

# Consensus document on asthma and smoking of the Regional Asthma Forum of SEPAR

## Documento de consenso sobre asma y tabaquismo del Foro Autonómico de Asma de la SEPAR

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### Abstract

The prevalence of active smoking in adults with asthma is similar in the total population. Smoking is associated with worse clinical control of the disease, a rapid reduction of lung function and a variable response to corticoids. Tobacco consumption negatively affects the quality of life of asthmatic patients as well as increasing the number of medical visits and hospital admissions due to exacerbations. Moreover, smoking entails a higher risk of developing lung cancer, cardiovascular comorbidities and death in asthmatic patients. Nevertheless, current asthma guidelines do not include specific recommendations on the management of smoking asthmatic patients and the treatment of the smoking habit in this subpopulation. For this reason, a narrative review of the literature was carried out for consensus using a nominal group methodology developed throughout 2019 to extract practical recommendations that would allow the diagnosis and treatment of asthma in smokers, as well as the treatment of smoking in asthmatics, to be improved. The conclusions and recommendations were validated at the SEPAR national congress of the same year. Among the most relevant, the need to address smoking in people with asthma through health advice, pharmacological treatment and behavioral therapy was emphasized, as this is a factor that negatively impacts the symptoms, prognosis and response to asthma treatment. In smokers with suspected asthma, the presence of emphysema and the differential diagnosis of other diseases should be evaluated and the impact of smoking on the result of diagnostic tests should be considered. It is also concluded that smoking reduces the response to treatment with inhaled corticosteroids, which is why combined therapy with bronchodilators is recommended.

**Keywords:** Asthma; smoking; treatment; consensus; recommendations.

### Resumen

La prevalencia de tabaquismo activo en adultos con asma es similar a la de la población general. El tabaquismo se asocia con un peor control clínico de la enfermedad, una disminución acelerada de la función pulmonar y una respuesta irregular a la terapia con glucocorticoides. El consumo de tabaco impacta negativamente en la calidad de vida de los pacientes asmáticos y provoca un incremento en el número de visitas y de hospitalizaciones por exacerbaciones. Además, el tabaquismo aumenta el riesgo de cáncer de pulmón, comorbilidades cardiovasculares y muerte en pacientes asmáticos. A pesar de todo ello, las guías actuales del manejo del asma no incluyen recomendaciones específicas para el manejo de los pacientes asmáticos fumadores. Por este motivo, se procedió a una revisión narrativa de la literatura para un consenso mediante metodología de grupo nominal desarrollada a lo largo del año 2019 para extraer recomendaciones prácticas que permitieran mejorar el diagnóstico y el tratamiento del asma en fumadores, así como el tratamiento del tabaquismo en asmáticos. Las conclusiones y recomendaciones fueron validadas en el congreso nacional de la SEPAR del mismo año. Entre las más relevantes, se incidió en la necesidad de abordar el tabaquismo en las personas con asma mediante consejo sanitario, tratamiento farmacológico y terapia conductual, al ser un factor que impacta negativamente en la sintomatología, el pronóstico y la respuesta al tratamiento del asma. En el fumador con sospecha de asma, se debe evaluar la presencia de enfisema y el diagnóstico diferencial de otras enfermedades y considerar el impacto del tabaquismo en el resultado de las pruebas diagnósticas. También se concluye que el hábito tabáquico reduce la respuesta al tratamiento con corticoides inhalados, por lo que se recomienda terapia combinada con broncodilatadores.

**Palabras clave:** Asma; tabaquismo; tratamiento; consenso; recomendaciones.

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Smoking is as prevalent in adults with asthma as it is in the general population (Cerveri et al., 2012). Furthermore, it has been estimated that around half of adult asthmatics are smokers or ex-smokers (Thomson, Chaudhuri & Livingston, 2004).

Smoking has significant negative effects on clinical symptoms, prognosis, and response to asthma treatment (Polosa & Thomson, 2013). Likewise, it is associated with more severe asthma and a worse response to glucocorticoid treatment (Polosa et al., 2013). In the most severe cases, it contributes to chronic airflow obstruction, leading to the development of chronic obstructive pulmonary disease (COPD), and is associated with a clinical profile called asthma-COPD overlap (ACO) (Gelb, Christenson & Nadel, 2016).

Moreover, it has been observed that active smokers, especially women or those patients with allergic rhinitis, have a higher risk of developing asthma, which is why smoking could contribute to the pathogenesis of the disease. In addition, it has been shown that smoking cessation reduces symptoms and improves lung function. However, asthmatic patients have a low rate of smoking cessation, which points to the need to improve strategies aimed at treating smoking in these patients (Cerveri et al., 2012).

Current asthma management guidelines do not include specific recommendations for managing asthmatic patients who smoke. For this reason, the Asthma Forum (FORASMA) of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) decided to review the available literature to develop this management consensus with the FORASMA panel.

## Method

A Coordinating Committee (CC) was formed, comprising three experts (FJA, MBA and JSCM), to supervise the quality and suitability of the consensus processes and methodology (Supplementary Material). A Recommendations Development Group (RDG) was also set up, with seven experts (EPE, JLGR, JGS, FJC, PJRP, JARM and CAJR), whose main function was to review and synthesize the available evidence for the manuscript and formulate conclusions (C) and recommendations (R). To validate the C and R formulated, a Recommendations Validation Group (RVG) was set up with 54 experts from different societies of pulmonology specialists in the autonomous communities of Spain.

A non-systematic literature search was carried out in PubMed and Scopus databases, limited to articles from the last 10 years in English or Spanish dealing with the thematic blocks to be covered in this study: the impact of smoking on the development and clinical treatment of asthma, the impact of smoking status on differential diagnosis and interpretation of diagnostic tests, prognosis and follow-up;

and the treatment of asthma in smokers and of smoking in asthmatics. To this end, the base keywords were tobacco, smoking and/or asthma, combined with other terms and their synonyms to refine searches (diagnosis, treatment/therapy, prognosis, smoking cessation, inhaled toxic substances, cannabis, passive smoking, e-cigarette etc.) The search results were reviewed and discussed by the RDG in order to identify the most relevant evidence regarding the management of asthma in smokers. Based on this review and the discussion conclusions, the RDG prepared some C and Rs to be evaluated in a face-to-face meeting of the 2019 Asthma Forum of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), which constituted the RVG. The recommendations were discussed in person, and RVG members expressed the extent to which they agreed or disagreed on a 1-4 scale (1 strongly disagree, 4 strongly agree). In the first round, all the Cs and Rs drawn up by the RDG were evaluated, the results were aggregated and the vote percentages of responses 1 and 2 (disagreement) and of 3 and 4 (agreement) were calculated. R and Cs with more than 70% agreement were considered consensual, while those scoring between 35% and 70% of agreement and those with 35% or below were considered doubtful or incompatible, respectively, and were discussed in a later review. Additional recommendations proposed by the panellists were collected. The modified and additional proposals were voted by the RVG in a second round using an online televoting system.

Finally, the CC and the RDG drafted the manuscript, which was submitted to successive reviews by the same group until final approval by all signatories.

## Smoking as a risk factor for developing asthma

The effect of smoking on the etiology of asthma in adults continues to be a matter of debate (Bakakos, Kostikas & Loukides, 2016). In most longitudinal studies, smoking is a risk factor for asthma development (relative risk from 1.4 to 3.0) (Coogan et al., 2015; Godtfredsen, Lange, Prescott, Osler & Vestbo, 2001; Lundback, Ronmark, Jonsson, Larsson & Sandstrom, 2001; Pallasaho et al., 2011; Plaschke et al., 2000; Toren, Olin, Hellgren & Hermansson, 2002; Vignoud et al., 2011). However, some studies do not report this association (Anto et al., 2010; Ekerljung et al., 2008; Huovinen, Kaprio & Koskenvuo, 2003; Toren et al., 2011).

### Link to sex

Other studies limit this relationship to the female sex, with a higher incidence of asthma observed in women who smoke (Nakamura et al., 2009; Piipari, Jaakkola, Jaakkola & Jaakkola, 2004). However, there are studies with contradictory evidence. On the one hand, it was shown that in the Canadian population, women who smoked had

a 70% higher prevalence of asthma than non-smokers, and that the link between smoking and asthma was stronger in women under 25 years of age and those with higher smoking intensity (Chen, Dales, Krewski & Breithaupt, 1999). Conversely, in Japan a relationship between smoking and the onset of asthma was observed only in men (Nakamura et al., 2009). The annual report of the United States Department of Public Health (Department of Health and Human Services, 2014) concludes that there is sufficient evidence to infer a causal relationship between smoking and asthma exacerbations in adults, but not between active smoking and the incidence of asthma.

Some studies indicate that ex-smokers also have an increased risk of asthma, determined at 1.34 in men and 2.38 in women (Piipari et al., 2004). However, this data is not supported by other studies (Polosa et al., 2014).

### **Relationship with atopy and rhinitis**

The association between smoking and asthma can be modified by the presence of atopy. In the European Community Public Health Survey (European Community Respiratory Health Survey [ECRHS]) (Anto et al., 2010), the frequency of asthma in atopic adults was higher among smokers compared to non-smokers (odds ratio [OR]: 1.45; 95% confidence interval at 95% [95% CI]: 0.81-2.61), while the opposite trend was observed for non-atopic patients (OR: 0.67; 95% CI: 0.40-1.15). However, in a Swedish study (Plaschke et al., 2000), while the probability of asthma onset increased among atopic smokers (OR: 1.8; 95% CI: 0.8-4.2) compared to non-smokers, this was even higher among non-atopic compared to atopic patients (OR: 5.7; 95% CI: 1.7-19.2). Furthermore, an increased risk of asthma was observed among smokers with allergic rhinitis in a cohort of Italian patients (Polosa et al., 2008).

### **Passive smoking and asthma in children and adolescents**

Passive smoking is a risk factor for developing asthma in children (Gilliland et al., 2006; Kalliola et al., 2013). A systematic review and meta-analysis of 76 studies showed that the risk of asthma in children exposed to pre- or postnatal smoking increased from 21% to 85% (Burke et al., 2012). Smoking during pregnancy can thus clearly increase the risk of asthma in offspring (Gilliland, Li & Peters, 2001; Neuman et al., 2012), and it is striking that approximately 50% of pregnant women do not quit smoking during this period (Schneider, Huy, Schutz & Diehl, 2010). Two large longitudinal studies with follow-ups of 14 and 20 years, respectively, have demonstrated the relationship between asthma and prenatal exposure to tobacco toxins (Grabenhenrich et al., 2014; Hollams, de Klerk, Holt & Sly, 2014). Furthermore, it has been shown that 41% of asthmatic children in Spain are passive smokers in their family environment, thus worsening their baseline situation and increasing the frequency of asthmatic attacks involving hospitalization (Lopez Blazquez, Perez Moreno, Vigil Vazquez & Rodriguez Fernandez, 2018).

Finally, smoking increases the risk of asthma among adolescents, especially in those without atopy and in those exposed to maternal smoking during pregnancy (Chen et al., 1999). Adolescents smoking more than 300 cigarettes/year have a much higher risk of developing asthma (OR 3.9; 95% CI: 1.7-8.5) than non-smokers (Gilliland et al., 2006).

Table 1 summarizes the clinical and functional effects of smoking in asthma, while Table 2 summarizes the conclusions and recommendations agreed on with reference to all of the above.

Table 1. Summary of the clinical and functional effects of smoking in asthma. Modified from (Polosa et al., 2013).

Adverse effects of smoking on asthma	Detailed effects
Increased prevalence of asthma	High prevalence, especially in women who smoke compared to non-smokers (especially those under 25 years of age). The relationship between smoking and gender is more evident in heavy smokers compared light or non-smokers (dose-effect relationship).
Incidence of asthma	Smoking is a strong predictor of the development of new cases of asthma in adult allergic patients (allergic rhinitis) with a clear dose-response effect to tobacco exposure.
Increased morbidity and mortality	Smoking asthmatics are at high risk of more severe symptoms, more exacerbations and poorer quality of life, as well as an increase in severe asthma attacks and high mortality.
Increased severity of asthma	Smoking and smoking duration are closely linked, in a dose-dependent way, to the severity level of asthma. The closest association with severity has been observed in smokers of >20 packs/year.
Uncontrolled asthma	The relationship between smoking and poor asthma control has been described in population studies and in controlled studies.
Faster decline in lung function	Lung function decline is faster in smoking asthmatics than non-smokers with asthma, although some negative studies exist.
Persistence of airflow obstruction	A proportion of smokers with asthma develop AFO.
Glucocorticoid insensitivity	Smoking asthmatics are less sensitive to the beneficial effect of glucocorticoids in relation to respiratory symptoms and lung function, regardless of the route of administration.

Table 2. *Conclusions and recommendations on smoking as a risk factor for developing asthma.*

- Smoking should be addressed in asthmatics as it can condition clinical symptoms, prognosis and response to asthma treatment.
- Smoking, especially in women, is a risk factor for developing asthma and is correlated with cumulative tobacco use.
- Patients with allergic rhinitis who smoke are at increased risk of developing bronchial asthma.
- Smoking during pregnancy increases the risk of asthma for the child, so prevention and treatment are essential.
- Passive smoking increases the risk of asthma in children and adolescents and increases severity if already present.

## Diagnosis, prognosis and monitoring of asthma in smokers

Current asthma management guidelines do not include specific treatment recommendations for smoking asthmatic patients. It is therefore necessary to improve understanding of the particularities of asthma in smoking patients, as well as what constitutes the most effective treatment for these patients.

### *How smoking affects the diagnosis of asthma and ACO*

Measuring lung function, especially obstruction reversibility, serves to confirm the diagnosis of asthma (Executive Committee of GEMA 5.0). This test has high specificity, but low sensitivity, so a negative result requires further testing. However, in a compatible clinical setting, a positive result mostly ensures a diagnosis of asthma.

In smokers, the possibility of obtaining a bronchodilator response may be hampered by tobacco use. This response is sometimes assessed after treatment with high-dose inhaled corticosteroids. Here, it has been observed that treatment with 1000 µg of fluticasone propionate daily for 3 weeks in asthmatic active cigarette smokers did not produce significant changes in the morning peak expiratory flow (PEF), the mean value of forced expiratory volume in the first second (FEV<sub>1</sub>) and PC20 after methacholine challenge (Chalmers et al., 2002). Regarding the bronchodilator response after treatment with oral steroids, a randomized, placebo-controlled, crossover study assessed active smokers, ex-smokers and never-smoker asthmatics after taking prednisolone (40 mg daily) or placebo for 2 weeks. Never-smoker patients showed a significant improvement in FEV<sub>1</sub> (237 ml) and morning PEF (36.8 L/min). With smokers and ex-smokers, there were no significant changes in any of the symptom control scores, while prednisolone treatment only led to an improvement in morning and evening PEF (29.1 and 52.36 L/min, respectively) (Chaudhuri et al., 2003).

### *Usefulness of FENO in the diagnosis of asthma in smokers*

Various authors have suggested that fraction of exhaled nitric oxide (FeNO) values could serve as a sensitive and specific diagnostic tool. Recently, the combination of FEV<sub>1</sub> and FeNO results has been described as providing high sensitivity and specificity for the diagnosis of asthma (Giovannelli et al., 2016). High FeNO values would thus

be highly compatible with asthma diagnosis, especially in patients with airway obstruction.

However, there is some controversy about the reference values for FeNO in smoking patients. The cut-off point has been set at 50 parts per billion (ppb) in adults (Dweik et al., 2011). According to the Spanish Guide for Asthma Management (GEMA) (Comité Ejecutivo de GEMA 5.0), the FeNO value is especially sensitive and specific for the diagnosis of asthma in non-smoking patients not using inhaled glucocorticoids (IGC), particularly if associated with reduced FEV<sub>1</sub>. However, a normal FeNO value does not exclude the diagnosis of asthma, especially in non-atopic people.

In most studies it has been observed that FeNO values are lower in active smokers than in non-smoking asthmatics (Giovannelli et al., 2016). The 30% lower cut-off value for smokers is associated with a specificity of 90% (22 vs. 31 ppb) and a sensitivity of 90% (7 vs. 10 ppb) (Malinovschi, Backer, Harving & Porsbjerg, 2012). However, this may apply to allergic asthmatic patients, but not to those without atopy (Rouhos et al., 2010). FeNO levels can discriminate the diagnosis of asthma in allergic vs. non-atopic, but only in non-smoking patients (Giovannelli et al., 2016).

A reduction in FeNO has been observed in asthmatics, passive and active smokers (Jacinto, Malinovschi, Janson, Fonseca & Alving, 2017), so passive smoking should also be considered when using FeNO as a diagnostic criterion for asthma (Nadif et al., 2010). Values may be associated with a sputum eosinophil count of ≥3%, although the IGC dose, and the patient's smoking level and atopy must be taken into account. In a retrospective study (Schleich et al., 2010), FeNO values discriminating and predicting sputum eosinophilia of >3% were ≥41 ppb. Sensitivity was 65% and specificity 79%, and there was a trend towards a lower threshold in smokers (27 ppb) compared to non-smokers. Finally, in COPD patients, FeNO values are able to discriminate between different types of patients (Alcázar-Navarrete, Romero-Palacios, Ruiz-Sancho & Ruiz-Rodríguez, 2016) and are associated with the presence of eosinophils in sputum (Chou et al., 2014), characteristically found in ACO. In a cross-sectional study carried out in Spain, FeNO levels were high in patients defined as ACO, with a cut-off point of 20 ppb for the diagnosis of ACO (Alcázar-Navarrete et al., 2016). Therefore, we conclude that FeNO can be a useful marker for detecting ACO in COPD patients, thus adding a clinical value to the determination of eosinophils in peripheral blood.

### ***Inflammatory profile in smoking asthmatics***

Smoking asthmatics have fewer eosinophils and a greater number of mast cells in the submucosa of the airway wall. They also present greater remodelling of the airways, with increased epithelial thickness and goblet cell hyperplasia. However, the mechanisms by which smoking modifies airway inflammation are currently unknown. Similarly, the mechanism underlying the decreased response to glucocorticoids is not known (Fattahi et al., 2011).

A strong association has been described between eosinophil levels and the risk of hospitalization in patients without a history of smoking (hazard ratio [HR]: 2.16; 95% CI: 1.27-3.68;  $p = 0.005$ ) but not in active smokers (HR: 1.00; 95% CI: 0.49-2.04;  $p = 0.997$ ) (Kerkhof et al., 2018). An analysis of data from the National Health and Nutrition Examination Survey (NHANES) ( $N = 3162$  patients with asthma and eosinophilia between 6 and 64 years of age) found that higher eosinophil values were linked to a greater number of asthma exacerbations in children but not adults (Tran, Khatry, Ke, Ward & Gossage, 2014). Smoking is believed to play a role in these results as more than half of these adults said they were smokers or ex-smokers. Therefore, smoking appears to exert a suppressive effect on eosinophilic inflammation (van der Vaart, Postma, Timens & ten Hacken, 2004).

Furthermore, non-smoking asthmatics with high levels of eosinophils have been shown to have a higher risk of suffering new exacerbations. A study by (Kerkhof et al., 2018) monitoring 2,613 asthmatics found that those patients with high levels of eosinophils ( $\geq 0.35 \times 10^9$  cells/L) had a higher risk of new exacerbations, especially if they were non-smokers or ex-smokers (HR: 1.84; 95% CI: 1.20-2.80;  $p = 0.005$ ) but not if they were active smokers (HR: 0.88; CI95%: 0.44-1.76;  $p = 0.73$ ).

### ***Prognosis and follow-up***

Smoking has been associated with increased severity of asthma, poorer quality of life, accelerated loss of lung function, and poorer response to corticosteroid treatment. Likewise, asthmatics who smoke need emergency services and hospitalization more frequently.

A study with 760 severe asthmatics, both smokers and non-smokers (Thomson et al., 2013), showed that active smokers had lower scores on the asthma control questionnaire (ACQ) compared with non-smokers, in addition to a greater number of medical visits and use of emergency services in the previous year. Additionally, smokers had worse scores on the EuroQol scale and higher scores on the HAD scale (Hospital Anxiety and Depression Scale), revealing a higher degree of emotional stress.

Current evidence confirms that active smokers with asthma have more severe symptoms and worse control of the disease than patients with asthma who have never smoked (McCoy et al., 2006; Pedersen et al., 2007; Polosa et al., 2011; Schatz,

Zeiger, Vollmer, Mosen & Cook, 2006; Siroux, Pin, Oryszczyn, Le Moual & Kauffmann, 2000; Thomson et al., 2013; Westerhof et al., 2014). In addition, it has been observed that ex-smokers also have worse control of the disease in comparison to never-smokers (Pedersen et al., 2007).

Additionally, both active and passive smoking increase hospital admissions rates and worsen the quality of life of asthmatics (Sippel, Pedula, Vollmer, Buist & Osborne, 1999). Moreover, the death rate is higher among active smokers with asthma than among never-smokers (Marquette et al., 1992).

### ***Lung function in smokers***

Bronchial asthma can cause faster loss of lung function, although loss is much more rapid in asthmatic smokers compared to non-asthmatics and non-smoking asthmatics (Apostol et al., 2002; Grol et al., 1999; Hancox, Gray, Poulton & Sears, 2016). Moreover, in terms of decreased FEV<sub>1</sub>, the combination of active smoking and asthma has a synergistic (Lange, Parner, Vestbo, Schnohr & Jensen, 1998) or additive effect (James et al., 2005). It has been shown that smoking reduces FEV<sub>1</sub> by a ratio of 69 ml per 100/year in smokers and by 1.5% of the FEV<sub>1</sub>/FVC ratio (forced vital capacity) ratio in asthmatic patients diagnosed de novo (Jaakkola et al., 2019). Finally, an annual decrease in FEV<sub>1</sub> of 58 ml was noted in actively smoking asthmatics compared to 33 ml in those who did not smoke (Lange, Colak, Ingebrigtsen, Vestbo & Marott, 2016).

It is estimated that approximately 20% of patients with asthma or COPD have ACO. To assess the effect of lung function loss in ACO patients, in addition to the risk of exacerbations and mortality, the authors of the Copenhagen City Heart Study conducted a subsequent study with the same cohort of patients (Lange et al., 2016). Results showed that patients with ACO and late-onset asthma experienced a drop in FEV<sub>1</sub> of 49.6 ml/year, significantly higher than that of patients with early-onset asthma ACO or patients with COPD (39.5 ml/year) or healthy non-smoking patients. The authors concluded that patients with ACO have a worse prognosis, although this depended on the age of asthma diagnosis, with a worse prognosis for those aged over 40 years when diagnosed. This implies the need for close monitoring of such patients in order to prevent rapid deterioration of lung function and exacerbations. A study by (Tommola et al., 2016) which analyzed the lung function of recently diagnosed asthmatic smokers and non-smokers, observed that those with a cumulative consumption of  $>10$  p/a (packs/year) had an accelerated loss of lung function.

### ***Clinical control of asthma and morbidity and mortality in smokers***

With regard to clinical control, smoking has been associated with poor long-term asthma control. The

Seinäjoki Adult Asthma Study (SAAS) (Tuomisto et al., 2016) followed patients with a recent diagnosis of late-onset asthma (N = 203) over a period of 12 years. During this time, it was found that 34% of the patients were controlled, 36% partially controlled, and 30% poorly controlled. The percentage of active smokers was higher in the partial (60.8%) and poor control (61.7%) groups than in the group of controlled patients (36.2%). Poor asthma control was linked to male sex, older age, high doses of IGC or combination with a long-acting beta-agonist (LABA), and history of smoking. Each increase of 10 packs/year increased the risk of worse asthma control (OR: 1.82; 95% CI: 1.06-3.12; p = 0.03). Another study with 200 patients and a two-year follow-up showed that smoking >10 p/a was the most important independent predictor of asthma severity (Loymans et al., 2016).

A prospective analysis in the Copenhagen General Population Study (Colak, Afzal, Nordestgaard & Lange, 2015) showed that 6% of all the individuals studied (N = 94,079) had asthma (2,304 non-smokers, 2,467 ex-smokers, and 920 active smokers). The HR for asthma exacerbations in asthmatics was 11 (95% CI: 5.8–22.0) for non-smokers, 13 (95% CI: 6.2–29.0) for ex-smokers and 18 (95% CI: 8.2–39.0) for active smokers. It should be noted that the risk of lung cancer, cardiovascular comorbidities and death only increased in smokers with asthma. It was thus shown that smoking is the main factor in poor prognoses for asthmatics, which is why it has been included in a predictive model of exacerbations (Loymans et al., 2016).

### **Smoking and use of resources in asthmatic patients**

Additionally, smoking predicts a greater frequency in the use of emergency services and an increase in mortality in patients with a history of exacerbation who have required mechanical ventilation (Marquette et al., 1992). A study of 344 asthmatics (Kauppi, Kupiainen, Lindqvist, Haahtela & Laitinen, 2014) showed that the risk of needing ER visits

was higher in smokers (HR: 3.9) or ex-smokers (HR 1.8) compared to non-smokers. In a multivariate analysis, the independent risk factors were active smoking (HR 3.6), poorer health-related quality of life (HRQoL) (HR 2.5), and FEV<sub>1</sub> <65% (HR 2.2).

### **Prognosis of ACO**

Mortality and exacerbation frequency in ACO patients have been assessed and compared with those of patients with asthma and airflow obstruction and patients with COPD (Kurashima et al., 2017). Patients with asthma and airflow obstruction had a better prognosis than patients with ACO or COPD, with the prognosis of ACO patients being better than those with COPD. A population study (Diaz-Guzman, Khosravi & Mannino, 2011) with 15,203 individuals recorded asthma with COPD in 357 subjects (2.7%), COPD in 815 (5.3%), and asthma in 709 (5.3%). The presence of both asthma and COPD was associated with greater airway obstruction as well as greater risk of mortality (HR = 1.83) throughout the study follow-up.

Taking into account all previous evidence, the RVG agreed on the conclusions and recommendations shown in Table 3 with regard to the diagnosis, prognosis and follow-up of asthma in smokers.

## **Treatment of asthma in smokers and ex-smokers**

### **Challenges in the treatment of asthma in smokers and ex-smokers**

The main problem for smoking asthmatics is the reduced response to IGC treatment, leading to poor control of asthma symptoms (Thomson, 2018). In fact, it has been proposed that the effect of IGC treatment in smoking asthmatics be assessed considering multiple indicators, since the observation of a single clinical result may suggest that the treatment is not effective (Hayes, Nuss, Tseng & Moody-Thomas, 2015).

Table 3. *Conclusions and recommendations on the diagnosis, prognosis, and follow-up of asthma in patients who smoke.*

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- Smoking favours the loss of lung function in asthmatics, especially if the cumulative consumption is over 10 p/a and if asthma is diagnosed after the age of 40 years.
  - In all smoking asthmatics with severe and not totally reversible obstruction, it is recommended that the presence of emphysema is assessed by means of a carbon monoxide diffusion capacity test (DLCO) and alpha-1-antitrypsin serum levels are determined (Comité Ejecutivo de GEMA 5.0).
  - In smoking asthmatics with severe and not totally reversible obstruction, computerized axial tomography (CAT) should be performed so that other diseases that can simulate asthma are ruled out (tumours, bronchiolitis, bronchiectasis, syndrome Churg-Strauss, etc.) (Chung et al., 2014; Comité Ejecutivo de GEMA 5.0).
  - In the diagnosis of asthma, it should be taken into account that FeNO (exhaled nitric oxide test) values can be up to 30% lower in smokers than in non-smokers.
  - In the diagnosis of asthma, it should be remembered that exposure to air polluted by tobacco smoke (passive smoking) is also associated with lower FeNO values.
  - In the diagnosis of asthma, it should be taken into account that patients who smoke present an alteration of the inflammatory profile in blood and sputum, with a lower proportion of eosinophils and indications of neutrophilic inflammation.
  - Smoking asthmatics have poorer clinical control of the disease, greater risk of exacerbations, cardiovascular diseases and higher mortality.
  - Patients with asthma, airflow obstruction and a history of smoking >10 p/a (patients considered ACO) have higher mortality and risk of exacerbations than patients with asthma and airflow obstruction, but with cumulative consumption <10 p/a.
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The inflammatory mechanisms involved in treatment response are currently unclear, but smoking is known to induce a rise in CD8 cells and neutrophils, which could alter the response to treatment. The main mechanism proposed for this reduced response is the decrease in the activity of the enzymatic system of histone deacetylase 2 (HDAC2). The efficacy of various HDAC2 enhancers, including low-dose theophylline, is therefore being studied for the treatment of smoking asthmatics. Anti-inflammatory therapies, including phosphodiesterase 4 (PDE4) inhibitors and p38 mitogen-activated protein kinase (MAPK) inhibitors (Spears, Cameron, Chaudhuri & Thomson, 2010; Thomson, 2018), are also being developed.

The RVG reached complete consensus on the recommendations related to this section, as shown in Table 4.

### ***Influence of smoking on the response to inhaled corticosteroids***

Multiple studies have compared the different IGC treatments in smoking and ex-smoking asthmatics. The OLIVIA study stands out, comparing treatments with extrafine and non-extrafine particle IGC in asthmatic smokers. However, no differences were observed in terms of efficacy and safety for these treatments (Cox et al., 2017).

Lastly, tobacco smoke has been shown to increase viral replication (Feldman & Anderson, 2013), and while inhaled glucocorticoids protect against rhinovirus-induced airway inflammation, they do not do so against viral replication (Bochkov et al., 2013), which could partly explain the poor response to treatment among smokers.

### ***Influence of smoking on the response to bronchodilators (combination of corticosteroids and bronchodilators)***

It is believed that smoking asthmatics may respond similarly to patients with chronic obstructive pulmonary disease (COPD). As a result, some studies have considered the possibility of using anticholinergic agents for the treatment of these patients (Ahmad & Singh, 2010).

## **Treatment of smoking in asthmatic smokers**

There is evidence indicating that asthmatics need a different approach to the treatment of smoking than other smokers. Around 25% of asthmatics are smokers, but

between 8 and 35% of them deny this in the interview with the health professional. The interview with asthmatics on smoking should therefore always be biochemically validated (through co-oximetry or the determination of cotinine in biological fluids) (de Granda-Orive et al., 2001). It should also be noted that although most are aware of the need to quit smoking, it is often difficult for them to do so (Perret, Bonevski, McDonald & Abramson, 2016; Saba, Dan, Bittoun & Saini, 2014), and the therapeutic intervention must therefore be adjusted to their characteristics. Some data suggest that people with asthma start smoking at an earlier age (Avallone et al., 2013). In addition, although attempts to quit smoking may be more frequent in smokers with asthma, they are shorter in duration than in non-asthmatics (Vozoris & Stanbrook, 2011).

The motivation to quit will be different for an asthmatic than for a healthy smoker or one without asthma and will be influenced by age, educational level and fear of exacerbations (Tankut, Mowls & McCaffree, 2015). Some studies have shown that asthmatics have a higher level of anxiety and this can lead to a greater risk of exacerbations (McLeish, Farris, Johnson, Bernstein & Zvolensky, 2015). It has also been observed that withdrawal symptoms in asthmatics are longer and more intense, which may imply a greater risk of relapse. Moreover, asthmatic women have been observed to have a higher degree of nicotine dependence than women without the pathology (Vozoris et al., 2011). Thus, longer and more specific treatments, with a higher level of intensity, are recommended (McLeish, Farris, Johnson, Bernstein & Zvolensky, 2016).

Current recommendations advocate specific and intensive interventions that make the relationship between smoking and worse clinical outcomes, the greater number of attacks and exacerbations and worsening lung function clear to the patient. The concept of keeping lung age as low as possible by quitting smoking should also be introduced (Perret et al., 2016).

Smoking cessation treatment should be offered to all smokers who are able and willing to quit.

The combination of psychological counselling and pharmacological treatment offer the best approach to the treatment of smoking in asthmatic smokers (Cahill, Stevens, Perera & Lancaster, 2013; Guichenez, Underner & Perriot, 2019; Jimenez-Ruiz et al., 2015; Perret et al., 2016; Rigotti, 2013). Both areas are outlined below from a practical perspective.

Table 4. *Conclusions and recommendations for the treatment of asthma in smokers.*

- 
- Smoking asthmatics have a worse response to inhaled corticosteroid treatment.
  - For smoking asthmatics, combination therapy (inhaled corticosteroids + bronchodilators) is more effective in reducing symptoms than therapy based solely on inhaled corticosteroids.
  - Smoking asthmatic patients benefit from anticholinergic treatment to a greater extent than non-smoking asthmatics.
-

### **General aspects of counselling**

The advice given to asthmatic smokers should include the following aspects (Jimenez-Ruiz et al., 2015):

1. An explanation of the close link between smoking and asthma should be provided with empathy and an understanding of the patient's attitude to the subject. The health professional must clearly explain to the smoker that quitting smoking is the most effective health measure to control the pathological process.
2. Smokers should be shown the need to find a day (D-day) on which to start. It is highly recommended that they choose a day which is expected to be calm, with few high-risk situations and on which the subject is willing to make a serious effort not to smoke at all.
3. The smoker must identify those daily life situations which they most closely associate with smoking, thereby helping to avoid them from D-day on. If they are unavoidable, the smoker should think about developing alternative behaviours to smoking in such circumstances.
4. Smokers should be informed of the different withdrawal symptoms that they may suffer as a result of the smoking cessation process. Informing them that symptoms last approximately 8-12 weeks and that they are intense and numerous during the first 4-6 weeks is essential in this regard. The use of pharmacological treatment is key to controlling withdrawal symptoms and helps avoid relapses and ensure success in the attempt to quit (Leone et al., 2020).

### **Psychological approach**

The combination of several techniques is recommended for this group of smokers in order to address the different factors maintaining smoking behaviour. Both behavioural and cognitive-behavioural techniques can be used (Becoña, 2004; Fernández Castillo & Esteban de la Rosa, 2017; Lancaster & Stead, 2017; Perret et al., 2016).

- The behavioural model suggests several coping techniques: a) stimulating control, which consists of breaking the association between external stimuli and smoking behaviour to facilitate cessation; b) systematic desensitization, through which patients are exposed to situations of "risk", from least to greatest difficulty for them; and c) reinforcement of abstinence behaviour and patients learning to congratulate and reward themselves. To this end, it is important not to reinforce behaviours indiscriminately, but only those that help maintain abstinence. Food should be avoided as reinforcement (Becoña, 2004; Fernández Castillo et al., 2017; Lancaster et al., 2017; Perret et al., 2016).
- The cognitive-behavioural model also has several coping techniques: a) cognitive restructuring,

which helps the patient to identify erroneous ideas regarding smoking; b) finding a thought process that can prevent those automatic and recurring thoughts preceding smoking behaviour; c) distraction techniques, the main aim of which is to train subjects to distract themselves from thoughts and feelings linked to the urge to smoke; d) self-instructions, through which patients can try to reduce distress by guiding the dialogue towards overcoming difficulties; e) self-control training, through which subjects learn to reduce activation at a physiological and cognitive level; f) imagination techniques, which allow patients to modify thoughts using their imagination (this can be achieved by substituting a negative image); and g) problem solving, through which patients learn to solve problems in ways that reduce the probability of resorting to smoking as a coping strategy (Becoña, 2004; Fernández Castillo et al., 2017; Lancaster et al., 2017; Perret et al., 2016).

### **Pharmacological approach**

Controlled studies analyzing the efficacy and safety of the use of different drugs for smoking cessation in asthmatic smokers are very scarce. However, three studies are worth highlighting (Lancaster et al., 2017; Perret et al., 2016; Tonnesen et al., 2005) whose main conclusion is that, in addition to psychological counselling, asthmatics who want to quit smoking should receive drug treatment, and that this should extend for over three months. In addition, no safety problems have been detected with the use of these drugs in asthmatic smokers (Lancaster et al., 2017; Perret et al., 2016; Tonnesen et al., 2005). Three types of drug treatments can be applied to treat smoking in asthmatic smokers: Nicotine replacement therapy (NRT), bupropion and varenicline. Some tips in this regard include:

1. For NRT, gum, tablets, mouth spray and nicotine patches can be prescribed, which are the treatments available in Spain. It is highly recommended that patches, a prolonged form of nicotine administration, be combined with gum, tablets or mouth spray as a temporary form of administration. Using both types of treatment helps smokers to better control withdrawal symptoms. Moreover, in terms of drug interactions, NRT does not conflict with bronchodilator drugs or inhaled steroids used by asthmatic patients.
2. Bupropion should be prescribed at a dose of 150 mg every 12 hours for a period of 12 weeks (Fiore et al., 2008; Gratiou et al., 2014; Jimenez-Ruiz et al., 2015). It should be taken into account that this is a drug which is metabolized by the liver, through the P450 enzyme system, and that this fact may be associated with important interactions with other medications occasionally used by some asthmatics: drugs that affect CYP2B6, drugs metabolized by CYP2D6, and



enzyme inducers/inhibitors (Tonstad et al., 2006). Finally, it should be remembered that bupropion produces adverse effects more frequently than NRT or varenicline. The most common include insomnia, headaches, and dry mouth (Tonstad et al., 2006). It should be used with caution in clinical situations when the seizure threshold is reduced since the production of seizures is another of the adverse effects that can appear in 0.1% of subjects using this medication. All these data favour the use of bupropion only as a second-choice drug for smoking cessation in asthmatics.

3. Varenicline should be used at standard doses and for a period of 12 weeks (Fiore et al., 2008; Gratziau et al., 2014; Jimenez-Ruiz et al., 2015; Westergaard et al., 2014). However, the only clinical trial that has been carried out using this medication in asthmatic subjects found that abstinence rates dropped off very significantly after three months of follow-up (Westergaard et al., 2014). Even in the open and follow-up study by Gratziau et al., abstinence rates were found to decrease upon termination of drug treatment. These data suggest that the use of varenicline in asthmatic smokers should be prolonged up to six months of follow-up. Indeed, a randomized, placebo-controlled clinical trial involving smokers without associated pathology showed that prolonging treatment with varenicline until six months of follow-up is more effective than using this drug for only twelve weeks (Tonstad et al., 2006).

### ***Follow-up in the treatment of smoking***

Follow-up plays a fundamental role in the treatment of smoking in asthmatics. It is essential that follow-up consultations be scheduled with the main aim of assessing the progress of the quitting process and of controlling both the subject's correct application of all psychological techniques and adherence to the different pharmacological treatments prescribed to quit smoking. Scheduling a follow-up regimen is recommended as of D-Day, starting after the first week and continuing in the second, fourth, eighth, twelfth, sixteenth and twenty-fourth weeks. At all points, it will be necessary to perform a psychological intervention appropriate to the respective moment in the quitting process. The few studies that have analyzed the efficacy of smoking treatments in asthmatics indicate that those subjects who adhered to an intensive treatment program, that is, those who combined psychological and pharmacological treatment, obtained the best results (Fiore et al., 2008; Gratziau et al., 2014; Westergaard, Porsbjerg & Backer, 2015).

### ***Inhaled Toxic Substances***

Many studies show a link between marijuana use and increased respiratory symptoms, although more studies are

needed to establish the long-term risks of marijuana use (Hancox, Shin, Gray, Poulton & Sears, 2015).

In a study assessing the association between cannabis use and respiratory symptoms (N = 1037 young adults), it was found that frequent use was associated with the presence of morning cough (OR: 1.97;  $p < 0.001$ ), sputum production (OR: 2.31;  $p < 0.001$ ) and wheezing (OR: 1.55;  $p < 0.001$ ). In addition, reducing or stopping use was linked to a fall in the prevalence of all three (Taylor, Poulton, Moffitt, Ramankutty & Sears, 2000). In another study, analyzing the relationship between cannabis use and respiratory symptoms and lung function in young adults (91 cannabis users [9.7%] and 264 [28.1%] tobacco users), it was observed that the respiratory symptoms associated with cannabis dependence, after controlling for tobacco use, were: wheezing, exercise-induced respiratory distress, waking at night with chest pressure, and sputum production in the morning (Chatkin, Zani-Silva, Ferreira & Zamel, 2019).

In addition, the results of a population survey with 2,602 young adults showed that the probability of a cannabis user needing asthma drugs was 1.71 (95% CI: 1.06-2.77;  $p = 0.028$ ) compared to non-cannabis users. According to the authors, this suggests that cannabis use is a risk factor for bronchial asthma or for the use of asthma medication, even when other risk factors are taken into account (Bramness & von Soest, 2019).

Finally, with regard to other substances, the evidence shows that the inhalation of cocaine or heroin is associated with an increase in asthma symptoms and a reduction in lung function. In addition, using crack, snorting cocaine or heroin, or smoking heroin have been reported to increase the risk of needing emergency services and hospitalization for asthma (Self, Shah, March & Sands, 2017). Another review shows that the proportion of heroin users is higher in asthmatics and that the prevalence of asthma and bronchial hyperresponsiveness is higher among heroin users. A positive association between heroin abuse and asthma exacerbations has also been shown (Underner, Perriot, Peiffer & Jaafari, 2017). Finally, one study compared the readmission rate for exacerbations in patients with current and past illicit drug use versus current tobacco users or ex-smokers. Results showed the rate of hospital admissions due to exacerbations to be higher in patients currently using or having used illicit drugs compared to tobacco smokers and ex-smokers (1.00 versus 0.22/0.26;  $p < 0.001$ ) (Yadavilli et al., 2014).

Finally, in a recent systematic review analyzing over 1,500 studies on the health effects of cannabis, Campeny et al. concluded that its habitual use is related not only to problems of a psychiatric nature but also to respiratory, cardiovascular and gastrointestinal problems (Campeny et al., 2020).

### ***Use of electronic cigarettes***

Regarding electronic cigarettes or new ENDS (Electronic Nicotine Delivery Systems), there is currently no scientific

evidence favouring their use as an aid to smoking cessation for smoking asthmatics (Chatkin & Dullius, 2016). Some studies have introduced the possibility of using e-cigarettes as a possible alternative, with the idea of “harm reduction” (Polosa et al., 2014). However, a recent longitudinal study conducted in the United States has concluded that e-cigarette use is in itself a risk factor for the development of respiratory disease (COPD, chronic bronchitis, emphysema, or asthma), with an adjusted OR for tobacco consumption and clinical and demographic characteristics of 1.34 (95% CI: 1.23-1.46) for former and 1.32 (95% CI: 1.17-1.49) for active electronic cigarette smokers. In addition, this study concluded that smoking both electronic and standard (combustible) cigarettes increased the risk associated with each one separately of suffering one of the respiratory diseases studied up to an OR of 3.3, compared to an individual never smoker or e-cigarette user (Bhatta & Glantz, 2020).

It is worth noting the increased use of electronic cigarettes in recent years, especially in the younger population. The composition of the aerosol generated by these devices includes numerous compounds (glycerine, propylene glycol, nicotine, flavouring agents, etc.) in addition to toxic compounds such as formaldehyde, acetaldehyde or metallic nanoparticles. The use of e-cigarettes has been associated with respiratory tract irritation, hypersecretion of mucus, or an inflammatory response (Bozier et al., 2020) as well as with the development of asthma (Osei et al., 2019). All the above increases respiratory symptoms and changes in respiratory function in e-cigarette users (Thirion-Romero, Perez-Padilla, Zabert & Barrientos-Gutierrez, 2019; Wang, Ho, Leung & Lam, 2016), in particular asthmatics (Hickman & Jaspers, 2020). A further important aspect is the surge in cases of acute lung damage associated with the use of electronic cigarettes or EVALI (E-cigarette or Vaping Product Use-Associated Lung Injury), with more than 2,000 cases and 42 deaths. The average age of those affected was 24 years (Centers for Disease Control and Prevention, 2020).

A recent study used a questionnaire with the aim of assessing the association between e-cigarette use and symptoms of chronic bronchitis in adolescents (N = 2,086). Most noteworthy among the results is the fact that the risk of suffering from bronchial symptoms in patients who had used electronic cigarettes in the past was almost two times higher than in patients who had never used them (OR: 1.85; 95% CI: 1.37-2.49) and 2.02 times higher (95% CI: 1.42-2.88) among current users. In addition, this risk remained high for subjects who had used electronic cigarettes in the past (OR: 1.70; 95% CI: 1.11-2.59) (McConnell et al., 2017) after adjusting for confounding factors, including tobacco use. Another survey, with 35,904 high school students, found that the risk of asthma for those who currently used electronic cigarettes compared to those who had never used them was 2.36 (95% CI: 1.89- 2.94). It should be noted that the adjusted risk of asthma among current smokers was 2.74 (95% CI: 1.30-5.78) (Cho & Paik, 2016).

Furthermore, it should be taken into account that the use of electronic cigarettes could increase the risk of initiating tobacco use. One study assessed the link between e-cigarette use and susceptibility to tobacco use and asthma attacks in adolescents (N = 36,085). Results showed an association between the ever or past 30-day use of e-cigarettes with increased susceptibility to tobacco use among participants with asthma who had never tried tobacco before (N = 2,410; prior use, AOR=3.96; 95% CI: 1.49-10.56; past 30-day use, AOR = 422.10, 95% CI = 50.29-> 999.99). Additionally, e-cigarette use in the past 30 days was associated with having at least one asthma attack in the previous 12 months among participants with asthma (N = 5,865, p <0.01) (Choi & Bernat, 2016). A review of the literature indicates that adolescent patients with asthma use e-cigarettes more frequently (12.4%) than non-asthmatics (10.2%). In addition, asthmatic patients often express positive ideas about tobacco-related products, especially e-cigarettes (Clapp & Jaspers, 2017).

The consensus recommendations regarding aspects of treating smoking in asthmatics are shown in Table 5.

Table 5. *Recommendations regarding aspects of the treatment of smoking in asthmatics.*

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- The therapeutic approach to smoking in asthmatics should be more intensive than the treatment of smokers without asthma.
  - The motivational interview for smoking cessation should stress the cause-effect link between smoking and increased lung age and greater risk of exacerbations.
  - The most effective strategy for the treatment of smoking in asthmatics includes health advice to stop smoking together with pharmacological treatment (replacement therapy with nicotine, varenicline, bupropion).
  - Cannabis abuse is associated with increased respiratory symptoms such as cough, sputum production or wheezing, regardless of the diagnosis of asthma and smoking.
  - Abusing cannabis, smoked in the form of marijuana or hashish, increases the risk of developing bronchial asthma.
  - Abusing inhaled cocaine and heroin is associated with an increased risk of bronchial hyperresponsiveness, asthma exacerbations, and emergency room visits for asthma.
  - There is no scientific evidence to support the use of electronic cigarettes or new devices (*Electronic Nicotine Delivery Systems* [ENDS]) in the treatment of smoking in asthmatics.
  - In adolescent asthmatics, the use of electronic cigarettes is associated with an increase in respiratory symptoms, even in those not smoking conventional cigarettes.
  - The use of electronic cigarettes among adolescent asthmatics increases the possibility of becoming smokers or initiating tobacco use.
-

## Discussion

This document details the recommendations for the diagnosis and treatment of smokers with asthma as agreed by pulmonologists treating asthma and smoking-related pathologies. The main conclusions of the working group and panellists in relation to the available evidence include the need when diagnosing asthma to take into account the effects of smoking, and it is recommended that the presence of emphysema as well as the exclusion of other diseases be assessed. Moreover, a combined therapy of inhaled corticosteroids with bronchodilators is recommended in the treatment of asthma in smokers, and the importance of smoking cessation should be stressed. The therapeutic approach to smoking in asthmatics must be adapted to the characteristics and motivations of these patients, making behavioural therapy combined with pharmacological treatment necessary.

The conclusions and recommendations of this consensus were quantitatively validated with the participation of a large panel of pulmonologists from all over Spain. However, the use of an approach involving a narrative review of the literature can be seen as a limitation. Although the RDG reviewed and debated the collected evidence, a systematic method involving exhaustive analysis of the literature or of the quality of the evidence was not employed.

This consensus document can be useful at a practical level, addressing fundamental aspects in the diagnosis, prognosis and treatment of smokers with asthma, and highlights the importance of including the use of tobacco and inhaled toxins in asthma management guidelines of asthma.

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## Conflict of interests

FJAG declares that in the last three years he has received fees for consultancy work and giving conferences or grants to attend congresses and scientific meetings by ALK, Astra-Zeneca, Bial, Boehringer-Ingelheim, Chiesi, GSK, Menarini, Mundipharma, Novartis, Orion and TEVA.

MBA declares receiving fees for participating in training activities by Astra-Zeneca, GSK, Teva, Novartis, Chiesi, Zambon, as well as financial support to attend congresses and meetings.

JSCM has received fees for lectures, participation in clinical studies, and publications from: AstraZeneca,

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EPE has received fees for participating in training activities from TEVA, Novartis, Pfizer, Dr. Esteve, Ferrer, Rovi and Boehringer, as well as financial support to attend conferences and meetings.

JLGR has received fees for participating as a speaker in meetings sponsored by Astra-Zeneca, Novartis, GSK, Boehringer-Ingelheim, Chiesi, ALK, Teva, Menarini, Rovi, Grifols and Esteve; and for advisory activities for Novartis, GSK, Astra-Zeneca, Teva, Boehringer-Ingelheim, Grifols, ALK and Esteve.

JGSC declares that in the past three years he has received fees for speaking at meetings sponsored by Astra-Zeneca, Boehringer, Novartis, and as a consultant from Astra-Zeneca, GSK, Chiesi, Novartis and Bial. He has received financial support from Boehringer, Menarini and Novartis to attend conferences and received grants for research projects from Novartis, GSK and Boehringer.

FJCG has received fees for conferences, grants for research, as a consultant and to support conference attendance from various pharmaceutical companies, such as GlaxoSmithKline, Chiesi, Boehringer Ingelheim, Mundipharma, Menarini, Pfizer, Novartis, Esteve, Teva Pharmaceutical, Ferrer, Rovi, Roche, Astra Zeneca, Bial, Actelion, Alter, CSL Behring, Faes Farma and Gebro Pharma.

PJRP declares that in the last three years he has received fees for consultancy work and giving lectures, or grants to attend scientific conferences and meetings from ALK, Chiesi, GSK, Menarini and Novartis.

JARM has received fees for conferences, grants for research, as a consultant and to support conference attendance from various pharmaceutical companies, such as GlaxoSmithKline, Chiesi, Boehringer Ingelheim, Mundipharma, Menarini, Pfizer, Novartis, Esteve, Teva Pharmaceutical, Ferrer, Rovi, Astra Zeneca, Bial, Faes Farma and Gebro Pharma.

CAJR has received fees for participating in training activities from Pfizer and Johnson & Johnson, as well as financial aid to attend conferences and meetings.

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