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REVIEW ARTICLE

Pharmacological Approach to Smoking Cessation: An Updated Review for Daily Clinical Practice

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Abstract
Tobacco use is one of the major public health concerns and it is the most preventable cause of morbidity and mortality worldwide. Smoking cessation reduces subsequent cardiovascular events and mortality. Smoking is a real chronic disorder characterized by the development of an addiction status mainly due to nicotine. This condition makes the smokers generally unable to quit smoking without help. Different strategies are available to treat smoking dependence that include both non-pharmacological (behavioral counselling) and pharmacological therapies. Currently, it is well accepted that smoking cessation drugs are effective and safe in real-world settings. Nicotine replacement therapy (NRT), varenicline, bupropion and cytisine are the main pharmacological strategies available for smoking cessation. Their efficacy and safety have been proved even in patients with chronic cardiovascular disease. Each of these drugs has peculiar characteristics and the clinician should customize the smoking cessation strategy based on currently available scientific evidence and patient's preference, paying particular attention to those patients having specific cardiovascular and psychiatric comorbidities. The present document aims to summarize the current viable pharmacological strategies for smoking cessation, also discussing the controversial issue regarding the use of alternative tobacco products, in order to provide useful practical indications to all physicians, mainly to those involved in cardiovascular prevention.

Keywords Smoking cessation · Nicotine addiction · Nicotine replacement therapy · Varenicline · Bupropion · Alternative tobacco products

1 Introduction

Tobacco use is one of the major public health concerns and it is the most preventable cause of morbidity and mortality worldwide. It is estimated that 16 million adults are currently living with a smoking-related disease in the United States [1]. Cigarette smoking is the main source of tobacco consumption and it is also the most dangerous one. Every year, more than 700,000 people die because of smoke-related diseases in Europe. More than one-quarter of Europeans smoke and one-third of smokers are 25–39 years of age [2]. There are nearly 12 million smokers in Italy, mostly men, although female smokers increased by over a million in 2016 [3].

It is known that smokers' life expectancy is on average 10 years shorter than non-smokers'. Moreover, half of the smokers lose about 20 years of healthy life before dying because of a smoke-related disease [4]. Besides being involved in the pathophysiology of several types of malignant neoplasms, not only in the lungs, smoking represents the first cause of chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) [5, 6], as well as a major determinant of cardiovascular (CV) diseases, such as myocardial infarction, stroke and peripheral arterial diseases. In patients with hypertension, despite optimal blood pressure control, smoking was independently associated with early markers of atherosclerosis [7].

Regarding CV risk, 10–30% of all CV deaths worldwide are related to cigarette smoking. Experimental epidemiological and clinical studies have demonstrated a non-linear

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trend between smoke amount and CV effects, so even a low amount of smoke is associated with a disproportionately high CV risk [8]. This non-linear trend explains why non-smokers exposed to passive smoking have a 25–30% increased CV risk and why it is important to warn all patients with heart disease to avoid second-hand smoke (SHS) [4].

Smoking cessation reduces subsequent CV events and mortality [9]. Regardless the duration and intensity of smoking habit, comorbidities or age, all smokers may take advantage by quitting smoking, even if cessation happens after the development of a CV disease [8]. Indeed, quitting smoking after a major cardiovascular event is likely the most effective secondary prevention measure [3], particularly in COPD patients, where it reduces both the risk of worsening chronic respiratory disease and the recurrence of CV events at the same time [9].

Cigarette smoking is also related to a higher susceptibility to pulmonary bacterial and viral infections, inducing structural changes in the respiratory tract and a decrease in immune response. In fact previous studies have shown that smokers are twice more likely to contract influenza and have more severe symptoms than non-smokers [1]. Moreover, in the current era of a viral pandemic due to the Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) causing the 2019 coronavirus disease (COVID-19), despite the limited data available, smoking has been assumed to be possibly associated with adverse prognosis. A recent study has demonstrated that ever-smokers (current and former) have an upregulated pulmonary angiotensin-converting-enzyme-2 (ACE2) gene expression, thus leading to an increased risk for viral binding and entry of both SARS-CoV and SARS-CoV-2 in their lungs [10]. This panorama warrants a compelling, prompt, and effective attempt for smoking cessation.

The present document aims to inform the overall population about the risks correlated to smoking as well as to provide useful practical indications to all physicians, mainly to those involved in CV prevention, about the current viable pharmacological strategies for smoking cessation.

2 Definitions and Tobacco Products

Smoking is a real chronic disorder related to the intermittent and compulsive consumption of an exogenous substance, sustained by the development of an addiction status, which is mainly due to nicotine [11]. "Addiction" is defined as the individual perception of a constraint of smoking with struggles to stop or reduce smoking for long intervals of time. The practice is continued despite harmful consequences and due to the occurrence of withdrawal symptoms when the exposure to nicotine ends [8]. A "smoker" is an individual who currently smokes tobacco every day and who has smoked at least 100 cigarettes in his/her entire life [2].

In the last decade, we witnessed the evolution of many tobacco products; at present, we can divide all these different products into two main categories:

- tobacco combustion products, in which tobacco burns producing smoke inhaled by the user (i.e. cigarettes). Inhalation of combustion products exposes the organism to a wider spectrum of harmful chemical substances, causing a greater risk for health compared to tobacco products that do not use combustion (i.e. snuff, chewing, dipping tobacco), even though no form of tobacco is entirely risk-free;
- alternative products without tobacco combustion, mainly represented by electronic devices that deliver nicotine, including electronic cigarettes (e-cigarettes), and other devices that heat tobacco instead of burning it (heat-not-burn, HNB). An e-cigarette heats a liquid containing nicotine, propylene glycol and/or vegetable glycerine, and flavored chemical substances in order to produce vapors inhaled by the user. Since the e-cigarette does not burn tobacco, it does not generate combustion smoke, but only vapors. In HNB products, the tobacco is heated to a lower temperature than a combusted cigarette to create aerosols, instead of smokes, inhaled by the user.

2.1 Nicotine Addiction

Smokers are generally unable to quit smoking without help, mainly because they develop a tobacco addiction. This condition represents a real nosological entity and not just a bad habit. The main determinant of tobacco addiction is nicotine [12]. Nicotine addiction is a chronic, relapsing disorder that needs a long-term management and an intensive treatment approach, like other chronic diseases. Nicotine addiction has two components: physical dependence and psychological dependence [11, 13].

The main feature of nicotine addiction is the desire to feel the pharmacological effects of nicotine and the avoidance of possible withdrawal symptoms. Indeed, nicotine is responsible for both positive, such as psychoactive stimulation, and negative effects, such as discomfort and uneasiness [13].

The mechanism responsible for addiction development and the resulting chronic and reiterated use has its base in the pharmacodynamics of nicotine. Nicotine binds specific acetylcholine receptors, mostly neuronal nicotinic acetylcholine receptors (nAChRs) α4β2 subtypes, in the central nervous system, and stimulates the release of neuromodulators (mainly dopamine) promoting pleasure and thus perpetuating consumption [13].

The degree of such addiction can be quantified through simple and validated screening tools, such as the Fagerström Test for Nicotine Dependence (FTND) [14] (see Table 1)

or the Heaviness of Smoking Index (HSI) [15]. The scores obtained from these tests can predict both the likelihood of starting tobacco consumption again after stopping ("relapse") and the selection of the most beneficial therapeutic strategy to quit smoking.

Epidemiological data showed that nicotine addiction is a chronic recurrent condition acquired primarily during adolescence [16]. "Relapse" means start again to smoke regularly after cessation. Among former smokers, relapse is common and occurs during the first days following the attempt of discontinuing smoking, when withdrawal symptoms are generally more severe. More than 75% of people who try to quit smoking by themselves relapse within the first week, making this time-period critical [17]. Nevertheless, the risk of relapse is quite common even in smokers who suspended smoking for longer periods. Patients who are free from smoking for at least 12 months have a likelihood of relapse of 35% during their life [17]. Nicotine addiction is characterized by a specific withdrawal syndrome, just like other pathological dependence syndromes. Nicotine withdrawal syndrome develops in the first 4–12 h following smoking cessation. The main symptoms include craving for smoking, irritability/aggressiveness/rage, anxiety, restlessness, fatigue, increased appetite, difficulty concentrating, depression, headache, insomnia, dizziness/vertigo [12]. The set of symptoms could vary from an individual to another. All of these manifestations are temporary and they reach the greatest intensity in the first 24–72 h, decreasing in the following 3–4 weeks. Symptoms usually persist for more than 3–4 weeks in 40% of patients [12].

3 How to Quit Smoking: The "5 A's" and the "5 R's" Models

Five steps are usually needed to treat tobacco use and dependence in the clinical setting, known as the "5 A's" model [18].

- *Ask* about tobacco use. Identify and document tobacco use status for every patient at every visit.
- *Advise* quitting. In a clear, strong and personalized manner, urge every tobacco user to quit at every visit.
- *Assess* willingness to make a quit attempt. Is the tobacco user willing to make a quit attempt at this time?
- *Assist* in quit attempt. For the patient willing to make a quit attempt, offer medication and provide or refer for

Table 1 Fagerström test for nicotine dependence (FTND)

1. How soon after you wake up do you smoke your first cigarette?
Within 5 min (3 points)
6–30 min (2 points)
31–60 min (1 point)
After 60 min (0 points)
2. Do you find it difficult to refrain from smoking in places where it is forbidden (i.e. in church, at the library, in the cinema, in the train, in restaurants)?
Yes (1 point)
No (0 points)
3. Which cigarette would you hate the most to give up?
The first one in the morning (1 point)
All others (0 points)
4. How many cigarettes per day do you smoke?
10 or less (0 points)
11–20 (1 point)
21–30 (2 points)
31 or more (3 points)
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?
Yes (1 point)
No (0 points)
6. Do you smoke if you are so ill that you are in bed most of the day?
Yes (1 point)
No (0 points)
Results
Score 0–3: LOW dependence
Score 4–6: MODERATE dependence
Score 7–10: HIGH dependence

counselling or additional treatment to help the patient quit.
- *Arrange* follow-up. For the patient willing to make a quit attempt, arrange follow-up contacts, beginning within the first week after the quit date and then for the next 12 months, managing the risk of relapse or the relapse itself. For patients unwilling to make a quit attempt at the time, address tobacco dependence and willingness to quit at the next clinic visit.

For smokers willing to quit at the time of the visit, it is recommended to provide immediately integrated support (pharmacological and behavioral). For patients unwilling to quit at the time of the visit, it is advised to implement interventions designed to increase future quit attempts.

In order to increase future quit attempts, the clinician should follow the "5 R's" model [18].

- *Relevance* of quitting to patient. The patient should answer the question "why it is so important to quit smoking?"
- *Risks* for the patient's health if he/she continues tobacco use.
- *Rewards* of quitting explaining the benefits for patient's health.
- *Roadblocks* to quitting, to understand what possibly could prevent the achievement of smoking cessation.
- *Repetition* of the discussion relative to the attempt of quitting, regardless of the patient's will to quit at the time of the conversation.

4 Pharmacological Approach to Smoking Cessation

Different pharmacological strategies are available to treat smoking dependence [19]. They should be associated with non-pharmacological strategies (behavioral counselling), which are validated approaches to promote the process of quitting.

The main pharmacological treatments available for smoking cessation are the following: nicotine replacement therapy (NRT), varenicline, bupropion and cytisine (see Table 2) [19].

The clinician should follow both currently available scientific evidence and patient's preference for a proper choice of one therapy over another, paying particular attention to those patients having contraindications to these drugs due to the presence of specific comorbidities (i.e. CV, renal, hepatic, psychiatric comorbidities) (see Fig. 1) [12].

4.1 Nicotine Replacement Therapy (NRT)

Nicotine replacement therapy is based on the controlled administration of nicotine, making it easier to abstain from tobacco by partially replacing the nicotine previously obtained from tobacco use. Nicotine replacement therapy aims both to stimulate nicotine receptors thus removing smoking craving and withdrawal symptoms (this effect is immediate), and to reduce the number of nicotine receptors (this effect is slower and continues for weeks progressively reducing tobacco dependence).

Controlled administration of nicotine reduces the positive effects induced by smoking thanks to a lower dosage and slower pharmacokinetics. Nicotine is more slowly absorbed generating lower but prolonged blood peaks, compared to cigarettes, thus reducing rewarding effects and withdrawal symptoms including irritability, anxiety, difficulty concentrating, dysphoria, increased appetite, weight gain, and sleep disorders [12]. Each different NRT product has demonstrated the same efficacy in achieving smoking cessation. Consequently, the choice of the NRT product should reflect the patient's preferences. Transdermal nicotine patch is commonly the first choice because it yields higher compliance rates than other NRT products [8].

Due to a more beneficial pharmacokinetic profile, combination NRT (short plus long-acting products) is superior to single NRT. A combination of transdermal nicotine patch with a more rapidly absorbed NRT (i.e. oro-nasal products) is more effective than the use of a single product [8, 20, 21]. Combination NRT is the current standard of therapy, once the clinician decides to use NRT as therapeutical strategy.

Transdermal nicotine patches deliver nicotine at a relatively steady rate ("controller" NRTs), so they are the most suitable routes of administration to reduce withdrawal symptoms. On the other hand, chewing gums, lozenges, inhalers and nasal sprays ("reliever" NRTs) reduce symptoms faster than patches, but they provide worse basal coverage [12].

It is important to note that uncontrolled use of nicotine inhalers or sprays could determine high blood peaks of nicotine, resembling what happens with traditional cigarettes, thus providing some of the contentment associated with smoking and hence slowing down the process of cessation [12].

Oral formulations contain nicotine absorbed by the oral mucosa. The main weakness of this class is the strict dosing scheme needed, sometimes with a fixed short interval of 1–2 h. Moreover, nicotine is absorbed by the oral mucosa only with a neutral mouth's pH. Therefore, the patient should be advised to avoid meals or drinks during or in the 15 min before drug use, paying attention to avoid mostly acid foods and beverages. Rather, inhalers have the advantage of mimicking cigarette usage, preserving the hand-to-mouth action of smoking [12].

Table 2 First-line agents recommended for smoking cessation

Drug	Posology	Method of administration	Possible adverse reactions	Advantages	Disadvantages	Precautions
NRT transdermal patch	If patient smokes at least 10 cigarettes per day: start with 21 mg/24 h for 4 weeks, then 14 mg/24 h for 2 weeks, then 7 mg/24 h for 2 weeks If patient smokes less than 10 cigarettes per day: start with 14 mg/24 h for 6 weeks, then 7 mg/24 h for 2 weeks	Apply a new patch every morning for 8–12 weeks on clean and dry skin Evidence of an efficacy increases if used for 3–6 months Change application site to prevent skin reactions Start using the day before or the same day the patient stops smoking	Skin reactions at the application site Insomnia or vivid dreams (in this case, patch could be removed before bedtime)	Easy to use Provide steady nicotine levels Maintenance therapy during combination NRT due to slow release ("controller")	If craving appears, combine with a rapid-release NRT form ("reliever")	Recent myocardial infarction (≤ 2 weeks) Serious arrhythmias Serious or worsening angina pectoris Pregnancy (category D) and breast-feeding[a] Adolescents (age < 18 years)
NRT gum	If patient smokes at least 25 cigarettes per day: 4 mg If patient smokes less than 25 cigarettes per day: 2 mg Recommended dose usually is 8–12 gums/24 h for at least 3 months	Chew until a slight oral tingling appears, then place the gum on the side of the mouth until the tingling vanishes, then start chewing again This procedure (chewing and placing aside) should be repeated for about 30 min, then the gum should be thrown away. Use a maximum of 1 gum per hour	Mouth irritation Jaw pain Heartburn Hiccup Nausea	Patient is aware of using the medication The method of administration "steals" the mouth to traditional cigarette It could be used in combination with patch as a "reliever" if craving occurs	Patient should be adherent to chewing technique It could be difficult to use with dentures and could damage teeth or dental works Eating and drinking should be avoided for 15 min before and during chewing of nicotine gum	Recent myocardial infarction (≤ 2 weeks) Serious arrhythmias Serious or worsening angina pectoris Temporo-mandibular joint disease Pregnancy and Breast-feeding[a] Adolescents (age < 18 years)
NRT lozenge	If patient smokes the first cigarette within 30 min of waking up: 4 mg If patient smokes the first cigarette 30 min after waking up: 2 mg Use for 3–6 months	Place the tablet in the mouth between the internal cheek and gum, leave there until it slowly dissolves Take 1 tablet every 1–2 h (maximum 20 per day)	Mouth irritation Jaw pain Heartburn Hiccup Nausea	Patient is aware of using the medication The method of administration "steals" the mouth to traditional cigarette It could be used in combination with patch as a "reliever" if craving occurs Easier to use in patients with denture, compared to chewing gum	Eating and drinking should be avoided for 15 min before and during tablet administration	Recent myocardial infarction (≤ 2 weeks) Serious arrhythmias Serious or worsening angina pectoris Pregnancy and breast-feeding[a] Adolescents (age < 18 years)

Table 2 (continued)

Drug	Posology	Method of administration	Possible adverse reactions	Advantages	Disadvantages	Precautions
NRT oral inhaler	6–16 cartridges per day Every cartridge releases 4 mg of nicotine through 80 inhalations Use up to 6 months	Puff through the mouthpiece in short breaths (do not inhale deeply) until craving decreases Change the cartridge when the flavour disappears Use 1 cartridge every 1–2 h (maximum 16 per day)	Mouth irritation Cough if deeply inhaled	Patient is aware of using the medication It mimics the ritual hand-to-mouth action of smoking It could be used in combination with patch as a "reliever" if craving occurs	Many inhalations are needed to have an adequate efficacy	Recent myocardial infarction (≤ 2 weeks) Serious arrhythmias Serious or worsening angina pectoris Bronchospastic disorders Pregnancy (category D) and breast-feeding[a] Adolescents (age < 18 years)
NRT nasal spray	0.5 mg in each nostril, start with 1–2 sprays per hour to a maximum of 8–40 sprays per day Use for 3–6 months	Spray once in each nostril, every 1–2 h (maximum dose: 40 sprays in each nostril per day)	Irritation of nose or back in the throat Rhinitis Sneezing Coughing Watery eyes	Patient is aware of using the medication Route of administration with the fastest absorption among NRTs Excellent "reliever" in combination with patch	Route of administration with the greatest prevalence of adverse reactions among NRTs (especially the nasal irritation makes it often unusable)	Recent myocardial infarction (≤ 2 weeks) Serious arrhythmias Serious or worsening angina pectoris Chronic nasal disorders (rhinitis, nasal polyps, sinusitis) Severe reactive airway disease Pregnancy (category D) and breast-feeding[a] Adolescents (age < 18 years)
Varenicline	Day 1–3: 0.5 mg once daily, in the morning Day 4–7: 0.5 mg twice daily, in the morning and in the evening Day 8 to end of treatment: 1 mg twice daily, in the morning and in the evening Start 1 week before the day of smoking cessation Use for 3–6 months	Swallow with a full glass of water and take with food to minimize the risk of nausea	Nausea Insomnia Vivid dreams Headache	Easy to use The first day of smoking cessation can be flexible (from 1 week to 3 months after the first dose) Double effect: reduces both nicotine withdrawal symptoms and the pleasure associated with smoking	Possible psychiatric adverse reactions (as reported in a previous FDA warning, then withdrawn), that are actually not so frequent	Severe renal impairment (dosage adjustment is necessary) Pregnancy (category C) and breast-feeding[a] Adolescents (age < 18 years) Treatment-emergent neuropsychiatric symptoms: FDA boxed warning removed (December 2016)

Table 2 (continued)

Drug	Posology	Method of administration	Possible adverse reactions	Advantages	Disadvantages	Precautions
Bupropion SR	Day 1–3: 150 mg once daily, in the morning from day 4: 150 mg twice daily for 3–6 months	Start therapy 1–2 weeks before target quit date	Insomnia Agitation Dry mouth Headache	Easy to use Could reduce weight increase typically associated with smoking cessation	Increased risk of seizures (do not use in patients with history of epilepsy or alcohol abuse)	Concomitant medications/conditions known to lower the seizure threshold Hepatic impairment Pregnancy (category C) and breast-feeding[a] Adolescents (age < 18 years) Treatment-emergent neuropsychiatric symptoms: FDA boxed warning removed (December 2016)

FDA Food and Drug Administration, *NRT* nicotine replacement therapy, *SR* sustained-release

[a]Given the insufficient evidence of effectiveness and theoretical safety concerns during pregnancy, pregnant smokers should be encouraged to quit without medication. Therefore, behavioral counselling interventions should be the first choice for pregnant smokers

Nicotine replacement therapy usually lasts 12 weeks, although treating heavy smokers for longer intervals may be reasonable, at least until the patient feels confident enough not to relapse. Long-term NRT is not associated with increased incidence of harm. Longer therapeutic intervals are particularly indicated in patients with psychiatric or other substance use disorders [12].

There are no contraindications to nicotine substitutes except evidence of allergy, which is rare for patients using patches and unusual for patients using oral formulations. In some countries, they are contraindicated during pregnancy.

Controlled, longitudinal, and case-controlled trials with NRT in patients with CV diseases did not report greater risks of adverse events compared to placebo. It has been found an increase in CV symptoms, such as tachycardia and arrhythmia, expected because of the sympathomimetic effects of nicotine, but no increase in major CV events (death, myocardial infarction, stroke) [8].

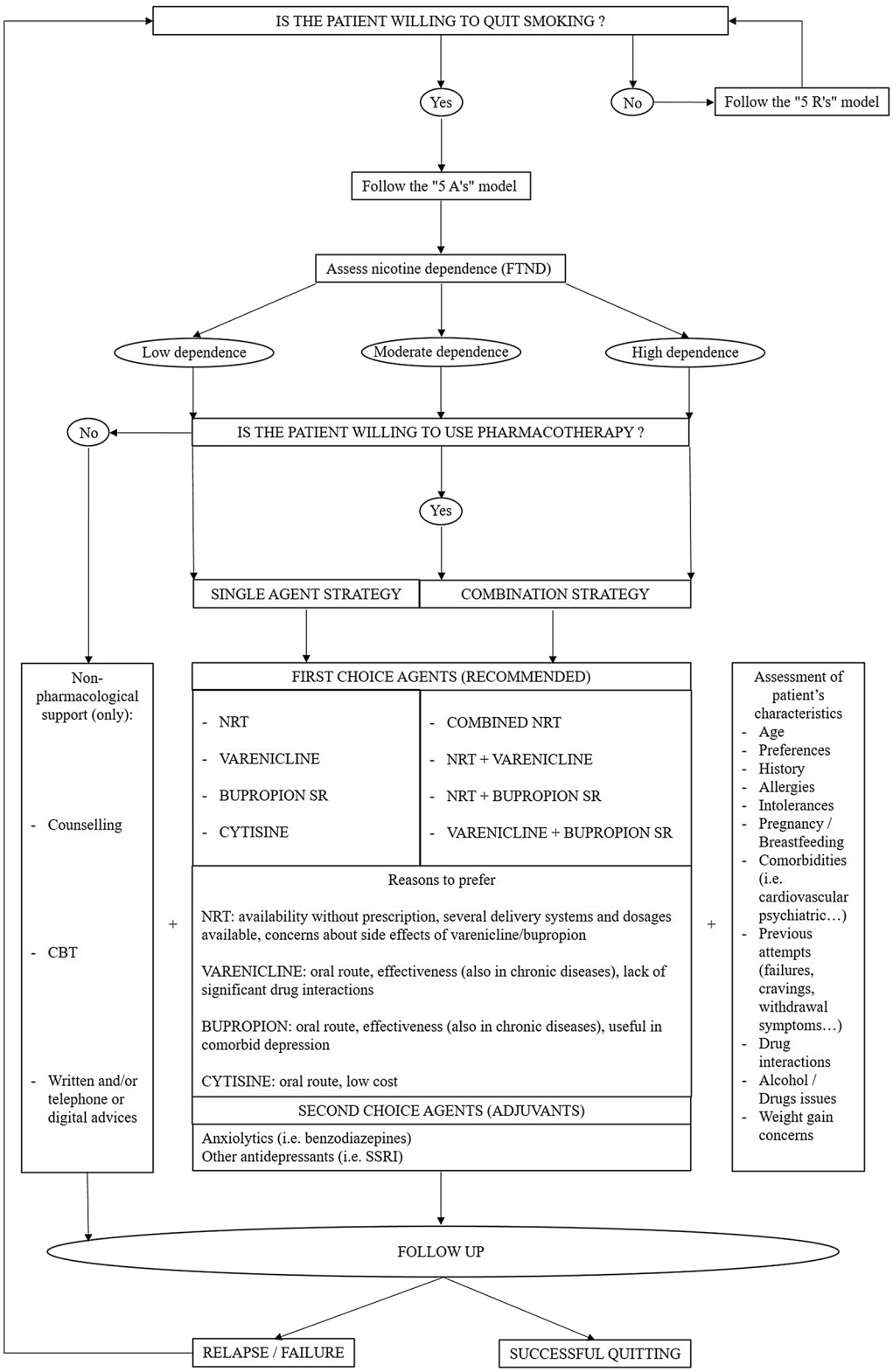
Nicotine could potentially worsen CV diseases through his sympathomimetic properties. However, nicotine levels in NRT are generally lower compared to those in tobacco products. Moreover, NRT does not expose users to the harmful products of combustion, which are major determinants in the pathogenesis of CV diseases. In conclusion, albeit NRT is not probably harmless, it is surely way less damaging than cigarette smoking.

Typical adverse events common to all NRT products include gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), dizziness, headache, local irritation according to the route of administration. Adverse event due to NRT could be managed by adjusting the dosage to minimize symptoms or, alternatively, by changing molecule [12].

Patients usually interpret some symptoms as adverse events due to treatment, instead of symptoms related to smoking cessation. Depression and sleep disorders are the most common withdrawal symptoms mistaken for adverse events to treatment. Many individuals who quit smoking show more or less severe signs and symptoms of depression.

Depression symptoms are not linked to the therapy itself but rather to the presence of a latent depression, unmasked by smoking cessation. Patients with a prior history of depression should be followed carefully to avoid a relapse of depression symptoms. Patients who are currently experiencing depression should start an antidepressant treatment, as indicated by current guidelines, simultaneously with strategies for smoking cessation [12].

When craving persists, there is no risk of overtreatment with NRTs. Conversely, in a patient who is not experiencing any desire for smoking, an overdose induces the impression of excessive smoking, associated with signs like nausea and tachycardia. These signs are transient and vanish quickly after treatment suspension. Therefore, it is possible



CBT: cognitive behavioral therapy; FTND: Fagerström test for nicotine dependence; NRT: nicotine replacement therapy; SR: sustained release; SSRI: selective serotonin reuptake inhibitors

Fig. 1 Proposed flow-chart for smoking cessation

to reintroduce the therapy at a lower dose. On the other hand, typical signs of underdosing are craving, irritability, anxiety, food craving with frequent snacks, insomnia and smoking despite NRT [19].

4.2 Varenicline

Varenicline is a partial agonist selective for α4β2 nicotinic acetylcholine receptors (nAChRs), one of the receptors related to dopamine release following nicotine binding. Varenicline activates the α4β2 receptor with a maximal effect about 50% that of nicotine, alleviating symptoms of craving and withdrawal (agonist activity), while simultaneously reducing the rewarding by preventing nicotine binding (antagonist activity). Ultimately, varenicline promotes smoking cessation by preventing withdrawal symptoms while moderate levels of dopamine are maintained in the brain [19].

Several meta-analyses suggest that varenicline is as effective as combination NRT. These two approaches are considered first-line therapy for smoking cessation, especially in patients with CV disease [22, 23].

Smokers should stop smoking one to two weeks after the first dose of varenicline, in order to reach the steady state. The pre-medication phase may be prolonged to 4 weeks to increase efficacy [24].

The drug is progressively titrated to minimize side effects, mainly gastrointestinal symptoms such as nausea (see Table 2). Varenicline is substantially excreted by the kidney. Dose reduction is needed in patients with severe renal impairment (estimated glomerular filtration rate below 30 ml/min). In these patients, the maximum recommended dose is 1 mg once daily. Varenicline is not recommended in patients with end-stage renal disease, due to the lack of data in this population. Patients who cannot tolerate adverse reactions of varenicline may lower the dose temporarily or permanently. Nausea could be reduced assuming varenicline with food or reducing the dose to 0.5 mg twice a day. Sleep disorders, particularly vivid dreams, could be avoided progressively reducing the evening dose until suspension, maintaining the morning dose only.

An additional course of 12 weeks treatment with varenicline at 1 mg twice daily may be considered for the maintenance of abstinence in patients who have successfully stopped smoking at the end of the therapeutic interval (12 weeks) [25].

Absolute or relative contraindications to varenicline use are hypersensitivity to the active substance or any of the excipients, age < 18 years old, pregnancy and breastfeeding [12]. Varenicline has no clinically meaningful drug interactions. Safety studies on varenicline in patients with stable CV disease found no increase in CV events, even though no univocal data are available in patients with acute coronary syndrome. Therefore, varenicline could be used safely in patients with stable CV disease and with caution in patients with acute coronary syndrome [26].

Soon after the introduction of varenicline, reports of an association with depression and suicidal ideation arose. A review of 11 published studies suggest that such association is likely to be weak [23]. Previous studies compared smokers having a previous psychiatric history (anxiety, depression, psychotic or bipolar disorder) with a control group demonstrating that treatment with varenicline was not associated with a higher risk of psychiatric adverse events [27]. Nevertheless, the possibility warrants patients' monitoring for clinical and therapeutical evaluation if neuropsychiatric symptoms occur, including behavioral changes, hostility, agitation, depressive mood, suicidal ideation.

The most common adverse events are nausea and sleep disorders. In the majority of cases, nausea is mild to moderate in intensity, occurs early in the treatment period, lasting on average for 12 days, and seldom results in discontinuation. Dosing titration is likely to reduce the incidence of nausea. Patients should be informed that this symptom usually solves within one week after starting treatment and could be avoided taking the drug with food [12]. Other side effects have been reported such as abdominal pain, constipation, abdominal distension, abnormal dreams, insomnia, dizziness, dry mouth, weight increase, increased appetite, and headache. These symptoms developed twice more frequently with varenicline than placebo [28].

In the majority of cases, they occur in the first 4 weeks of treatment, are mild to moderate in severity and temporary. Varenicline may influence the ability to drive. Previous reports found higher incidence of car accidents among patients taking varenicline. However, subsequent studies did not confirm this correlation [29].

4.3 Bupropion, Sustained-Release (SR)

The precise mechanism of action of bupropion is not well understood. Bupropion is likely to exert its pharmacological effects by weakly inhibiting the reuptake of both dopamine and norepinephrine, therefore prolonging their duration of action within the neuronal synapse and their downstream effects. When taken to quit smoking, bupropion may confer both anti-craving and anti-withdrawal effects by inhibiting dopamine reuptake, which mediates the reward pathways associated to nicotine use, and through the antagonism of the nicotinic acetylcholinergic receptor [30].

Bupropion also acts by alleviating some of the symptoms of nicotine withdrawal, which include depression, reducing the overall severity of withdrawal syndrome. Highly nicotine-dependent smokers who receive bupropion are more likely to experience a decrease in depressive symptoms associated with abstinence. Nevertheless,

bupropion efficacy for nicotine addiction is due to a distinct property other than its anti-depressant activity. In fact, its positive outcomes regarding smoking cessation have been demonstrated even in patients not suffering from depression [31].

Bupropion nearly doubled smoking cessation rates compared to placebo, and it was equally effective in men and women [31].

Bupropion is recommended also to avoid weight increase after smoking cessation. Indeed, Hays et al. reported both better weight control and higher smoking cessation rates than placebo one year after bupropion discontinuation [30]. Furthermore, it could be useful to prevent relapse both in smokers and in alcoholic patients. Patients who quitted smoking using bupropion for 7 weeks delayed relapse if they continued taking it for a total of 52 weeks. In COPD patients, bupropion could impair ventilatory responses to hypoxia and hypercapnia, leading to potentially harmful effects on disease progression. However, no studies on COPD patients taking bupropion confirmed such hypothesis [32].

Bupropion should be started before the patient's planned quit day. The patient should set a "target quit date" within the first 2 weeks of therapy and could continue smoking during treatment since this does not significantly affect the pharmacodynamics of bupropion. Steady-state blood levels are usually achieved after 1–2 weeks of treatment. If the patient is not able to quit within the target date, it is possible to delay smoking suspension until the third or fourth week of treatment or when abstinence is reached [12].

The recommended and maximum dosage of bupropion is 300 mg daily (150 mg twice daily). The dosage could be decreased to 150 mg daily if the patient does not tolerate the entire dose due to adverse reactions occurrence. Two previous RCTs found similar efficacy between bupropion 300 mg daily and 150 mg daily doses, but the latter was associated with fewer side effects [33].

Bupropion should be used with caution in patients with liver disease and renal disease. The dose recommended in these patients is 150 mg daily.

Absolute or relative contraindication to bupropion use are pregnancy and breastfeeding, history of seizures, epilepsy, brain and cranium neoplasms, current or prior diagnosis of bulimia or anorexia nervosa, simultaneous discontinuation of alcohol or sedatives/benzodiazepines, current use of monoaminoxydase inhibitors or use of these drugs in the previous 14 days [12].

Regarding patients with CV disease, no clinical study highlighted any safety concern [34]. Insomnia, dry mouth, and headache are the most common adverse events associated with bupropion use. Insomnia is certainly the most frequent adverse event and it could be avoided by taking the first dose of bupropion early in the morning and the second dose in the late afternoon, at least 4 h prior bedtime. Insomnia could be limited even reducing the dose to 150 mg daily [12].

A very small risk of seizure exists, and it is the most alarming adverse event associated with bupropion. It is quite rare (1:1000) and it is facilitated by some pre-existing risk factors, such as severe head injury, epilepsy, food disorders, arteriovenous malformations, cerebral neoplasms or infections, severe stroke and cerebrovascular disease, concomitant use of other medications that lower the seizure threshold [12]. Rare cases of angioedema [35] and syndrome of inappropriate antidiuretic hormone secretion have been reported, with the latter frequently associated with antipsychotic therapy [36].

4.4 Cytisine

Cytisine is a natural alkaloid found in several plant genera, such as Cytisus Laburnum and Sophora Tetraptera. Cytisine acts similarly to varenicline. It is a partial agonist selective for α4β2 nicotinic acetylcholine receptors, responsible for nicotine effects, and it prevents nicotine binding, thus reducing rewarding and both withdrawal symptoms and craving. Cytisine is available as oral tablets containing 1.5 mg of active principle [37].

Clinical data on cytisine found an efficacy similar, or even higher, than NRT regarding the likelihood of smoking cessation. However, cytisine has a greater propensity to adverse events, even though they are mainly minor such as nausea, vomiting, and sleep disorders [38, 39].

The recommended dose is 1 tablet (1.5 mg) every 2 h up to 6 tablets per day on day 1–3. In the meantime, the patient should reduce smoking to avoid nicotine overdosing symptoms. If the desired therapeutic effect is not obtained, the treatment should be interrupted and another cycle could be attempted after 2–3 months. If indeed a good response is achieved, the patient continues the treatment with 5 tablets per day (1 tablet every 2.5 h) on day 4–12, suspending smoking on day 5. The following therapy proceeds with 4 tablets per day (1 tablet every 3 h) on day 13–16, then with 3 tablets per day (1 tablet every 5 h) on day 17–20, lastly with 1 or 2 tablets per day (1 tablet every 6–8 h) on day 21–25 [19].

Italian experience reports a longer treatment schedule (up to 40 days), which begins with a progressive increase in dosage of cytisine 1.5 mg. The maximum dose of 6 tablets per day is gradually reached in 7 days. Target quit date should be set between the 8th and the 14th day. Then the dose decreases slowly until the 40th day [40]. Cytisine overdosing is similar to nicotine intoxication and produces nausea, vomiting, clonic seizures, tachycardia, mydriasis, headache, fatigue, respiratory pump failure.

4.5 Anxiolytics and Other Antidepressants

Many smokers are also affected by anxiety and depressive disorders, which could be emphasized by nicotine deprivation and/or the loss of smoking habit. Almost every smoker who attempts to quit manifests withdrawal symptoms such as irritability, restlessness, psychomotor agitation, insomnia, and anxiety. Although there are no specific data regarding the use of anxiolytics for smoking cessation, their role remains essential to manage associated anxiety disorders. Anxiolytics such as benzodiazepines (i.e. low dose and sustained-release alprazolam), could be helpful for the management of withdrawal symptoms [41]. Specific treatment is indicated if an overt mixed anxiety-depressive disorder is present, together with the smoking cessation drug regimens.

The most effective and safe antidepressants are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), atypical antidepressants (i.e. mirtazapine), and serotonin modulators (i.e. trazodone). Due to their proven effectiveness and tolerability, and the amount of available evidence, SSRI should be the first choice. Among SSRIs, sertraline and escitalopram have a good efficacy/safety profile [42].

5 Therapeutic Efficacy and Combination Therapy

Currently, it is well accepted that smoking cessation drugs are effective in real-world settings and in different conditions coexisting with smoking habit (i.e. other substances abuse, depression, anxiety) [43]. Previous studies found that treatments for smoking cessation doubled abstinence rates after 6 months compared to placebo. Combination NRT and varenicline were associated with higher abstinence rates (33% and 37%, respectively) [43]. It is important to note that several studies took into account also psychological and behavioural counselling. Following studies confirmed that combination NRT and varenicline had comparable efficacy and both of them had higher efficacy than single NRT or bupropion [43].

Drug therapy for smoking cessation typically lasts 12 weeks. However, these strategies could be personalised based on the clinician and/or patient's experience. Nicotine replacement therapy could last longer and even indefinitely, if needed. Indeed, the Food and Drug Administration (FDA) approved NRT for more than 3 months since it does not produce significant risks. Similarly, varenicline use can be extended for an additional 3-month period to prevent relapses. Indeed, varenicline was found to be effective and safe if administered for 24 weeks [25].

Long-term use of bupropion is possible, extending the treatment for further 7–9 weeks [44]. If bupropion is used to treat a depressive disorder, therapeutic changes or suspension should take into account also the possible relapse of depressive symptoms.

If we consider pharmacodynamics, it is possible to speculate that combination therapy with different drugs having complementary modes of action should achieve better outcomes. Indeed, the FDA approved both the combination NRT and the combination of single NRT and bupropion for smoking cessation [20].

The Italian Society of Tobaccology (Società Italiana di Tabaccologia—SITAB) guidelines suggest the following combination therapies: long-term use of nicotine patches (more than 14 weeks) plus a short-term NRT product (gum or spray) or nicotine patches plus bupropion SR. There is no evidence of contraindications for the use of NRT plus varenicline, but results on efficacy are not univocal. Further research is needed to support the efficacy of this approach in clinical practice. In conclusion, all treatments including NRT, varenicline and bupropion are effective for smoking cessation. Their efficacy and safety have been proved even in patients with chronic CV disease. Combination therapies are justified for patients with a major nicotine addiction or who have used monotherapies which have failed because of relapses [40].

5.1 Focus on Smokers with CV Disease

Several meta-analyses showed that both varenicline and combination NRT are more effective than bupropion or single NRT in smokers suffering from a chronic CV disease [4], making the first two approaches the first-line therapies for smoking cessation in patients with a history of CV disease (see Table 3). Few evidence is available in patients with acute coronary syndromes, especially regarding safety concerns. Based on the current state of the art, it is advisable to start a therapeutic approach once the CV condition has been stabilized. A progressive strategy could be helpful to improve compliance, since drug regimens after an acute coronary syndrome may be complex. Therefore, it is allowed to introduce further drug therapies gradually. Given the shorter latency for efficacy and the greater ease of use, it is generally advised to start with NRT rather than varenicline or bupropion, since the latter ones need an imbrication period while the patient is still smoking [4].

6 Alternative Tobacco Products

In the last years, several alternatives to traditional cigarettes have spread, such as electronic cigarettes (e-cigarettes) and heat-not-burn (HNB) devices. The marketing claims the potential of these products as an approach for smoking cessation. However, there is no definitive evidence supporting

Table 3 Pharmacological approach to smoking cessation in patients with CV disease

	Outpatients with chronic stable CV disease	Inpatients with acute CV disease (i.e. myocardial infarction)
First choice	Varenicline or combination NRT (i.e. patch + gum)	During hospitalization: single NRT (patch) or combination NRT (i.e. patch + gum) At discharge: combination NRT or Varenicline[a]
Second choice	Bupropion SR or single NRT	At discharge: single NRT
Third choice	Other molecules (i.e. SSRI)	Bupropion SR[b]
If single therapy is not sufficient to obtain smoking cessation	Varenicline + single NRT Varenicline + bupropion SR Bupropion SR + single NRT	No available data

CV cardiovascular, *NRT* nicotine replacement therapy, *SR* sustained-release, *SSRI* selective serotonin reuptake inhibitor

[a]Varenicline administration could be started during hospitalization. It is suggested to continue administering NRT (slow or fast release) for 1 week during titration of varenicline

[b]There is neither evidence of efficacy nor particular safety concern regarding starting bupropion during hospitalization

this claim, with the majority of the studies run by the same manufacturing companies instead of independent parties. E-cigarette may be helpful in suspending conventional smoking [45]. However, 80% of former smokers continued using e-cigarettes after quitting traditional smoking, thus remaining nicotine-addicted. On the other hand, 14 out of 15 longitudinal real-life studies demonstrated how e-cigarettes use undermined abstinence significantly, with 60–80% of patients continuing to smoke conventional cigarettes [4]. Regarding HNB products, there is no evidence supporting their efficacy and the use of concomitant traditional cigarettes is highly prevalent.

Another matter of debate is the supposed harmlessness of these alternative products. Almost all independent studies underlined potential harm. It is well-established that e-cigarettes' liquids vaporization and aerosolization may produce harmful substances such as benzene and formaldehyde.

Studies on animals have highlighted the onset of endothelial cells dysfunction and the induction of oxidative stress damages. Human studies showed the emergence of airways obstruction, the deregulation of normal pulmonary homeostasis, and the increase in chronic asthma exacerbations even in the short-term [4].

Furthermore, HNB products effects on human health are even more obscure. Data on animals found pro-inflammatory effects and data on humans found no improvement in pulmonary function after switching from combusted to heated tobacco. Independent studies found that HNB products are likely to have the pathogenic potential for COPD development [46].

The advent of alternative tobacco products generated a great appeal on new generations, thus largely increasing e-cigarette use among younger adults in both Europe and US. Indeed, e-cigarettes have become the most commonly used tobacco product among young people. This "epidemic" highlighted two aspects. The first one has a major impact on the short-term and it is the occurrence of increasingly acute respiratory syndromes, widely described in the scientific literature [47]. The second aspect has major consequences in the long-term and it represents the risk of switching back from alternative to conventional smoking [4].

A recent study conducted in Italy showed that almost all e-cigarette users among Italian smokers consumed liquids containing nicotine and most of them used these devices in indoor environments where conventional cigarette smoking is usually banned [48]. Consequently, to avoid the dual use (i.e. concomitant use of electronic and conventional cigarettes), we support the recent suggestion made by the World Health Organization (WHO) to forbid e-cigarettes, at least in public places and workplaces where conventional smoking is already prohibited.

At present, there is no sufficient evidence to adequately evaluate health hazards associated with alternative products use. Furthermore, there is no sufficient evidence regarding alternative products efficacy to support their use for smoking cessation. There are in-vivo data and clinical reports describing the clinical harm of using alternative tobacco products [49].

Therefore, taking into account the scarce evidence sustaining the use of alternative tobacco products, health workers should not recommend them as a treatment strategy for smoking cessation [49]. Moreover, these alternative devices may be harmful, even if they have been considered less dangerous than conventional smoking in the beginning.

7 Role of Air Pollution on CV Health

Air pollution is formed by the combination of particulate matter (PM), mainly derived from the combustion of carbonaceous particles, and several gaseous pollutants, such as nitrogen dioxide, nitric oxide, sulphur dioxide, carbon

monoxide, volatile organic compounds and ozone. The size of PM determines its classification into coarse (PM_{10}), fine ($PM_{2.5}$) and ultrafine particles [50].

Epidemiological studies found that exposure to air pollution increases both long-term and short-term CV mortality through an increased incidence of major CV events [50]. Pathophysiological studies found acute functional consequences of air pollution exposure in both myocardial and pulmonary blood flow regulation, but also in coagulation function, mainly driven by the sharp increase in reactive oxygen species generation, which impairs vasodilatation mediated by nitric oxide and promotes vascular inflammation [50]. Indeed, short-term exposure to $PM_{2.5}$, even at low concentrations within current air quality standards, was associated with significant blood pressure increase in high CV risk patients [51]. Although both the level and duration of exposure are directly associated with increased CV risk, there is no safe threshold below which there is no effect, and concentrations of fine and especially ultrafine particles in ambient air are thought to be strongly underestimated by actual standards and measurements [50]. Therefore, alongside the efforts to reduce the burden of CV diseases related to smoking, the promotion of safer air quality is going to be the next challenge in CV disease prevention, as recognized by the European Society of Cardiology's campaign "Environment & the Heart".

8 Conclusion

Smoking reduces the quantity and above all the quality of life. Smoking cessation strategies should be implemented in every clinical context, particularly in those involved in CV risk management and prevention. The pharmacological approach to smoking cessation is safe and effective, and therefore should be offered to everyone willing to quit smoking. It is never too late to quit smoking, and we should be able to make morbidity and mortality related to smoking a thing of the past.

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Compliance with ethical standards

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