Smoking cessation and vaccination

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Number 1 in the Series "Non-pharmacological interventions in COPD: state of the art and future directions" Edited by Geert M. Verleden and Wim Janssens

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~40% of COPD patients continue smoking. They have high nicotine dependence, and low self-efficacy and self-esteem. Combined counselling and pharmacotherapy is the best treatment. There is no evidence on e-cigarette or harm reduction benefits in COPD. https://bit.ly/3BATHeK

Cite this article as: Montes de Oca M, Laucho-Contreras ME. Smoking cessation and vaccination. *Eur Respir Rev* 2023; 32: 220187 [DOI: 10.1183/16000617.0187-2022].

This article has an editorial commentary: https://doi.org/10.1183/16000617.0028-2023

Received: 30 Sept 2022
Accepted: 8 Dec 2022

Abstract

A significant proportion of COPD patients (~40%) continue smoking despite knowing that they have the disease. Smokers with COPD exhibit higher levels of nicotine dependence, and have lower self-efficacy and self-esteem, which affects their ability to quit smoking. Treatment should be adapted to the needs of individual patients with different levels of tobacco dependence. The combination of counselling plus pharmacotherapy is the most effective cessation treatment for COPD. In patients with severe COPD, varenicline and bupropion have been shown to have the highest abstinence rates compared with nicotine replacement therapy. There is a lack of evidence to support that smoking cessation reduction or harm reduction strategies have benefits in COPD patients. The long-term efficacy and safety of electronic cigarettes for smoking cessation need to be evaluated in high-risk populations; therefore, it is not possible to recommend their use for smoking cessation in COPD. Future studies with the new generation of nicotine vaccines are necessary to determine their effectiveness in smokers in general and in COPD patients.

Introduction

Cigarette consumption is the leading risk factor for COPD, especially in developed countries. However, COPD can result from other environmental exposures, such as passive smoking exposure or indoor pollution from biomass, repeated infections, poverty and genetic factors that can alter lung growth during early life.

A systematic review and meta-analysis that aimed at identifying risk factors for COPD in nonsmoking adults showed that second-hand smoking was the main risk factor in this population [1]. Among patients included in the analysis, 56% had active smoking as the risk factor and 44% were nonsmokers; in the latter population, 46.9% of patients had passive smoke exposure. Therefore, smoking (active or passive) was associated with 76% of COPD cases. Patients who were exposed to smoke as passive smokers and who were healthy had a probability of developing COPD of 94.6% (pooled OR 52.97, 95% CI 44.65–62.83) [1].

There is evidence that about half of COPD cases are due to accelerated loss of lung function related to adult smoking. The rest are due to failure to achieve normal lung function in early adulthood, followed by age-appropriate decline rates [2–5]. Therefore, the pathogenesis of COPD may begin before birth since passive fetal exposure to smoke *in utero* is associated with an increased risk of COPD in adults, independently of subsequent active smoking, as well as passive smoke exposure in childhood or active smoking in adolescence [2, 5]. For all these reasons, smoking cessation has been considered as the single most cost-effective strategy to prevent and reduce disease progression. Nevertheless, despite the existence of different effective smoking cessation interventions, the evidence shows that the chances of COPD patients sustaining quitting smoking are still relatively low [6].

Importance of smoking cessation in COPD

In integrated care programmes for patients with COPD, part of the standard care is to help the patient in their attempts to stop smoking. For decades, the benefits of quitting smoking have been proven beyond any doubt. ANTHONISEN *et al*. [7] in the Lung Health Study (smokers with mild COPD) showed that all-cause mortality was significantly lower in people who received smoking cessation intervention compared with those who received no intervention (8.83 *versus* 10.38 per 1000 person-years; p=0.03) after 14.5 years of follow-up. ANTHONISEN *et al*. [8] also report that smoking cessation significantly reduces the age-related decline in forced expiratory volume in 1 s (FEV_1) (−72 mL per 5 years for sustained quitters *versus* −301 mL per 5 years for continued smokers). It has also been reported that quitting smoking improves daily symptoms [9] and decreases exacerbations [10], which are the main markers of disease activity and progression [11].

Tobacco dependence

Tobacco is the second most used psychoactive substance worldwide, with more than 1 billion smokers globally [12]. Tobacco dependence is a chronic relapsing disease driven by nicotine addiction, often requiring multiple therapeutic interventions and long-term support. Nicotine is the leading psychoactive agent in tobacco and electronic cigarettes (e-cigarettes). This agent acts as an agonist at nicotinic acetylcholine receptors (nAChRs), localised throughout the brain and peripheral nervous system [13]. Both brain localisation and the type of nAChR are critical elements in mediating the various effects of nicotine. However, other factors, such as the rate of nicotine delivery, may also modulate the addictive effects of nicotine [14, 15].

The reward obtained from nicotine is related to the mesolimbic pathway, which has dopaminergic neurons in the ventral tegmental area (VTA). These neurons project to the nucleus accumbens and the prefrontal cortex. These regions express several nAChR subtypes in dopaminergic, GABAergic and glutamatergic neurons. This distribution causes nicotine administration to increase dopamine levels by firing dopaminergic neurons into striatal and extra-striatal areas (such as the ventral pallidum). The subject experiences a feeling of reward, mediated primarily by the action of nicotine on the α_4- and β_2-containing nAChRs in the VTA [16].

The genetic basis of nicotine dependence has been widely studied. In the Older Finnish Twin Cohort (n=2923 monozygous and n=6018 dizygous), the authors reported that genetic factors are important in the amount smoked and smoking cessation, and are largely independent of genetic influences on age at initiation [17]. Other findings have linked increased vulnerability to nicotine addiction and increased cigarette smoking per day to allelic variation in the *CHRNA5–CHRNA3–CHRNB54* gene cluster, which encodes α_5, α_3 and β_4 nAChR subunits [18, 19]. Allelic variation in *CYP2A6* (encoding the enzyme cytochrome P450 2A6, which metabolises nicotine) has been associated with less predisposition to nicotine dependence. These allelic variations result in slow metabolism of nicotine, so individuals consume less nicotine per day, experience less severe withdrawal symptoms and are more successful at quitting smoking than people with normal or fast metabolism. The slow nicotine metabolism is due to an increase in the duration of action at the receptor, letting its levels build up over time. Thus, lower levels of intake are needed to maintain nAChR activation [20–22].

Other studies in large samples showed different genes associated with alcohol and nicotine addiction or dependence [23]. However, in patients with COPD specifically, two single nucleotide polymorphisms in *CHRNA3/5* (rs8034191 and rs1051730) were associated with the Fagerström test in active smokers and in those with nicotine dependence [24].

Epidemiological aspects of smoking in COPD

Despite the clear evidence of the benefits of smoking cessation in COPD, a significant proportion (over a third) of patients continue to smoke even knowing that they have moderate-to-severe disease and are experiencing significant symptoms.

Several studies in different populations worldwide have evaluated the smoking status in patients with COPD. The proportion of COPD patients who are current smokers varies considerably between populations and world regions (figure 1). In population-based studies the proportion of current-smoker COPD patients ranged from 34% in Spain to almost 48% in China, with an average of 35.6% [25–28], whereas in observational studies the proportion ranged from 30% (Daxas in COPD Therapy (DINO) study) to 43.4% (COPDGene cohort) [29–33]. On the other hand, an analysis of individuals with COPD enrolled in some COPD pharmacological clinical trials showed that the proportion of current smokers ranged between 20% and 48%, with an average of 38% [34–43].

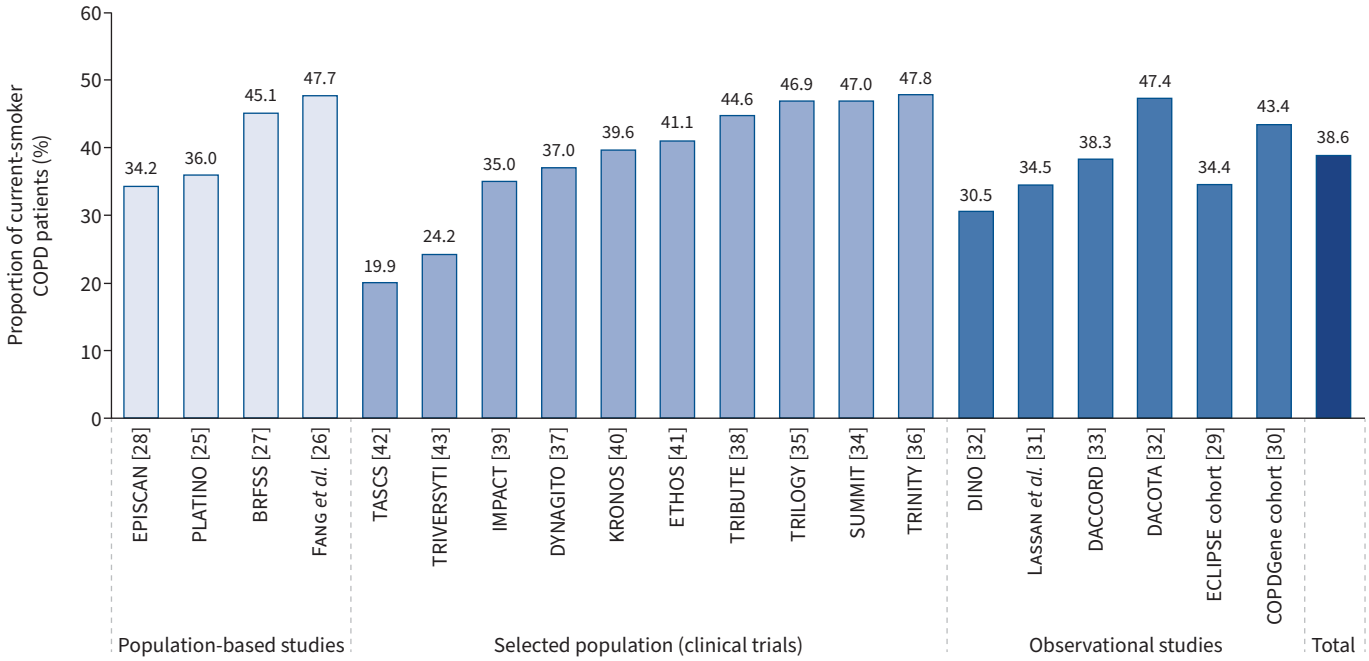

FIGURE 1 Prevalence of current-smoker COPD patients in different settings.

Assessment and approach to the smoking patient with COPD (motivation and tobacco dependence)

There are differences in clinical characteristics between smokers with and without COPD. Smokers with COPD exhibit higher dependence on nicotine, smoke more cigarettes per day, have higher cotinine concentrations, and have lower self-efficacy and self-esteem than those without the disease, all of which affect their ability to quit smoking [44–46]. These characteristics are neither linked to a lack of motivation to quit (because this was similar between smokers with and without COPD) nor to differences in the stage of the self-change process or the number of quit attempts [45, 46]. Nevertheless, depression has been reported to be more frequent in smokers with COPD, a fact that can influence the behaviour of these patients [47]. Regarding treatment, smokers with COPD seem to have similar susceptibility to smoking cessation interventions compared with those without COPD. Results from real-world studies and clinical trials have shown that the combination of brief or intensive counselling in smokers with COPD had comparable abstinence rates over 1 year to smokers in general [48–51]. However, a study showed that 1-year quit rates in smokers with COPD were higher than in those without COPD [52].

Other studies have investigated the clinical characteristics of patients with COPD who continue smoking *versus* sustainers quitting smoking [6, 48, 53, 54]. The main characteristics associated with current smoking in COPD patients are younger age, longer duration of smoking, fewer daily cigarettes, lower socioeconomic status, earlier stages of the disease, milder symptoms, poor quality of life and worse self-perceived general health [6, 53, 54]. Self-efficacy in smokers with COPD is usually low [46]. Perception of better health might be associated with higher self-efficacy to abstain from smoking, leading to more successful quit attempts. At the same time, psychological distress, including depressive symptoms, might contribute to unsuccessful attempts to quit smoking in COPD patients [6].

The approach to smokers with COPD, and smokers in general, should consider the mental situation in which the subject is in at the time of consultation, paying particular attention to aspects linked to tobacco consumption (motivation and dependence).

An accurate evaluation of motivation to classify the patient according to the Prochaska–DiClemente phase model [55] (table 1), as well as the strengthening of motivation and the construction of self-efficacy, is essential to increase the chances of quitting smoking in patients with COPD. The stages of change for smoking cessation represent a cycle. Therefore, patients may return to a previous state several times before absolute abstinence. Due to this cycle, it is crucial to establish the patient's current stage frequently and

TABLE 1 Stages of change for smoking cessation (Prochaska–DiClemente model [55])

Precontemplation	Active smokers not interested in quitting in the next 6 months
Contemplation	Active smokers considering quitting sometime in the next 6 months
Preparation	Active smokers planning on quitting in the next 30 days
Action	Quit smoking within the last 6 months
Maintenance	Quit smoking more than 6 months ago

continue providing a positive support system, as it may take multiple quit attempts before cessation. It is not recommended to initiate pharmacotherapy for smoking cessation until the patient is in the preparation stage.

Stopping smoking is complex and smokers often fail due to nicotine addiction; therefore, an accurate evaluation of nicotine dependence is crucial in the cessation process. As in any smoker subject, assessment of smokers with COPD involves evaluation of the number of pack-years, degree of physical dependence on nicotine using the Fagerström test [56] or its short version (Heaviness of Smoking Index) [57], analysis of previous attempts to quit and determination of carbon monoxide levels in exhaled air (figure 2). Some indicators of high nicotine dependence (figure 2) are smoking within 30 min after waking up, nocturnal smoking, consuming ⩾20 cigarettes per day and a score of 7–10 points on the Fagerström scale or 5–6 points on the Heaviness of Smoking Index.

Smoking cessation interventions in patients with COPD

Advice, counselling interventions and spirometry as a motivational tool

A Cochrane review in general smokers showed that individual counselling was more effective than minimal contact when pharmacotherapy was not offered to participants (risk ratio 1.57, 95% CI 1.40–1.77) and was estimated to increase cessation by 40–80% after at least 6 months [58]. On the other hand, a pooled analysis of smokers with and without pharmacotherapy indicated that more intensive counselling has a small benefit over less intensive counselling (risk ratio 1.29, 95% CI 1.09–1.53) [58].

In patients with COPD, offering straightforward advice to quit or smoking cessation counselling (SCC) by healthcare professionals is an effective smoking cessation intervention, especially when combined with

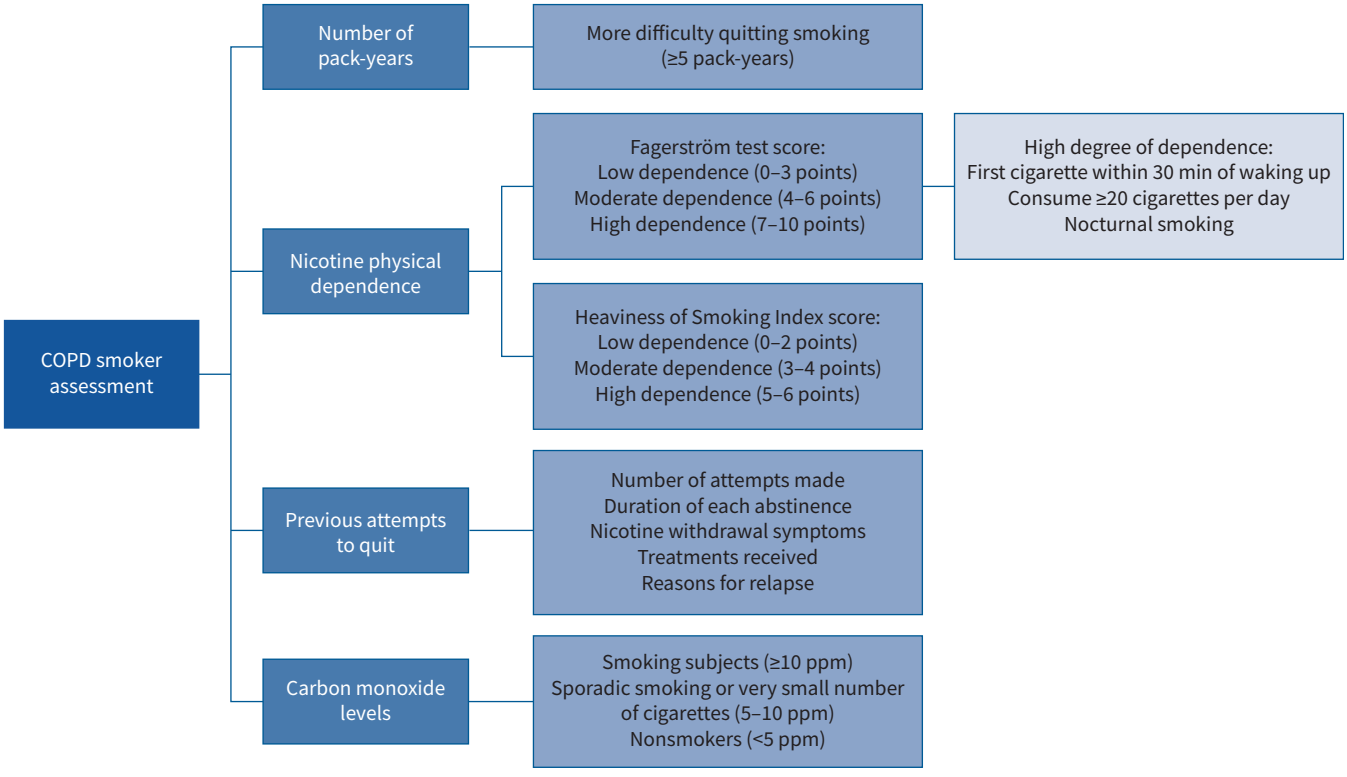

FIGURE 2 Assessment of smokers with COPD.

pharmacological treatment. A network meta-analysis in COPD patients showed a trend of SCC alone to be superior to usual care (OR 1.82, 95% CI 0.96–3.44; p=0.07) [59]. The odds of prolonged abstinence for SCC in combination with nicotine replacement therapy (NRT) were 5 times higher compared with no intervention or usual care (OR 5.08, 95% CI 4.32–5.97; p<0.0001), 3 times higher compared with SCC alone (OR 2.80, 95% CI 1.49–5.26; p=0.001) and 1.5 times higher compared with SCC in combination with an antidepressant (OR 1.53, 95% CI 0.71–3.30; p=0.28) [59]. Other systematic reviews reported average 12-month continuous abstinence rates of 1.4% for usual care, 2.6% for minimal counselling (<90 min), 6% for intensive counselling (≥90 min) and 12.3% for intensive counselling with pharmacotherapy [60].

Regarding the effectiveness of high-intensity compared with low-intensity counselling interventions in patients with COPD, a meta-analysis showed that the odds ratios were not significant for the comparisons of high-intensity SCC alone *versus* low-intensity SCC alone (OR 1.46, 95% CI 0.44–4.90; p=0.54) and high-intensity SCC in combination with an antidepressant *versus* low-intensity SCC in combination with an antidepressant (OR 1.55, 95% CI 0.35–6.91; p=0.56) [59]. Only high-intensity SCC plus NRT was significantly more effective than low-intensity SCC plus NRT (OR 1.81, 95% CI 1.04–3.15; p=0.04) [59]. Therefore, it is unclear whether more intensive individual counselling is more effective when combined with pharmacotherapy. On the other hand, high-intensity behavioural treatment increased abstinence rates when compared with usual care (risk ratio 25.38, 95% CI 8.03–80.22) or low-intensity behavioural treatment (risk ratio 2.18, 95% CI 1.05–4.49) [6].

Obtaining lung function testing and providing those results to individuals who smoke has been proposed as a motivational tool to improve smoking cessation. A systematic review showed insufficient evidence to determine whether providing lung function values to patients improves smoking cessation compared with other methods [61]. A subsequent systematic review of seven randomised controlled trial (RCT) studies showed mixed results [62]. Two of the studies found an improved rate of smoking cessation when smokers were provided with lung function results in addition to SCC, whereas the other five studies showed no significant differences [62]. Therefore, there is not enough evidence to support that providing lung function results (FEV_1 and/or lung age) to smokers contributes to a higher rate of smoking cessation.

Pharmacotherapy: controllers (NRT patch, bupropion and varenicline) and relievers (rapidly acting NRT)

Given that nicotine dependence in patients with COPD is usually high, these patients should be treated with various interventions (counselling, psychological-behavioural support and pharmacological treatment). The results of a meta-analysis indicated that smokers with COPD who receive a combination of high-intensity behavioural support and medication were more than twice as likely to quit as those who receive behavioural support alone [6].

In general, pharmacological treatments for smoking cessation include controller medications that aim at long-term abstinence (nicotine patch, bupropion and varenicline) and those that rapidly relieve acute cravings and withdrawal symptoms (fast-acting nicotine). The pharmacological approach to smoking cessation in COPD depends on the severity of dependence and the presence and intensity of withdrawal symptoms during treatment. Treatment should be adapted to the needs of individual patients with different levels of tobacco dependence. Once treatment starts, the pharmacotherapy intensity should be adjusted up or down, guided by the level of control of tobacco dependence. Table 2 shows the doses and duration of pharmacological treatments to quit smoking.

Pharmacological treatment compared with placebo in smokers with COPD

Some studies have compared simple controller pharmacotherapy (NRT, bupropion, nortriptyline and varenicline) with placebo in smokers with COPD [6, 63]. A meta-analysis showed that all pharmacotherapy groups (except for nortriptyline) increased the chance of quitting smoking compared with placebo [6]. Prolonged abstinence rates in the pharmacotherapy groups ranged from 14% to 27%, while in the placebo group rates ranged from 5% to 9% [6]. The pooled (6–12 months follow-up) risk ratio for prolonged abstinence at the most extended follow-up was 2.53 (95% CI 1.83–3.50) compared with placebo and for each one of the pharmacotherapy groups was: NRT (12 months follow-up) 2.60 (95% CI 1.29–5.24), bupropion (6 months follow-up) 2.03 (95% CI 1.26–3.28), varenicline (12 months follow-up) 3.34 (95% CI 1.88–5.92) and nortriptyline (6 months follow-up) 2.54 (95% CI 0.87–7.44) [6].

Comparison between different pharmacological interventions and combined controller therapies in smokers with COPD

A study that compared bupropion with NRT patch showed a prolonged abstinence rate at 12 months of 16% in the bupropion group and 21% in the NRT patch group (risk ratio 0.74, 95% CI 0.27–2.05) [64].

TABLE 2 Doses and duration of pharmacological treatments to quit smoking

Medication	Mechanism of action	Dosage and treatment duration	Side-effects
Nicotine replacement therapy	Acts at the level of nicotinic central nervous system receptors	16-h patches >10 cigarettes per day: 25 mg once daily×6 weeks 15 mg once daily×4 weeks 10 mg once daily×2 weeks 5 mg once daily×2 weeks <10 cigarettes per day: 10 mg once daily×6 weeks 5 mg once daily×2 weeks 24-h patches >10 cigarettes per day: 21 mg once daily×6 weeks 14 mg once daily×4 weeks 7 mg once daily×2 weeks <10 cigarettes per day: 14 mg once daily×6 weeks 7 mg once daily×2 weeks Chewing gum 2–4 mg or tablets 1–2 mg if craving	Redness or itching of skin where patch applied, urticaria, headache, dizziness, nausea/vomiting, insomnia Mouth soreness, throat irritation, jaw ache, dyspepsia, flatulence, nausea, emesis, unpleasant taste, possible allergic reactions
Bupropion	Inhibits neuronal reuptake of dopamine and norepinephrine in the nucleus accumbens and locus coeruleus	⩾12 weeks: 150 mg per 12 h First week progressive dose	Insomnia (most common), dry mouth, anxiety, irritability, restlessness, headache, tinnitus, skin rash, seizures (rare and most alarming)
Varenicline	Partial agonist for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor (dopamine release in the nucleus accumbens)	⩾12 weeks: Days 1–3: 0.5 mg once daily Days 4–7: 0.5 mg twice daily Days 8+: 1 mg twice daily	Nausea (most common), insomnia, abnormal dreams, sleep disturbance, dyspepsia, abdominal pain, constipation, flatulence, emesis, dizziness, dry mouth

In another study which enrolled patients with severe and very severe COPD, varenicline and bupropion yielded higher abstinence rates compared with NRT patch [65]. Continuous abstinence rates through weeks 9 to 24 were 38.2% for NRT, 55.6% for bupropion and 58.3% for varenicline [65]. Varenicline was more effective than nicotine patch in inducing sustained abstinence (OR 1.98, 95% CI 1.25–3.12) and as effective as bupropion at 6 months follow-up (OR 1.43, 95% CI 0.49–2.2) [65]. Nevertheless, the group who had received varenicline compared with bupropion smoked a higher number of cigarettes daily [65].

Combination of controller therapies to induce smoking cessation has also been considered a valid approach to increase the overall efficacy of the intervention. In COPD patients, a study assigned an intervention programme with counselling and advice about NRT (and additional bupropion-SR in one of the programmes) or usual care [66]. The results indicate that the two intervention groups were equally effective in terms of abstinence rates (risk ratio 2.25, 95% CI 0.87–5.85; p=0.10) [66]. However, there might have been some issues interfering with combination effectiveness such as the inclusion of some unmotivated COPD smokers, less intensive counselling, and poor compliance with the use of bupropion and NRT [66]. Combinations of varenicline with other controller therapies have also been proposed for smoking cessation; however, there are no studies that have assessed the effectiveness of these combinations in patients with COPD.

Smoking reduction-to-quit interventions for reducing harm and increasing long-term quitting

Quitting smoking is the best thing that a COPD patient can do to reduce the harm caused by smoking. However, some patients may not want to do this or feel that they cannot stop smoking completely. On the other hand, relapse is common during smoking cessation; therefore, harm reduction has been considered as an alternative approach for smokers with COPD unable or unwilling to quit. The possible approaches to reduce the exposure to toxins from smoking include reducing the amount of tobacco used and using less toxic products, *e.g.* pharmaceutical nicotine and potential reduced-exposure tobacco products.

It has been postulated that in smokers who cannot quit abruptly, reducing smoking increases the probability of quitting in the future. In general smokers, a meta-analysis did not show clear evidence that

reduction-to-quit interventions resulted in better quit rates than no smoking cessation intervention (risk ratio 1.74, 95% CI 0.90–3.38) [67]. In addition, the comparison between reduction and abrupt smoking cessation interventions showed no difference in long-term quitting rates (risk ratio 1.01, 95% CI 0.87–1.17) [67]. A subgroup analysis found some evidence that reduction-to-quit interventions may be more effective than abrupt quitting interventions if varenicline is used as an aid to reduction; this result was based on a single study and should be viewed with caution [67].

On the other hand, another meta-analysis that evaluated the effects of interventions aimed at reducing the health harm of continued tobacco use in smokers who are unable or unwilling to quit found that none of the studies directly tested whether harm reduction strategies reduced the harms to health caused by smoking (long-term change in health status) [68]. Most of the studies tested NRT as an intervention to assist reduction and the pooled analysis showed that people unwilling to quit can be helped to cut down the number of cigarettes they smoke (reduction of ⩾50% in cigarettes per day: risk ratio 1.75, 95% CI 1.44–2.13) and to quit smoking in the long-term (risk ratio 1.87, 95% CI 1.43–2.44) using NRT [68]. There is a lack of evidence to support the use of other aids (bupropion, varenicline, e-cigarettes or snus (oral tobacco product)) to reduce the harm caused by continuous tobacco smoking [68] and to support that reducing the number of cigarettes smoked daily can improve health or help patients with COPD to quit smoking completely in the long-term.

E-cigarettes for smoking cessation

The use of e-cigarettes has increased probably due to the presumption that it is associated with less damage, as well as reducing the symptoms of anxiety and withdrawal from tobacco by sharing the same visual and sensory characteristics.

A meta-analysis showed a significant association of e-cigarette use with COPD (adjusted for cigarette smoking and other covariates), with a pooled adjusted OR of 1.49 (95% CI 1.36–1.65) for e-cigarette users compared with non-e-cigarette users [69]. The authors concluded that e-cigarette use has consequences for asthma and COPD, which is of concern for respirology and public health [69].

There is a perception that e-cigarette use is safer or an effective NRT during the smoking cessation process. A recent study assessed the effectiveness, tolerability and safety of using e-cigarettes for smoking cessation [70]. There was moderate-certainty evidence (limited by imprecision) that quit rates were higher in people randomised to nicotine e-cigarettes than in those to NRT (risk ratio 1.53, 95% CI 1.21–1.93) and low-certainty evidence (limited by very serious imprecision) that the rate of occurrence of adverse events was similar (risk ratio 0.98, 95% CI 0.80–1.19) between groups [70].

On the other hand, the results of a trial aimed at evaluating the 1-year efficacy of e-cigarettes compared with NRT as a smoking cessation treatment in general smokers showed that the abstinence rate was 18% for the e-cigarette group and 9.9% for the NRT group (risk ratio 1.83, 95% CI 1.30–2.58) [71]. However, an important finding to highlight in this study was that among participants with 1-year abstinence, 80% were using e-cigarettes at 52 weeks in the e-cigarette group in comparison with 9% of those in the NRT [71].

There is very limited information on the health consequences (COPD outcomes) of e-cigarette use among smokers with COPD, as well as on their effectiveness to help these patients attenuate the consumption of cigarettes or achieve long-term smoking abstinence.

A small retrospective study in 48 patients with COPD who had reported regular daily use of e-cigarettes found that patients were able to quit or substantially reduced their tobacco consumption by switching to regular e-cigarette use, with improvement in COPD exacerbations, FEV_1 decline, COPD Assessment Test (CAT) scores and 6-min walk distance (6MWD) [72]. Subsequently, the same group of authors prospectively assessed respiratory parameters in 44 COPD patients who ceased or substantially reduced conventional cigarette use with e-cigarettes [73]. They reported a decline in the use of conventional cigarettes in the e-cigarette user group and improvements in exacerbation rates, CAT scores and 6MWD, but no change in lung function over the 3-year period [73].

The possible evidence of respiratory health benefits of e-cigarette use from these studies in COPD patients contrasts with the results of two large observational studies [74, 75] and with the concerns raised in experimental models (*i.e.* cell cultures and animal models) that suggest that chronic exposure to e-cigarettes may elicit features of COPD/emphysema and damage the airway epithelium, among other harmful effects in the respiratory system [76–83]. A study in two prospective large cohorts (COPDGene (n=3536) and SPIROMICS (n=1060)) that aimed to determine the usage of e-cigarettes in older adults at

risk for or with COPD showed that e-cigarette users had a heavier conventional cigarette smoking history (higher nicotine dependence), worse pulmonary-related health outcomes (more chronic bronchitis and exacerbations) and were less likely to reduce or quit smoking conventional cigarettes [74]. Another large prospective study showed an increased risk of respiratory disease among former (incidence risk ratio 1.28, 95% CI 1.09–1.50) and current e-cigarette users (incidence risk ratio 1.31, 95% CI 1.08–1.59) even when adjusted for cigarette and other combustible tobacco product use, demographic characteristics, and chronic health conditions [75]. Therefore, these findings do not support a reduction in harm using e-cigarettes, and may even suggest higher nicotine exposure and higher risk of respiratory diseases [74, 75].

Taking into account the incomplete information on the safety and efficacy of e-cigarettes as an aid for smoking cessation, it is necessary to carry out a frequent and balanced review of the probable benefits and damages with which they are associated before recommending their use. The long-term efficacy and safety of e-cigarettes for smoking cessation also need to be evaluated in larger high-risk populations. Therefore, based on the available evidence and on the largely unknown long-term health effects of e-cigarettes, it is not possible to recommend this intervention for smoking cessation or for reducing conventional cigarette use in patients with COPD.

Nicotine vaccine

The idea of an immunotherapy approach for treating addictions can be found in the literature since the 1960s [84]. The development of vaccines related to drug abuse is a public health approach that has been explored for over a decade. The nicotine vaccine is intended to treat drug abuse through active immunisation by inducing nicotine-specific monoclonal antibodies (nic-mAbs) to sequester and reduce nicotine distribution inside the brain.

The nicotine-blocking effect of nic-mAbs has been successfully studied in pre-clinical models, with up to ∼80% reduction in brain nicotine levels within minutes of an intravenous dose of nicotine [85, 86]. nic-mAbs are particularly effective in reducing the early distribution of nicotine to the brain, which is important because the greatest reinforcing and subjective effects occur within the first few minutes of smoking [87]. However, a Cochrane systematic review including four studies with a total of 2642 smokers found no evidence that nicotine vaccines improve long-term smoking cessation [88]. None of the included studies detected a significant difference in long-term cessation between participants who received the vaccine and those who received placebo. The risk ratio for 12-month cessation in active and placebo groups was 1.35 (95% CI 0.82–2.22) in the NIC002 trial and 1.74 (95% CI 0.73–4.18) in one NicVAX trial [88]. However, one RCT in 301 smokers evaluating 200 and 400 µg doses of NicVAX (a nic-mAb) showed that subjects with the highest serum antinicotine antibody response (top 30% by area under the curve) were more likely to attain 6 weeks of continuous abstinence from weeks 19 through 26 than the placebo recipients (24.6% *versus* 12%; OR 2.69, 95% CI 1.14–6.37; p=0.0024) [89].

A recent systematic review that included 15 clinical trials (11 RCTs, three non-RCTs and one cohort study) demonstrated conflicting information around the vaccine [90]. Factors that contributed to these findings were the inclusion of low or unsustained antibody response between individuals and continued nicotine use despite the antibody response. The explanation is not straightforward because there are many challenges and complexities associated with nicotine dependence (genetic factors, drug design and clinical trial designs). Many of the trials for nic-mAbs are not published in peer-reviewed journals after completion, which suggests that this is related to insignificant findings. However, there are several conclusions from those first clinical studies: the nicotine vaccines need to generate high levels of antibodies and improve the design, maybe using nanoparticles instead of a protein conjugate [84, 90]. Future studies with the new generation of nicotine vaccines will be necessary to clarify whether they are more effective in human trials.

Smoking cessation during the coronavirus disease 2019 pandemic in smokers with COPD

The recent coronavirus disease 2019 (COVID-19) pandemic resulted in more than 600 million cases and 6 million deaths worldwide [91]. COPD patients and smokers are at increased risk of poor outcomes and severe disease from COVID-19 [92]. The biological explanation could be the upregulation of the angiotensin-converting enzyme 2 receptors and the epithelial damage present in COPD patients and smokers. Another explanation is more mechanistic and involves hand-to-face movement, which would accelerate viral transmission [93], making the care of COPD patients with COVID-19 particularly challenging.

In a recent consensus built from surveys of COPD patients and doctors during the pandemic, there was a consensus (84% of participants) that remote care, although it limits face-to-face interaction, should reinforce smoking cessation [94].

The impact of the COVID-19 pandemic on smoking behaviour is complex and unclear. A recent systematic review that included 11 publications (58 052 participants) found that smoking consumption decreased during the pandemic in most cases [95]. Fear and social restrictions could be leading to an excellent opportunity to reduce or quit smoking.

Regarding patients with COPD, it is important to highlight the need to: 1) warn the population of the increased risk that smokers have of contracting COVID-19 and of the worse prognosis of the disease, 2) highlight the importance of quitting smoking through new methods such as applications or remote evaluations of outpatients, 3) discourage the use of new electronic nicotine devices and water pipes, which can favour the development of this disease, and 4) emphasise the importance of smoke-free environments, as well as continue generating evidence on the impact of smoking on the development of COVID-19 [96]. To the best of our knowledge, there is no evidence of the development of unique measurements to increase smoking cessation in COPD patients during the pandemic.

The efficacy of vaccination is related to the capacity to produce high levels of antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Several studies evaluated the relationship between antibody levels after vaccination and smoking status [97–99]. One study found that smoking is a risk factor for low antibody titres even 3 months after the second dose of mRNA vaccination against SARS-CoV-2 independent from the Brinkman index or cigarettes per day [97]. The age-adjusted antibody titres were lower in ever-smokers in comparison with never-smokers (median (interquartile range) −174 (−378 to 145) and 90 (−174 to 512) $U \cdot mL^{-1}$, respectively; $p<0.0001$).

In summary, rather than an obstacle, the COVID-19 pandemic represents an opportunity to discuss smoking cessation with COPD patients, highlighting the benefits of improving their response to the virus, their prognosis and their response to the vaccination.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: M. Montes de Oca has received honoraria for lectures on COPD from AstraZeneca and GSK, outside the submitted work. M.E. Laucho-Contreras has received an honorarium for Medical Affairs Staff from GSK Colombia and owns GSK stock, all outside the submitted work.

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