes. The use of nicotine gums should be avoided in the presence of dental prostheses and gastropathies. Patches with transdermal nicotine release are more manageable and effective than gums; they contain from 5 to 30 mg of nicotine with release at 16 or 24 hours, thus allowing stable plasma nicotine concentrations throughout use. Nicotine patches are to be avoided in case of dermatopathies and glue allergy.

The 15 and 10 mg nicotine inhalers feature a mouthpiece containing a cartridge fitted with a porous filter soaked in mentholated nicotine. From the cartridges containing 10 mg of nicotine, 4 mg are inhaled, and 2 mg absorbed. It is advisable to explain to patients, especially to asthmatics and COPD patients, to inhale very slowly to avoid coughing, and to use from a minimum of 4 to a maximum of 10 capsules per day in the initial stages of cessation.

Sublingual nicotine tablets have pharmacokinetic characteristics very similar to those of chewing gum. The dosage is 2 mg and they reach peak blood in about 20 minutes. The tablet is dissolved slowly under the tongue without chewing or swallowing. This formulation should also be avoided in patients with gastropathies.

Oral sprays should not be inhaled; a delivery (puff) of 1 mg of nicotine can be repeated once every 30 min but with no more than 2 puffs at a time. The maximum dose is of 64 puffs in a 24-hour day, progressively upscaled over a maximum period of 6 months.

Nasal sprays reach a nicotine blood level faster and more effectively than other forms of NRT [82, 97].

There exists high-certainty evidence that combining NRTs (fast-acting form + patch) results in higher long-term quit rates than a single form (risk ratio 1.25, 95% CI: 1.15-1.36; 14 studies; 11,356 participants; I^2=4%) but no evidence of the effect of duration of nicotine patches (low-certainty evidence) [97]. The reduction in the estimated absolute benefit of NRT between one-year and long-term follow-up is a 30% relapse between the two, with only 2.7% due to the slight reduction in the odds ratio. Tobacco addiction might be better viewed as a chronic, relapsing disorder requiring repeated treatment (more similar to the long-term treatment of other chronic diseases, such as hypertension) rather than to the treatment of acute diseases like infections; nonetheless, this treatment is still likely to be highly cost-effective in terms of life-years gained [104].

Bupropion

Bupropion is an antidepressant which, by acting on the two neurotransmitters dopamine and noradrenaline, can counter nicotine withdrawal symptoms. In one-year controls, used alone for one month, it showed a 33% success rate for smoking cessation, compared to 21% of those using nicotine patches. The combination of bupropion and nicotine patches was more effective (38% *vs* 18% of placebo. Similar results were obtained by Jorenby [105] in a controlled and double-blind study on the effectiveness of slow-release bupropion (244 subjects), transdermal nicotine (244 subjects) and the combination of the two systems (245 subjects) compared to placebo (160 subjects). The 12-month smoking abstinence rate was 15.6% for placebo, 16.4% for transdermal nicotine, 30.3% for bupropion and 35.5% for combination therapy, which showed no statistically significant difference with bupropion alone. The drug is administered with 150 mg/day for 8-10 days, and later with 150 mg twice a day, to achieve complete smoking cessation. Its main contraindications include a history of seizures and eating disorders (bulimia and anorexia). Its possible side effects include seizures, insomnia, dry mouth. Bupropion is marketed as a smoking cessation drug in the form of an extended-release preparation. The usual duration of bupropion treatment is 12 weeks, but prolonged therapy for one year reduces relapses and increases long-term cessation rates [69]. Several studies have documented much higher recurrence rates in COPD patients with higher pack-year history, higher degree of nicotine addiction, higher risk of depressive symptoms, and lower motivation to quit [106, 107].

Though developed as an antidepressant, bupropion affects smoking cessation in ways other than alleviating depressive symptoms [108]. The safety, tolerability, and effectiveness of bupropion for smoking cessation in patients with COPD has also been established thanks to one-year continuous abstinence rates of 16% for bupropion compared to 9% for placebo [109]. Wagena *et al.* [110] also confirmed that the use of bupropion and nortriptyline resulted in higher prolonged abstinence rates compared to placebo. More specifically, they found that bupropion and nortriptyline were effective in patients with COPD, achieving prolonged abstinence while no statistically significant differences were found with placebo in participants at risk for COPD.

It should be noted that patients with COPD struggle for many years to stop using nicotine permanently and may require prolonged treatment and/or sustained nicotine use. After repeated failed attempts under specialist healthcare, the use of alternative methods – electronic cigarettes or heated tobacco – is being proposed, but the topic is controversial due to the use of these same methods by no-smokers, their effectiveness and safety, their short- and long-term health effects, and their adverse effects from passive exposure [66; 111, 112] (for an insight into these topics, see below "electronic cigarettes, EC, and heated tobacco products, HTP").

Varenicline

Varenicline is a partial agonist of the α4β2 nicotinic acetylcholine receptor (nAChR), the main receptor in nicotine addiction. Varenicline activates approximately 50% of the maximum effect of nicotine and blocks nicotine's effects on the α4β2 receptor. The agonist effect serves to reduce withdrawal symptoms, while the antagonistic effects reduce the gratification of nicotine in cigarette smoking. Varenicline treatment before quitting is often associated with a reduction in smoking, presumably because it becomes less satisfactory, which may later facilitate quitting. Safety and effectiveness of varenicline have been investigated in patients with mild to moderate COPD: for treatments ranging between 9 and 52 weeks, the abstinence rate was 18.6%, compared with 5.6% in the case of placebo (OR 4.04; 95% CI: 2.13-7.67; p<0.0001), while safety was found to be comparable with previous studies [113]. In clinical trials, varenicline resulted more effective than bupropion or nicotine patches in promoting smoking cessation, as also the combination of multiple NRT formulations [114]. Varenicline is a molecule approved by the Food and Drug Administration (FDA) in 2006 and authorized in Europe, Middle East and Africa in September 2006 under the trade name of Chantix (USA) – Champix (EU). The drug is used orally, and the recommended regimen dose is 1 mg twice a day. The dosage protocol indicates starting with 0.5 mg and continuing with 0.5 mg once a day for the first 3 days, 0.5 mg twice a day from day 4 to 7, and 1 mg twice a day from day 8. The treatment starts 7 days before the total cessation of tobacco smoking and continues for at least 12 weeks. Varenicline binds to the neuronal nicotinic receptors of acetylcholine α4β2 with a high level of affinity and selectivity. It has a dual action mechanism: 1) a partial agonist effect by stimulating nAChRs to a significantly lower extent than nicotine; 2) an antagonist effect by blocking nicotine's capacity to activate the α4β2 receptors, thus stimulating the dopaminergic mesolimbic system especially in the *nucleus accumbens* (NACc). Varenicline is administered orally and has a high systemic bioavailability, regardless of the alimentary regime or the time of administration. It exhibits linear kinetics, and the maximum plasma concentration (Cmax) is reached within 3-4 hours after oral administration. Varenicline is low in plasma protein binding. Elimination is renal, mainly through glomerular filtration together with active tubular secretion. It has a mean half-life of 24 hours and steady-state concentration (Css) is achieved within 4 days. The drug is contraindicated in subjects with moderate and severe renal insufficiency (creatinine clearance <50 ml/min). Clinical trials and experience have given encouraging results on the effectiveness of this drug: at 6 months, Varenicline was more effective than placebo, NRTs and bupropion SR [61, 115]. According to the American Thoracic Society Clinical Practice Guideline, varenicline performed better than NRT and bupropion in controlling tobacco addiction [116]. Since 2021 the drug has been suspended after an information note agreed with the EMEA on the presence of N-nitroso-varenicline impurity above daily intake levels deemed acceptable by the manufacturing company, which prudently stopped the distribution of the drug pending further checks. Shortly after, the first FDA-approved generic varenicline became available [117]. Both the European Medicines Agency (EMA) and the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) should also consider this option and this is why the Authors of this review have included varenicline in the section on pharmacological therapy for smoking cessation.

Cytisine

Cytisine is an alkaloid extracted from the seeds of *cytisus laburnum*, commonly known as "golden chain" or "golden shower", a common garden plant in central and southern Europe. Cytisine has been used for smoking cessation in Central and Eastern Europe for over 50 years. Like varenicline, it is a partial agonist of nAChR α4β2. Therefore, it has similar effects to those of nicotine, while at the same time desensitizes and/or blocks the effects of tobacco nicotine on nAChR α4β2. The recommended treatment regimen is a dose reduction over 25 days, a treatment cycle shorter than the 12 weeks recommended for most other smoking cessation drugs, with recorded significant effects compared to placebo (meta-analysis; RR, 1.74; 95% CI, 1.38 to 2.19) [118]. In Italy, to facilitate greater adherence to therapy and based on experiences with other partial nicotine agonists, the Italian Society of Tobaccology (Società Italiana di Tabaccologia, SITAB) has adopted a therapy scheme with: i) 1.5 mg tablets at 40 days with a slow induction of cytisine intake; ii) the following smoking advice: smoking patients are advised to reduce the number of cigarettes in the first four days of treatment, with a recommended stop smoking date of the fifth day. SITAB has been proposing this scheme for about ten years, i.e., since the active ingredient became available in Italy; the scheme, first tested at the Center for the Treatment of Smoking (Centro per il Trattamento del Tabagismo, CTT) in Monza, Italy, consists of induction (2 to 6 tablets/day for the first 7 days), maintenance (6 tablets/day for 7 days) and gradual reduction for 26 days [118, 119]. The cost of cytisine in Europe is several times lower than that of other smoking cessation drugs. The drug is well tolerated, and the most common side effects are nausea, vomiting, dyspepsia, and dry mouth [118, 119]. Cytisine is defined as "a drug with positive effects and without significant adverse events". Since 2024, the drug based on the active ingredient Cytisine (approved by AIFA on April 2023) has also been on the market in Italy.

Combination pharmacotherapy

According to Cochrane Meta-analysis [97], nicotine replacement therapy (NRT) combined with a patch and a more immediate-acting product results in higher smoking cessation rates than NRT alone, with a hazard ratio (RR) of 1.34 and a 95% confidence interval (CI) from 1.18 to 1.48. The combination of varenicline and nicotine patch was evaluated with mixed results [120]. The mechanism through which NRT purportedly enhances the effects of varenicline is unclear, but the combination appears to be safe. This combination may be considered in a smoker who does not quit after using NRT in two forms or varenicline alone. Bupropion in combination

with a nicotine patch or NRT in two forms increases smoking cessation rates compared to the same drugs administered alone. A study with the combination of varenicline and bupropion reported promising results, although neuropsychiatric adverse effects were greater in the first 2 weeks than with varenicline alone [121].

Electronic cigarettes (EC) and heated tobacco products (HTP)

Electronic cigarettes (ECs) are battery-powered devices that work by heating a metal coil which vaporizes a solution (e-liquid): mainly glycerol, propylene glycol (PG), distilled water and flavorings, with or without nicotine. The user inhales the aerosol generated by vaporizing the e-liquid in a process commonly referred to as "vaping". ECs' safety and nicotine delivering efficiency have improved since their introduction on the market in 2006. However, the huge number of devices marketed and the great variety of chemicals used to flavor the e-liquids represent additional sources of complexity when evaluating their toxicity and safety.

Another class of non-burning products aimed at replacing traditional cigarettes are heated tobacco products (HTP). They consist of a support which, instead of burning tobacco, transfers electronically controlled heat at temperatures <350 °C, to tobacco sticks, caps or capsules which then generate aerosols. The user places the tobacco product in a small box and inhales it in the same way as cigarettes or cigars.

Disposable ECs represent the latest product on the market: it is a device that vaporizes a liquid of various flavors, from kiwi to coke, similarly to traditional electronic cigarettes; but unlike the latter, it has a limited duration and is not rechargeable. Once finished, disposable ECs must be disposed of in battery containers. Compared to the traditional ones, this cigarette emits fewer carcinogenic substances but contains nicotine salts, which are 4 times more addictive.

Vaping has been proposed as a potential smoking cessation tool and has been found to increase abstinence [111], but its use among non-smokers has raised great concerns [112]. Moreover, even if carcinogen reduction is observed with ECs [122], vaping is not harmless [123]: it has pro-inflammatory effects, increases airway resistance, friability, and edema, and exposes its users – including passive users – to ultrafine particles and heavy metals [112]. Vaping has been associated with acute lung injury, even before the EVALI outbreak [112]. Furthermore, many smokers are "dual users", smoking both traditional and electronic cigarettes, which makes it more difficult to assess the impact of vaping alone [112].

The use of HTPs is associated with similar problems. While in "dual users" there seems to be a reduction in carcinogenic load, in levels of carbon monoxide in exhaled breath, and in biomarkers, they are still harmful, and their effects on health have started to appear in literature [124, 125]. The latest ISS Italian guidelines [63], which have been developed according to the GRADEpro program (https://gradepro.org/), recommend *not* using the ECs with nicotine (compared to NRT) in traditional tobacco cigarette's smokers who have chosen to follow pharmacological treatment for cessation. This is a conditional recommendation, based on moderate quality of evidence. "Moderate quality" means that further research could change the results on the estimate of the effect; for this reason, among the research priorities listed in the guidelines are future studies aimed at providing further independent evidence that considers as valid outcomes the absence of nicotine consumption, i.e., the cessation of the use of ECs; the evaluation of the effectiveness and safety of ECs; and, above all, the need for long-term longitudinal studies that *specify the dosage, method and frequency of consumption of ECs,* as well as the type of setting and counseling. The Guidelines also recommend addressing the issue of addiction to other components (for example flavourings), and conducting studies to evaluate the quantity of nicotine (which varies with the electronic device used) absorbed by the consumer, since this can influence the comparison of the response with nicotine substitutes or other products. Also, further studies are necessary to understand the degree of dependence on the gestural component linked to the use of these nicotine delivery systems. A recent review published in Cochrane [126] highlighted that, although biomarkers are not indicators of disease rates, the significant reduction in exposures showed by ECs users is a positive indicator for tobacco risk reduction; the review, which is a living systematic review and which has been last updated on November 17th 2022, reported high-certainty evidence (based on 6 RCT studies) that ECs with nicotine increase quit rates compared to NRT, and moderate-certainty evidence (5 studies, limited by imprecision) that ECs with nicotine increase quit rates compared to ECs without nicotine. These results should be considered cautiously for several reasons, such as the still limited number of available high-quality studies and of participants, data variability and imprecision (including dosage, method and frequency of consumption of ECs with nicotine), limited and variable information on adverse and serious adverse short and long-term effects, differences in the quality of nicotine delivery between older and more recent ECs.

As for HTPs, the ISS Italian Guidelines [63] states that they should *not* be used as a treatment for smoking cessation. This recommendation relies mainly on the most relevant outcomes of a 2022 systematic review [127]. The review Authors, who followed standard Cochrane methods for screening and data extraction, searched for measures like abstinence from smoking at the longest follow-up point available, adverse events, serious adverse events, and changes in smoking prevalence or cigarette sales. They included 11 RCTs, all funded by tobacco companies and all judged either at unclear or at high risk of bias, and 2 time-series studies. None of the studies reported on cigarette smoking cessation, and insufficient evidence was found with respect to the risk of adverse or serious adverse events when comparing HTPs smokers, tobacco smokers, and people attempting short-term tobacco abstinence. Thus, the main message from [63] and [127] is that independently funded research is still needed to address the issue of effectiveness and safety of HTPs.

As for the risks associated with the use of ECs and

HTPs, it should be noted that these devices produce numerous harmful substances: metals, organic compounds, and aldehydes, which can also harm those passively exposed to these devices' vapors or smoke, whose longitudinal effects on health are currently unknown [128-130]. The presence of formaldehyde is particularly worrying, the indoor concentration of which is 2.7, 1.2 and 40 µg/m3, respectively for HTP, EC and traditional cigarettes [131]. The evidence of this substance's toxicity, which have already shown to be harmful in numerous epidemiological studies and which has been classified as a group 1 carcinogen [132], highlights the need to make restrictive changes to the legislation governing the use of these devices in public, especially in the presence of minors or pregnant women. The considerable spread of these products among the very young is also worrying, as it may represent their first experience of nicotine addiction [133].

To recap, while the use of ECs by the general population is to be discouraged, in an anti-smoking setting and in selected patients, and after having experienced all the counseling and pharmacological approaches available in the guidelines, the use of ECs can represent an additional tool for smoking cessation centers and in particularly problematic patients such as, for example, psychiatric patients. In Italy this is also the position of experts and scientific societies such as those with which the Authors of this paper are associated. The latest position paper of the Italian Society of Tobaccology (SITAB) on new tobacco products stated that "the use of electronic cigarettes cannot be considered a public health policy applicable to the general population, but an individual intervention, practiced by experts, in selected cases not responding to treatment and in dedicated health settings" [134].

To conclude, specifically for COPD patients, there is the need for independent, well-controlled, clinical trials and large-scale prospective cohort studies with a long-term follow-up, to obtain conclusive, reliable, and independent evidence, for or against the use of ECs.

Pre-cessation pharmacotherapy

Many smokers would like to quit, but are unwilling to set a date when first visiting a healthcare provider. Starting pharmacological therapy while the patient is still smoking, on the basis that it would make later quitting easier, was studied through the use of nicotine patches and varenicline. The pharmacological basis for this approach is that nicotine patches, by desensitizing nicotinic receptors, reduce withdrawal symptoms in the interval between successive cigarettes, while varenicline, by antagonizing the effects of nicotine in cigarettes and providing relief from withdrawal symptoms, reduces smoking satisfaction, thus decreasing the daily number of cigarettes. Evidence of pre-cessation drug therapy with nicotine patches has shown conflicting benefits, although some studies have shown large beneficial effects [135]. Studies on varenicline have shown benefits with a flexible quit date and this approach is FDA approved [136]. Several studies report that a great number of smokers with respiratory diseases make many unsuccessful attempts to quit. The study, based on the administration of a specific online survey by the European Lung Foundation (ELF) [137] found that: 54% of smokers participating in the ELF survey had made 1 to 5 attempts to quit smoking in the previous 12 months; 4% had made more than 20 attempts; 55% wanted a quick stop while 45% preferred to gradually reduce their tobacco addiction. Although most patients wanted to break this addiction, 90% found quitting difficult or very difficult. For these reasons, it is always important to first share the possible smoking cessation options with the smoker. The benefit of pre-release pharmacotherapy is that physicians can propose any smoking patient (and regardless of the patient's willingness to quit at the time of the visit) a drug therapy, explaining that it will help to quit smoking over time, much in the same way any patient with high blood pressure would be advised to take medication so as to prevent future diseases. In this regard, a small study involved heavy smokers with COPD initially unprepared to quit, who were prescribed varenicline for as long as they wanted and with no fixed date to quit; 18 months later, most had quit [138]. Currently, the 2021 NICE guidelines [64] for smoking cessation include a chapter dedicated to smokers who are not ready to quit smoking yet or just want to reduce their habit, recommending the use of medications containing nicotine to prevent relapses or limit smoking for long periods of time.

CONCLUSIONS

Although a gold standard method for smoking cessation does not exist yet, there are some common key-points in the methodologies used in national and international guidelines. Worthy of note are the following:

1) counseling;
2) nicotine replacement therapies;
3) counseling and pharmacotherapy.

In particular, managing a smoker patient with COPD must be done with a global approach. Quitting smoking is the priority goal whatever the stage of the disease, due to several well proven beneficial effects [139, 140].

Tobacco cessation therapists must learn to adapt the integrated supports (counselling + pharmacotherapy) to the specific problems of their patients, in order to adjust cessation programs to each individual context and to each smoker's culture and personal life [141].

Finally, research efforts should include the study of novel EBM strategies such as those currently based on EC/HTP and digital therapies, to further enhance the cost-effectiveness that current smoking cessation therapies have shown [60], also in patients with COPD [37].

Authors' contributions

Conceptualization and methodology: RP, VZ, MSC. Investigation: RP, VZ, MSC. Formal analysis: RP, VZ, MSC. Data interpretation: RP, VZ, PM, LDM, CB, AS, MSC, CG. Writing - original draft: RP, VZ. Writing, review & editing: RP, VZ, PM, LDM, CB, AS, MSC, CG. Project administration: RP.

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