Update on the approach to smoking in patients with respiratory diseases

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ABSTRACT

Smoking is the leading cause of respiratory disease (RD). The harmful effects of smoking on the respiratory system begin in utero and influence immune responses throughout childhood and adult life. In comparison with “healthy” smokers, smokers with RD have peculiarities that can impede smoking cessation, such as a higher level of nicotine dependence; nicotine withdrawal; higher levels of exhaled carbon monoxide; low motivation and low self-efficacy; greater concern about weight gain; and a high prevalence of anxiety and depression. In addition, they require more intensive, prolonged treatment. It is always necessary to educate such individuals about the fact that quitting smoking is the only measure that will reduce the progression of RD and improve their quality of life, regardless of the duration and severity of the disease. Physicians should always offer smoking cessation treatment. Outpatient or inpatient smoking cessation treatment should be multidisciplinary, based on behavioral interventions and pharmacotherapy. It will thus be more effective and cost-effective, doubling the chances of success.

Keywords: Respiratory tract diseases/therapy; Respiratory tract diseases/drug therapy; Tobacco use disorder/epidemiology; Smoking cessation; Counseling; Lung neoplasms.

INTRODUCTION

Smoking is the leading cause of preventable death worldwide, annually accounting for 7 million deaths, 890,000 of which are associated with passive smoking.(1) In Brazil, 156,000 people die each year from smoking-related diseases.(2) Worldwide, there are approximately 1.1 billion smokers, most of whom live in low- and middle-income countries, where the morbidity and mortality burden of smoking is higher.(1)

The prevalence of smoking in Brazil has dropped significantly, as evidenced in the 2006-2017 historical series of the Brazilian "Telephone-based System for the Surveillance of Risk and Protective Factors for Chronic Noncommunicable Diseases Survey", which showed that the prevalence fell from 19.5% to 10.1%, translating to a 48.2% reduction.(3) The survey showed that, although smokers accounted for only 10.1% of general population in 2017 (13.2% of the male population and 7.5% of the female population), there were still 18.2 million smokers ≥ 18 years of age in that year.(3,4)

The Framework Convention on Tobacco Control(5) lists offering smoking cessation treatment as one of the six most cost-effective policies in the MPOWER package, the acronym MPOWER standing for Monitoring tobacco use and prevention policies; Protecting people from tobacco smoke; Offering help to quit tobacco use; Warning about the dangers of tobacco; Enforcing bans on tobacco advertising, promotion and

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Patients to give up the habit and offering smoking cessation treatment. This approach should be taken in conjunction with the treatment of the underlying disease. Therefore, physicians need to be trained not only in the management of the smoking cessation pharmacotherapy but also in cognitive-behavioral therapy techniques.(13,15)

From the first visit, the physician should inform the patient of the fact that quitting smoking is the only measure that will slow the decline in lung function, improve the response to treatment, and reduce the frequency of exacerbations. The approach should be multidisciplinary and should be applied at all levels of health care, for outpatients and inpatients.(20,21)

Smokers with respiratory diseases have peculiarities that can hinder smoking cessation, such as a higher level of nicotine dependence and withdrawal symptoms that are more severe; low motivation; low self-efficacy; excessive concern about weight gain; and a high prevalence of psychiatric disorders. In addition, they require treatment that is more intensive and prolonged.(21,22)

Identifying the predictive factors and knowing the techniques for achieving smoking cessation are fundamental to the approach to smokers. The level of motivation is predictive of the frequency of attempts to quit smoking, and the level of nicotine dependence is predictive of the outcomes of those attempts. The concomitant use of alcohol or drugs can make smoking cessation more difficult.(23,24)

Before starting treatment, smokers should undergo a full clinical evaluation, as detailed in Chart 1.(10,13) The objectives of the anamnesis include analyzing the smoking habits of patients, as well as their level of motivation, dependence, and self-efficacy, together with their experience in previous attempts at smoking cessation, their history of smoking-related diseases, contraindications for specific medications, their beliefs, and their preferences.(10,25) The physician should perform a complete physical examination and order ancillary tests, depending on the local demand and availability.(25) Spirometry and imaging findings can be useful in motivating such patients to quit smoking.(24,26,27)

Knowing the level of nicotine dependence is important to guide the treatment (Chart 2). The most widely used instrument is the Fagerström Test for Nicotine Dependence.(28) In 2012, it was renamed the Fagerström Test for Cigarette Dependence.(29) The instrument most widely used in assessing the level of motivation for quitting smoking is the transtheoretical model of change developed by Prochaska & DiClemente,(30) which is useful for developing a smoking cessation plan (Chart 3).

CURRENT EVIDENCE REGARDING THE EFFECTIVENESS OF COUNSELING AND PHARMACOTHERAPY

Cognitive-behavioral counseling

After identifying the level of nicotine dependence for each patient, the main subsequent step is a brief evaluation of smokers.

Smokers with respiratory diseases have a greater need and urgency to quit smoking; therefore, physicians need to take a proactive role in encouraging such patients to give up the habit and offering smoking cessation treatment. This approach should be taken in conjunction with the treatment of the underlying disease. Therefore, physicians need to be trained not only in the management of the smoking cessation pharmacotherapy but also in cognitive-behavioral therapy techniques.(13,15)

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It is known that self-efficacy and self-esteem affect the capacity of an individual to quit smoking; therefore, constructive advice should be directed at addressing issues related to the level of motivation to quit smoking and to remain abstinent. Whenever possible, the physician should individualize smoking cessation treatment, discussing the relationship that the individual has with the smoking habit and the reasons why the individual continues to smoke, as well as the therapeutic options available in terms of psychological and pharmacological support. In the initial counseling sessions, the physician should be empathetic and should be aware of smoking cessation strategies, in order to help the smoker through this early stage. The negative effects of smoking and the benefits of smoking cessation should be addressed. In the treatment protocol, it is essential to establish a date of cessation; to identify situations in which the risk of relapse is high and teach the skills required in order to cope with them; to explain the withdrawal symptoms; and to follow the patient closely through physician consultations, telephone calls, e-mails, WhatsApp messages, and text messages. The physician should educate the patient regarding the potential complications of treatment and benefits of quitting smoking. In addition, minimizing fatalistic beliefs and addressing depression improve self-efficacy, self-esteem, and the feeling of having control over the treatment. In patients with asthma or COPD, it is possible to increase the level of motivation by contextualizing the results of spirometry.
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In smokers with tuberculosis, application of the directly observed treatment, short-course (DOTS) strategy in combination with smoking cessation treatment has been shown to improve quality of life. For those patients, it is recommended that a brief intervention be provided at the time of diagnosis and that monthly behavioral support be maintained throughout the duration of the tuberculosis treatment. (32)

PHARMACOLOGICAL APPROACH

In patients with COPD, pharmacological intervention combined with intensive behavioral counseling has been shown to be effective, one meta-analysis demonstrating a high quality of evidence in pooled results, with a relative risk (RR) of 2.53 (95% CI: 1.83-3.50). (33) Comparing placebo with the use of monotherapy, that same meta-analysis showed that the chance of smoking cessation doubled when bupropion was used (RR = 2.03; 95% CI: 1.26-3.28), more than doubled when nicotine replacement therapy (NRT) was used (RR = 2.60; 95% CI: 1.29-5.24), and was three times higher when varenicline was used (RR = 3.34; 95% CI: 1.88-5.92). (33)

Nortriptyline, a second-line medication, shows no superiority over placebo in terms of achieving smoking cessation in patients with COPD. (34) Among smokers with asthma, the rate of cessation is low, although there have been few studies of the issue. Possible reasons for that include a lack of motivation to quit smoking, as well as other factors, such as depression, low socioeconomic status, and a low level of education. (35) A randomized clinical trial (RCT) involving patients with asthma showed no difference between the use of varenicline and that of placebo in terms of the smoking cessation rate (RR = 1.25; 95% CI: 0.38-4.14). (36)

With the use of NRT, bupropion, or varenicline, as with any other medication, adverse events may occur. Therefore, all patients using medications for smoking cessation should be monitored. Charts 4 and 5 present the first-line medications for smoking cessation and their main characteristics.

Extended and combined treatment

There are still few data in the literature to support the long-term use of varenicline. An open observational study showed that the benefit of varenicline was maintained over time, and that there was no evidence of tolerance. (37) Long-term use of varenicline may be beneficial for patients who have difficulty quitting smoking, as it can help to reduce the number of cigarettes smoked per day and to increase the likelihood of smoking cessation. (38) Further research is needed to determine the optimal duration of treatment and the best approach to smoking cessation in patients with COPD.
A study involving patients with severe to very severe COPD who used varenicline for 24 weeks showed that the smoking abstinence rate, as assessed by an intention-to-treat analysis, was 17.7%.(40) However, when studies involving smokers in general were evaluated, pooled data from four RCTs, involving a collective total of 2,170 individuals, indicated that long-term treatment with varenicline was effective (RR = 3.64; 95% CI: 2.1-4.72).(32) To our knowledge, there have been no RCTs examining the use of reduced doses of varenicline in patients with respiratory diseases. There have been only four RCTs, involving a collective total of 1,266 subjects, showing that varenicline is effective even at doses lower than those recommended for the general smoking population (RR = 2.08; 95% CI: 1.56-2.78).(33) A retrospective study of more than 14,000 patients diagnosed with COPD, with or without cardiovascular or psychiatric comorbidities, showed that, in comparison with the use of NRT, the use of bupropion or varenicline did not increase the risk of cardiovascular or neuropsychiatric events within the first six months of treatment. (41) The combination of two forms of NRT has the same effectiveness as does the use of varenicline (OR = 1.06; 95% CI: 0.75-1.48).(42) A meta-analysis of the pooled data from two RCTs, involving a total of 787 individuals, showed that the combination of varenicline and NRT (the nicotine patch) was more effective than
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**Chart 5. Mode of use, precautions, adverse effects, contraindications, efficacy, and combinations of first-line smoking cessation drugs.**

| Medication                  | Characteristic                        | Points to consider |
|-----------------------------|---------------------------------------|--------------------|
| Nicotine replacement therapy| **Prescription** Standard prescription| Initiation: recommended to start on the scheduled cessation date; can be used as pre-cessation therapy on a case-by-case basis |
|                             | **Mode of use**                        | Patch: apply to the trunk every morning, in hairless areas that are not exposed to the sun; leave in place for 24 h; no need to remove for bathing; rotate sites |
|                             |                                       | Gum: chew until tasting the flavor or feeling a tingling sensation; then leave between the gingiva and the cheek; chew again for 20-30 min |
|                             |                                       | Lozenge: slowly move it around in the mouth, without sucking, chewing or swallowing; dissolves in the oral cavity after 20-30 min |
|                             | **Precautions**                        | Avoid citrus drinks and food for 15-30 min after using nicotine gum or lozenges. |
|                             | **Adverse effects**                    | Patch: erythema and infiltration of the dermis at the site of application, sialorrhea, nausea, vomiting, diarrhea, and insomnia |
|                             |                                       | Gum: gingival lesions, sialorrhea, unpleasant taste, dental softening, nausea, vomiting, dyspepsia, hiccups, and pain in the TMJ |
|                             |                                       | Lozenges: hiccups, sialorrhea, unpleasant taste, and dyspepsia |
|                             | **Contraindications**                  | In the presence of cerebrovascular disease or cardiovascular disease that is severe or acute (< 15 days), discuss with the specialist and assess the risk-benefit ratio. Avoid the use of nicotine gum or lozenges in patients with active peptic ulcer or TMJ pain. |
|                             | **Efficacy**                           | Relative risk of success = 2.60 (95% CI: 1.29-5.24) |
|                             | **Combinations**                       | Patch used in combination with nicotine lozenges or gum |
| Bupropion                   | **Prescription** Restricted prescription, in duplicate | Addition of bupropion or varenicline in cases that are more difficult |
|                             | **Mode of use**                        | Start 7 days before the scheduled cessation date. Take the second tablet in the afternoon, at least 8 h after the first. |
|                             | **Precautions**                        | If possible, avoid taking the 2nd dose after 5:00 p.m., to reduce the risk of insomnia. Patients with gastritis should use an antacid and take bupropion with food. |
|                             | **Adverse effects**                    | Reduced reflexes (poor performance on tasks that require motor skills), dry mouth, insomnia, dizziness, headache, agitation, anxiety, tremors |
|                             | **Contraindications and drug interactions** | Numerous drug interactions Relative: harmful use of alcohol; and the use of carbamazepine, barbiturates, phenytoin, antipsychotics, antidepressants, cimetidine, theophylline, systemic corticosteroids, oral hypoglycemic agents, and insulin Absolute: epilepsy and seizures (including febrile seizures), recent alcohol withdrawal, cerebrovascular disease, bulimia, anorexia nervosa, panic attacks, use of MAO inhibitors in the last 14 days, < 16 years of age, pregnancy, and breastfeeding |
|                             | **Efficacy**                           | Relative risk of success = 2.03 (95% CI: 1.26-3.28) |
|                             | **Combinations**                       | Addition of nicotine replacement therapy or varenicline in cases that are more difficult |
| Varenicline                 | **Prescription** Standard prescription | Addition of nicotine replacement therapy or varenicline in cases that are more difficult |
|                             | **Mode of use**                        | Start 7 days before the scheduled cessation date. 0.5-mg tablets only for the 1st week, then 1-mg tablets twice daily for 11 weeks |
|                             | **Precautions**                        | The bioavailability is not affected by eating or by the schedule of administration; it can be taken after meals. |
|                             | **Adverse effects**                    | Most common: nausea (in 33%, rarely requiring discontinuation); and vivid dreaming Some patients report dizziness, dry mouth, drowsiness, and flatulence. It can be associated with depressive mood, suicidal ideation, and lack of control of psychiatric disorders, although such symptoms can also occur due to withdrawal syndrome. |
|                             | **Contraindications and drug interactions** | Few drug interactions Use with caution in smokers with severe psychiatric disorders (psychotic outbreak, suicidal ideation/attempt, etc.): discuss with the psychiatrist. |
|                             | **Efficacy**                           | Relative risk of success = 3.35 (95% CI: 1.89-5.92) |
|                             | **Combinations**                       | Addition of nicotine replacement therapy or varenicline in cases that are more difficult |

Based on Reichert et al.\(^{12}\); Fiore et al.\(^{13}\); Jiménez-Ruiz et al.\(^{22}\); van Eerd et al.\(^{33}\); Cahill et al.\(^{38}\); European Network for Smoking and Tobacco Prevention\(^{38}\); Brazilian National Ministry of Health\(^{38}\); and the (U.S.) National Comprehensive Cancer Network.\(^{39}\) TMJ: temporomandibular joint; and MAO: monoamine oxidase.
was the use of varenicline alone (OR = 1.62; 95% CI: 1.18-2.23). (43)

SMOKING AND RESPIRATORY DISEASES

Asthma and smoking

Asthma is a heterogeneous disease, with a variety of phenotypes, that results from complex interactions between environmental and genetic factors. Prenatal and postnatal exposure to environmental tobacco smoke (ETS) is associated with an increased risk of developing asthma-like symptoms in childhood. (44,45)

In a systematic review with meta-analysis, (44) prenatal and postnatal exposure to ETS were found to be associated with a 30-70% increase in the risk of incident wheezing among children ≤ 2 years of age. In that study, postnatal maternal smoking was shown to have a greater effect on the development of wheezing among such children (OR = 1.70; 95% CI: 1.24-2.35), with a 21-85% increase in the risk of incident asthma, whereas prenatal maternal smoking was shown to have a greater effect on the development of asthma (OR = 1.85; 95% CI: 1.35-2.53).

In another systematic review with meta-analysis, (45) prenatal maternal smoking was found to be associated with an increased risk of wheezing in children < 6 years of age (OR = 1.36; 95% CI: 1.19-1.55), as well as with an increased risk of wheezing or asthma in children ≥ 6 years of age (OR = 1.22; 95% CI: 1.03-1.44). One study showed that postnatal exposure to ETS was associated with wheezing in children < 6 years of age (OR = 1.21; 95% CI: 1.13-1.31 and OR = 1.30; 95% CI: 1.13-1.51 for maternal and paternal smoking, respectively), although it was often impossible to separate the role of postnatal exposure from that of prenatal exposure. (46)

In some patient samples, it has been shown that the likelihood of incident asthma increases after smoking cessation. (47-49) In one such sample, continued smoking during follow-up was also found to increase the risk of incident asthma significantly. (47)

To our knowledge, there have as yet been no studies evaluating asthma mortality attributable to smoking or the fraction of asthma attributable to active and passive smoking in Brazil. In 2013 in Brazil, there were more than 120,000 hospitalizations for asthma and 2,047 asthma-related deaths (5 deaths/day). (50) In individuals with asthma, smoking is associated with an accelerated decline in lung function, (51) as well as with a poor response to inhaled systemic corticosteroids. (52-55) In addition, smokers with asthma have a lower chance of achieving control of the disease, as well as a higher frequency of asthma exacerbations and hospitalizations due to such exacerbations. (56-59)

An association between marijuana smoking and the worsening of asthma symptoms has been recognized since the 1970s. (60-62) Smoking marijuana also exacerbates bronchial asthma and provokes symptoms consistent with asthma. (60-64) Passive exposure to marijuana smoke (inhalation of toxic substances) worsens the symptoms of asthma. (65) Therefore, individuals with asthma or bronchial hyperresponsiveness should avoid active and passive smoking of tobacco or marijuana.

Smoking cessation reduces asthma symptoms and allows better control of the disease. (66,67) There is some evidence to suggest that smokers with asthma are less likely to quit smoking than are those without asthma. (68,69)

In every patient with asthma or bronchial hyperresponsiveness, the physician should inquire about the smoking status. In the counseling sessions, physicians should emphasize the following:

- Individuals with asthma or bronchial hyperresponsiveness should avoid active and passive smoking of tobacco and marijuana.
- Nonsmokers should be advised not to start smoking.
- Tobacco smokers and marijuana smokers should be informed of the difficulties and risks of continuing to smoke those products and should receive support for smoking cessation.

The main benefits of smoking cessation in individuals with asthma include improving asthma control, reducing exacerbations, slowing the functional decline, and improving the therapeutic response.

COPD and smoking

COPD is a multisystem inflammatory disease that results from the interaction between genetic and environmental factors. Although cigarette smoke continues to be the main cause of the disease, there are regions in which the inhalation of smoke from biomass burning, occupational exposure, and air pollution also play relevant roles. (70-74)

The smoking history, which is related to the development, progression, and severity of COPD, is typically expressed in pack-years. However, the duration of smoking in years, in addition to being easier to evaluate, might correlate better with the risk of the development and progression of the disease. (75)

The prevalence of COPD varies depending on the risk factors, functional criteria, and analytical criteria. (76,77) The estimated prevalence of COPD worldwide and in Brazil is 12% and 15.8%, respectively. (70,78) Because age and smoking have a cumulative effect, it is estimated that 50% of smokers will develop the disease during their lifetime. (70,80)

COPD is now the third leading cause of death worldwide. A study conducted in the capital cities of Brazil found that 65% of the deaths attributable to smoking are in individuals with COPD, ischemic heart disease, lung cancer, or cerebrovascular disease. (81)

In another study, comparing mortality rates in Brazil between 1990 and 2015, (82) there was a 31% reduction in the rate of mortality from COPD (from 64.5 to 44.5/100,000 inhabitants), compared with a reduction of only 2.1% in the rate of mortality from lung cancer. In that same period, there was a 36.1%
reduction in the number of years of life lost due to death or disability.

Patients with COPD tend to conceal the fact that they still smoke from their physicians, even when their cotinine or exhaled carbon monoxide level belies their self-reported smoking status. Smokers with COPD have a greater smoking intensity and a higher level of nicotine dependence, requiring more guidance on the risks of and need to quit smoking, than do smokers without COPD. The level of motivation to quit smoking differs little between patients with and without COPD. However, self-efficacy is lower in smokers with COPD, partly because of the high prevalence of anxiety and depression among such individuals. In a sample of smokers with COPD in Denmark, the factors related to the lower chance of smoking cessation were being < 65 years of age; having mild airflow obstruction; being classified as being in Global Initiative for Chronic Obstructive Lung Disease risk group A; scoring low on the Medical Research Council scale; and having a low socioeconomic status. In that sample, depression was not found to worsen the smoking cessation rate, as was shown in another study.

Smoking cessation is the only intervention that alters the natural history of COPD. Smokers with COPD are more likely to be questioned about their smoking, receiving more guidance and treatment, than are those without COPD. However, when they are not encouraged to quit smoking or referred to smoking cessation programs, they maintain their smoking habits almost unchanged for several years.

Chart 6 summarizes the treatment recommendations and benefits of smoking cessation in patients with COPD.

**Lung cancer and smoking**

Cigarette smoke contains more than 7,000 compounds. According to the International Agency for Research on Cancer, more than 60 of those compounds have been shown to be carcinogenic in laboratory animals, and there is sufficient evidence that 12 of those are carcinogenic to humans. There is a strong correlation between lifetime smoking and genetic changes (DNA methylation and microRNA changes) leading to inactivation of tumor suppressor mechanisms. Active and passive smoking are responsible for more than 90% of lung cancer cases, with a direct correlation between pack-years of smoking and an increased risk of cancer.

Studies conducted in Brazil have shown that the incidence and mortality rates of smoking-related cancer, particularly in the lungs, oral cavity, and larynx, are high in the country. A study evaluating the proportion of cancer cases attributed to modifiable risk factors in Brazil estimated that, by 2020, the proportion of cases of lung cancer attributable to smoking will be 83.28% in men and 64.80% in women.

In a systematic review of studies involving patients with early-stage lung cancer who continued to smoke, continued smoking among those with non-small cell lung cancer was found to increase the risk of relapse (RR = 1.86; 95% CI: 1.01-3.41) and all-cause mortality (RR = 2.94; 95% CI: 1.15-7.54). In patients with limited small cell lung cancer who continued to smoke, there were also increases in the risk of relapse (RR = 1.26; 95% CI: 1.06-1.50), a second primary tumor (RR = 4.31; 95% CI: 1.09-16.98), and all-cause mortality (RR = 1.86; 95% CI: 1.33-2.59). Among the patients with non-small cell lung cancer ≥ 65 years of age, the authors found that the survival rate was 33% for those who continued to smoke and 70% for those who had quit smoking. The 5-year survival rate in the small cell tumor group was 29% among those who continued to smoke and 63% among those who had quit.

Smokers with cancer live with the pressure to quit smoking exerted by their physician and their family, as well as internal pressure to do so, blaming themselves

### Chart 6. Recommendations for the approach to smoking cessation and benefits of cessation in patients with COPD.

| Description | Recommendations |
|-------------|-----------------|
| Consultation | All patients with COPD should be asked if they smoke and, if so, should be encouraged to stop smoking and referred to a smoking cessation program. |
| Start of treatment | Smoking cessation treatment alters the natural course of COPD. Begin smoking cessation treatment as part of COPD treatment. |
| Treatment strategy | Combining behavioral counseling with first-line drugs (nicotine replacement therapy, bupropion, and varenicline) is the most effective approach. Patients who have more difficulty in quitting smoking can benefit from the use of more than one drug or high-dose nicotine patches. |
| Benefits of smoking cessation | In patients with COPD, the benefits vary depending on age, severity, and comorbidities. Main benefits: Slows the progressive decline in FEV, Reduces exacerbation and hospitalization rates Minimizes respiratory symptoms and improves quality of life Reduces the limitations in activities of daily living Improves the ability to perform activities of daily living Improves the control of comorbidities Improves the response to bronchodilators and inhaled corticosteroids |

Based on Jiménez-Ruiz et al.; Jiménez-Ruiz et al.; van Eerd et al.; the Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease; the U.S. Department of Health and Human Services; Bai et al.; Tonnesen et al.; Godtfredsen et al.; Anthonisen et al.; and Anthonisen et al. 102
for the development of the disease, although most such smokers want to quit. The threats of physical pain, psychological suffering, and death, as well as future challenges, hamper the decision-making process of some patients and motivate others to quit smoking. The distorted thought of it being too late to quit smoking also hampers that process.\(^{103}\)

A patient can oscillate between moments of high and low self-efficacy to quit smoking. That requires the physician to be sensitivity to the difference between those two states and to promote an individualized approach focusing on the benefits of smoking cessation, which will promote better treatment outcomes.\(^{103,105}\)

Approximately 50% of all smokers diagnosed with cancer continue to smoke.\(^{106}\) Smokers with lung cancer are more motivated to quit smoking than are those in the general population, although they can require care that is more intensive and comprehensive.\(^{103}\)

Smoking is an independent prognostic factor for lung cancer, the only one that is under the direct control of the patient. Although smoking abstinence rates are high after diagnosis, relapse rates are also high. Treatment and prevention of relapse are imperative since the first visit.\(^{103}\) Chart 7 summarizes the key recommendations in the approach to smoking cessation treatment in patients with lung cancer, as well as emphasizing the benefits of cessation during cancer treatment.

**Tuberculosis and smoking**

In 2016, there were 10.4 million new cases of tuberculosis and 1.7 million tuberculosis-related deaths, more than 95% of which occurred in low- and middle-income countries.\(^{110}\) Brazil is among the 22 countries that account for 80% of all cases of tuberculosis worldwide. According to the Brazilian National Ministry of Health, there were 4,374 tuberculosis-related deaths in Brazil in 2014.\(^{111}\) Tuberculosis and smoking are both more common in low- and middle-income countries. According to the World Health Organization, more than 20% of all new cases of tuberculosis can be attributed to smoking.\(^{112}\)

Smoking was identified as a risk factor for tuberculosis a century ago.\(^{113}\) In the last decade, several studies have demonstrated that, even after adjustment for other risk factors, there is a significant association between exposure to tobacco smoke and tuberculosis.\(^{114}\)

There is evidence that active and passive smoking are associated with active tuberculosis, as well as with the treatment response, relapse, and tuberculosis-related mortality.\(^{71,112,114-116}\) These effects appear to be independent of other risk factors for tuberculosis, such as alcoholism and socioeconomic conditions.\(^{71,112,114}\)

Tobacco smoke impairs the pulmonary defense mechanisms by effecting structural changes, cellular changes, and an altered immune response. Smoking

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**Chart 7. Recommendations for the approach to smoking cessation and benefits of cessation in patients with lung cancer.**

| Description                          | Recommendation                                                                 |
|--------------------------------------|-------------------------------------------------------------------------------|
| Consultation                         | All patients should be asked if they smoke.                                  |
| Chart                                 | Insert a category for smoking status in the patient chart, as one more vital sign.\(^a\) |
| Start of treatment                   | Initiating treatment in the preoperative period increases cessation rates.  |
|                                      | Smoking cessation treatment should be integrated into the cancer treatment strategy. |
| Treatment strategy                   | Counseling alone is indicated only when pharmacotherapy is contraindicated or refused by the patient. |
|                                      | Pharmacotherapy is usually similar to that used in the general population.  |
|                                      | First-line pharmacotherapy, in combination with counseling, is cost-effective and should be offered to all patients who smoke, including those in follow-up treatment. |
| Nicotine replacement therapy         | Pre-cessation nicotine replacement therapy and counseling provide the best results. |
|                                      | Consider using combined therapy, extended therapy, and higher doses of nicotine replacement therapy. |
|                                      | Patch: its use is inadvisable in patients with graft-versus-host disease. |
|                                      | Gum/lozenges: can accentuate mucositis after chemotherapy.                    |
| Bupropion                            | Its use is indicated in patients with depressive symptoms.                    |
|                                      | It can inactivate tamoxifen and is contraindicated in patients with metastases in the central nervous system. |
| Varenicline                          | It can exacerbate the nausea caused by chemotherapy.                          |
| Benefits of smoking cessation        | Greater chances of survival; a lower risk of relapse; a lower incidence of a second smoking-related primary tumor |
|                                      | Better treatment efficacy and response; improved quality of life and pain control; and higher self-esteem |
|                                      | Lower risk of surgical complications (pulmonary embolism, suture dehiscence, and infections), as well as of complications of radiotherapy and chemotherapy |
|                                      | Lower risk of developing or worsening of other smoking-related diseases       |

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\(^a\)Increases the rate at which physicians and other health professionals intervene for smoking cessation.
disrupts the integrity of the airway epithelium, alters mucociliary clearance, and reduces the phagocytic capacity of alveolar macrophages, which increases the likelihood that *Mycobacterium tuberculosis* will reach the alveoli, where tuberculosis infection begins.\(^{[71,117-121]}\) Some studies suggest that increased susceptibility to pulmonary tuberculosis is due to reductions in circulating immunoglobulin levels and in the CD4/CD8 ratio, both of which are caused by exposure to tobacco smoke.\(^{[71,122-126]}\)

Passive smoking increases both the risk of tuberculosis infection and the occurrence of active tuberculosis, especially in children. That risk is increased up to ninefold in individuals under 15 years of age, even those who have had no contact with pulmonary tuberculosis in the home. There is a strong dose-response relationship between the risk of tuberculosis and the volume of tobacco smoke (number of cigarettes) to which children are exposed per day.\(^{[127,128]}\) Nonsmokers exposed to tobacco smoke in closed spaces are also at an increased risk of developing pulmonary tuberculosis.\(^{[129]}\) Among individuals with tuberculosis, those who smoke are at an increased risk of the most severe clinical manifestations, mortality, a delay in achieving sputum negativity, treatment failure, tuberculosis relapse, resistance to antituberculosis drugs, cavitary lesions, greater sputum positivity, and sequelae that are more extensive.\(^{[71,114,115,124,130-133]}\)

Among individuals with active tuberculosis who have no previous history of tuberculosis, the risk of death from tuberculosis is nine times higher in smokers than in those who have never smoked.\(^{[134]}\)

Smoking control is an important strategy to reduce the number of individuals infected with *M. tuberculosis* and that of those who will develop the disease. Therefore, it is essential to advise smokers with tuberculosis to quit smoking and to support them in that endeavor. When smokers with tuberculosis quit smoking, they reduce their risk of death from tuberculosis by approximately 65% in comparison with those who continue to smoke.\(^{[134]}\) The World Health Organization recommends that tuberculosis control programs work in an integrated way with anti-smoking programs, so that smoking cessation treatment is offered to every patient with tuberculosis.\(^{[112,114,115]}\)

### Environmental respiratory diseases and smoking

Smoking, environmental air pollution, and indoor air pollution are risk factors for mortality, respectively accounting for 7.13, 4.3, and 2.6 million deaths/year, ranking second, sixth, and eighth, worldwide.\(^{[135]}\) In Brazil, environmental air pollution ranks eleventh among mortality risk factors.

Diseases related to exposure to particulate matter, gases, and carcinogens occur due to oxidative stress, pulmonary inflammation, systemic inflammation, and DNA damage. The main diseases related to exposure to environmental pollutants are ischemic cardiovascular diseases, neoplasms, COPD, and respiratory infections.\(^{[137]}\)

According to the World Health Organization estimates for 2016, environmental air pollution and indoor air pollution in Brazil were respectively responsible for 51,800 and 14,100 deaths, with standardized mortality rates of 24/100,000 population and 7/100,000 population.\(^{[138]}\) One group of authors, estimating the level of inhaled particulate matter at 12 mg/cigarette and the exposure to air pollution at 13-30 µm\(^2\) of air/day, concluded that those exposures increase the risk for lung cancer, cardiovascular disease, and lung disease in general.\(^{[129]}\)

In one study, lung function values were found to be lower in women (smokers and nonsmokers) who lived in environments with high levels of pollution than in those who lived in environments with lower levels of pollution.\(^{[140]}\) The authors also found that exposure of smokers to ETS increases their risk of lung cancer, showing an additive effect.

No differences have been identified among the various profiles of smokers in terms of the risk of diseases related to air pollution. Although the isolated impact of smoking cessation in individuals exposed to pollution is not yet known, the ban on smoking indoors has had a significant impact on reducing morbidity and mortality. A meta-analysis of 44 studies showed significant reductions in the rates of hospitalization and death from respiratory diseases.\(^{[141]}\) This suggests that people living in the same city, without changes in pollution levels, could benefit from reduced ETS exposure. The same holds true for the impact of smoking cessation on the reduction in the incidence of respiratory diseases observed in cohort studies.\(^{[142]}\)

### Occupational respiratory diseases and smoking

The combination of exposure to tobacco smoke and occupational exposure to pollutants is associated with deleterious and sometimes synergistic effects, potentiating injuries to the airways and the pulmonary interstitium. Inhibition of mucociliary clearance and other changes in the airways result in increased retention of inhaled particles, as well as facilitating damage from the inhalation of gases, mists, or chemical vapors. The pro-inflammatory nature and DNA toxicity of both exposures can increase the risk of becoming ill.\(^{[97,143,144]}\)

Occupational exposure to pollutants is a major risk factor for morbidity and mortality worldwide, the various occupational risks collectively estimated to be responsible for 1.53 million deaths/year and 75.93 million years of life lost to death or disability.\(^{[145]}\) According to data on the global burden of diseases in 2016, exposure to ETS in the workplace alone was associated with 433,200 deaths, having the greatest impact on mortality from ischemic cardiovascular diseases (252,000 deaths), followed by mortality from COPD (52,000 deaths) and mortality from lung cancer (44,400 deaths).\(^{[146]}\)
The prevalence of smoking among workers varies depending on the type of company and its activity, being lower among workers in the health and education sectors, whereas it is higher among those in the industrial, janitorial, mining, and construction sectors. In the latter groups of workers, the prevalence is higher than in the general population, in several countries: 53.2% vs. 40.2% in China; 66.3% vs. 43.0% in Turkey; and 49.8% vs. 15.1% in Brazil. Those high rates reveal the impact of smoking among the less educated and those with lower incomes, who make up the workforce that engages in insalubrious activities or is exposed to greater occupational risks.

Smoking cessation reduces the risk of morbidity and mortality, an earlier age at cessation translating to a greater benefit. It is recommended that the occupational health departments of companies develop policies to encourage smokers and their families to quit smoking and to support them in that endeavor, from the hire date onward. Providing treatment to smokers should be incorporated into the routine at primary health care clinics and in companies.

Conducting research with brief questionnaires to monitor the health/illness relationship not only helps identify the need for interventions in the workplace but also can create important motivational moments, thus increasing the chance of success in smoking cessation. Chief among the various motivating factors for quitting smoking presented by groups of workers who are more exposed and more socially vulnerable are the presence of respiratory symptoms and established respiratory disease.

**Interstitial respiratory diseases and smoking**

In recent years, concern about the harmful effects of smoking has begun to focus on the development of interstitial lung diseases (ILDs). Among such diseases, three are considered to be etiologically related to smoking: ILD accompanied by respiratory bronchiolitis; desquamative interstitial pneumonia; and pulmonary Langerhans cell histiocytosis.

Certain interstitial diseases are more likely to develop in smokers, such as idiopathic pulmonary fibrosis and rheumatoid arthritis-related ILD. Some individuals also develop a combination of pulmonary fibrosis and emphysema. That combination is considered a distinct phenotype of idiopathic pulmonary fibrosis.

It is important to identify the role of smoking in ILD, because understanding the pathogenic pathways could allow the development of new medications. From a clinical point of view, the recognition of a smoking-related phenotype would facilitate early diagnosis and treatment.

One group of authors analyzed four prospective cohort studies, involving a collective total of 11,691 participants, and assessed mortality in subjects with interstitial lung abnormalities. The abnormalities were associated with greater smoking intensity in two of those studies and with higher mortality rates in all four.

Although smoking-related ILDs are less well recognized, there is a well-defined causal correlation, based on epidemiological data, between smoking and the development of an ILD. Smoking cessation is the primary therapy for the control of such ILDs, and the approach requires perfect integration of clinical, functional, radiological, and histopathological data.

**Infectious respiratory diseases and smoking**

Deposition of the toxic constituents of tobacco smoke in the airways affects the pulmonary defense mechanisms in multiple ways: by impairing mucociliary transport; by increasing bacterial adherence to the respiratory epithelium; and by increasing alveolar and epithelial vascular permeability. In addition, continued exposure to tobacco smoke is associated with significant changes in the nasopharyngeal microflora, which favors colonization by opportunistic pathogens.

One experimental study in mice demonstrated that chronic exposure to ETS increased levels of inflammatory cytokines and TNF-α in the lungs, as well as impairing adaptive immunity, after chronic infection or intranasal immunization with the recombinant P6 protein of *Haemophilus influenzae*. The authors concluded that there is unequivocal evidence that exposure to ETS has long-term effects that are detrimental to the lung microenvironment (promoting inflammation), as well as impairing immunity to infection and the response to vaccination.

In one systematic review, the risk of contracting bacterial pneumonia was shown to be higher in smokers than in former smokers (hazard ratio = 1.37; 95% CI: 1.06-1.78) and nonsmokers (hazard ratio = 1.73; 95% CI: 1.44-2.06). Pneumonia and influenza increase the risk of morbidity and mortality. When the individual is a smoker, the social, medical, and pension costs are further increased. A 2017 study showed that pneumonia is the third leading smoking-related illness in Brazil. Chart 8 summarizes the scientific evidence regarding the exposure and risks of smokers.

**Smoking among inpatients with respiratory diseases**

The reported prevalence of smoking among hospitalized patients in Brazil ranges from 15% to 22%. In one study, the authors found a 25% prevalence of smoking among inpatients at a smoke-free hospital, and 55% of the patients who were smokers experienced withdrawal symptoms during their hospital stay. In a systematic review, the prevalence of smoking among inpatients was found to range from 15% to 27%.

Hospitalization creates a window of opportunity to initiate anti-smoking measures with a high chance of success, especially if there is follow-up after hospital discharge. Addressing the issue of smoking among inpatients who are smokers should be part of...
the hospital routine. Although such patients are often highly motivated and amenable, only a minority receive smoking cessation treatment and most of those relapse after hospital discharge.\(^\text{(12,169)}\)

The recommended course of action in the approach to inpatients who are smokers is to offer counseling during hospitalization and follow-up for at least four weeks after discharge, either in person or by telephone. In a meta-analysis of 50 studies,\(^\text{(172)}\) it was concluded that intensive approaches with follow-up after discharge were more effective, because relapse typically occurs during the first month after discharge. Identifying the level of craving and other factors that indicate a greater chance of failure, such as dependence on alcohol or other drugs, allows the treatment of inpatients at higher risk of relapse to be individualized.

In a study evaluating the efficacy of a smoking cessation program for patients hospitalized for respiratory disease or heart disease, 31% of the patients with respiratory diseases were reported to be abstinent at six months after discharge.\(^\text{(172)}\) Patients receiving individual counseling and medication for smoking cessation during hospitalization and after discharge showed greater adherence to the treatment, even after hospital discharge.\(^\text{(173)}\)

Hospital admission should be transformed into an opportunity for smoking cessation. Smokers hospitalized for respiratory diseases should be advised of the benefits of quitting smoking, as well as being assessed in terms of their level of motivation and level of nicotine dependence in order to receive specific treatment, which is similar to that recommended for patients with other conditions. Smoking cessation programs involving teams trained in dealing with smokers have good cost-effectiveness ratios.\(^\text{(176)}\) Follow-up for at least six months after discharge improves outcomes and increases the chance of successful abstinence.\(^\text{(175,176)}\) Intensive intervention combined with pharmacological treatment for smoking cessation in patients with respiratory disease, started during hospitalization, is effective, with a high level of evidence.\(^\text{(12)}\)

### FINAL CONSIDERATIONS

All patients with respiratory diseases should be asked if they smoke. If so, they should be encouraged to quit smoking and referred for smoking cessation treatment, regardless of their age and disease stage. Smoking cessation treatment, based on cognitive-behavioral therapy and pharmacotherapy, is the first measure to be taken in the treatment of lung diseases and has major benefits: fewer exacerbations and hospitalizations; a reduction in respiratory symptoms; an improvement in quality of life; fewer limitations in activities of daily living; better control of comorbidities; improved response to bronchodilators and inhaled corticosteroids; greater chances of survival; a lower risk of relapse; a lower incidence of a second smoking-related primary tumor; better pain control; improved self-esteem; and a lower risk of complications from surgery, radiotherapy, and chemotherapy.

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