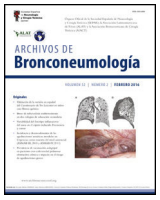
Archivos de Bronconeumología 59 (2023) 651–661

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

www.archbronconeumol.org



SEPAR's Voice

Clinical Practice Guideline of Spanish Society of Pneumology and Thoracic Surgery (SEPAR) on Pharmacological Treatment of Tobacco Dependence 2023

Carlos Rábade-Castedo[a,*], José Ignacio de Granda-Orive[b,c], Juan Antonio Riesco-Miranda[d,e,f], Eva De Higes-Martínez[g,h], Ángela Ramos-Pinedo[g,h], Eva Cabrera-César[i], Jaime Signes-Costa Miñana[j,k], Marcos García Rueda[l], Esther Pastor-Esplá[m], Carlos A. Jiménez-Ruiz[n]

[a] *Servicio de Neumología, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, La Coruña, Spain*
[b] *Servicio de Neumología, Hospital Universitario 12 de octubre Madrid, Spain*
[c] *Universidad Complutense, Madrid, Spain*
[d] *Servicio de Neumología, Hospital Universitario de Cáceres, Cáceres, Spain*
[e] *Centro de Investigación en Red de enfermedades respiratorias (CIBERES), Madrid, Spain*
[f] *Instituto Universitario de Investigación Biosanitaria de Extremadura (INUBE), Spain*
[g] *Unidad de Neumología, Hospital Universitario Fundación Alcorcón, Spain*
[h] *Universidad Rey Juan Carlos, Madrid, Spain*
[i] *Servicio de Neumología, Hospital Universitario Virgen de la Victoria, Málaga, Spain*
[j] *Servicio de Neumología, Hospital Clínico Universitario de Valencia, Spain*
[k] *Instituto de Investigación Sanitaria de Valencia (INCLIVA), Valencia, Spain*
[l] *Servicio de Neumología, Hospital Carlos Haya de Málaga, Málaga, Spain*
[m] *Servicio de Neumología, Hospital Universitario San Juan de Alicante, Alicante, Spain*
[n] *Unidad Especializada en Tabaquismo de la Comunidad de Madrid, Hospital Clínico San Carlos, Madrid, Spain*

ARTICLE INFO

Article history:
Received 20 July 2023
Accepted 21 July 2023
Available online 28 July 2023

Keywords:
Tobacco
Smoking
Dependence
Treatment
Cessation

ABSTRACT

Introduction: There are multiple systematic reviews and meta-analyses on the efficacy and safety of pharmacological treatments against nicotine dependence. However, there are few guidelines to answer frequent questions asked by a clinician treating a smoker. Therefore, the aim of this paper is to facilitate the treatment of tobacco addiction.
Material and methods: 12 PICO questions are formulated from a GLOBAL PICO question: "Efficacy and safety of pharmacological treatment of tobacco dependence". A systematic review was carried out to answer each of the questions and recommendations were made. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system was used to grade the certainty of the estimated effects and the strength of the recommendations.
Results: Varenicline, nicotine replacement therapy (NRT), bupropion and cytisine are more effective than placebo. Varenicline and combined nicotine therapy are superior to the other therapies. In smokers with high dependence, a combination of drugs is recommended, being more effective those associations containing varenicline. Other optimization strategies with lower efficacy consist of increasing the doses, the duration, or retreat with varenicline. In specific populations varenicline or NRT is recommended. In hospitalized, the treatment of choice is NRT. In pregnancy it is indicated to prioritize behavioral treatment. The financing of smoking cessation treatments increases the number of smokers who quit smoking. There is no scientific evidence of the efficacy of pharmacological treatment of smoking cessation in adolescents.
Conclusions: The answers to the 12 questions allow us to extract recommendations and algorithms for the pharmacological treatment of tobacco dependence.

* Corresponding author.
E-mail address: crabcas1@gmail.com (C. Rábade-Castedo).

https://doi.org/10.1016/j.arbres.2023.07.024

Introduction

Smoking is an addictive and chronic disease with a high population impact and, as such, requires treatment based on drugs against nicotine dependence and psychological counseling, thus tripling the chances of smoking cessation.[1,2] A recently published study shows that the implementation of both treatments would lead to a reduction in mortality by the year 2050 of 180 million people. In other words, the availability of effective and safe treatments for smoking cessation is one of the most powerful measures to control mortality from this disease.[3]

Therefore, one of the ethical responsibilities of scientific societies is to provide health professionals with the best tools through guidelines and consensus so that they can offer the best care to patients who smoke.

The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) prepared 2 documents of recommendations in 2003 and 2008 on the pharmacological treatment of smoking quitting.[4,5] However, in the last fifteen years there have been important changes in the therapeutic approach to the disease, such as the appearance of new drugs like cytisine and the numerous studies on drug treatment optimization (clinical trials, observational studies, meta-analyses and systematic reviews) as well as its use in specific populations and circumstances.[6] Varenicline and extended-release bupropion hydrochloride are temporarily withdrawn from the market. However, we have decided to include both treatments in this guide for the following reasons:

A) Varenicline is currently authorized for marketing outside the European Union.
B) Changes are being made in the formulation of varenicline that will allow it to be remarketed in Europe in the coming months.[6]
C) The reintroduction of extended-release bupropion is not ruled out soon.

Thus, the main objective of this document is to provide all healthcare professionals in general and, in particular, those working in the field of smoking cessation with updated scientific information on some clinical questions relevant to the treatment of tobacco addiction. For all these reasons, we in the area of Tobacco Control proposed a document that attempts to answer a global PICO question (efficacy and safety of pharmacological treatment of tobacco dependence). From this, 12 PICO questions were generated, grouped in 4 thematic blocks: I. Efficacy and safety in standard regimen. II. Efficacy and safety using optimization strategies III. Efficacy and safety in specifics populations. IV. Efficacy and safety in specifics situations (Fig. 1).

Based on the answers to these PICO questions, we made a pharmacological treatment proposal during the initial visit and in the follow-up process of the smoker who is quitting smoking.

Methodology

This update document follows the SEPAR regulations regarding Treatment Guidelines. The elaboration of this guideline consists of the following phases.

Formation of the guideline collaborating group and formulation of the clinical questions. Selection criteria and search strategy

The methodology was discussed in on-line meetings and the clinical scenarios to address the questions to be developed were selected. A first exhaustive search was carried out to define the feasibility of answering, based on scientific evidence, the questions initially posed; subsequently, the final questions to be answered were discussed and agreed upon (Fig. 1). In order to concentrate the search for the available evidence, all the clinical questions were transformed into the PICO format or its variant PECO: Patient (Problem or Population), Intervention or Exposure, Comparison and Outcome (relevant outcome).[7] The bibliographic search strategy was performed simultaneously in 3 meta-search engines in the title of the article, abstract and keywords (descriptors) as well as terms in free text, with equivalent search fields in each database consulted: PubMed, Embase and Cochrane Library (Tables 1MS, 2MS and 3MS of the supplementary material). As limits we searched only articles in humans, and in English or Spanish, but limiting the same until June 2022. The access protocol has not been registered.

Systematic literature review (SLR)

The hierarchical SLR protocol was designed following the principles of the Cochrane Collaboration and PRISMA (see Fig. 2 and Table MS3).[8,9] In a first step, 12 PICO questions mentioned in Fig. 1 were formulated.

Based on these, the following inclusion and exclusion criteria were established: studies that included smoking population, regardless of duration, severity or other characteristics of smoking and smoking population (P); in treatment with varenicline, cytisine, bupropion or nicotine replacement therapy (NRT) regardless of dose, duration or treatment strategy (I); studies with a placebo or active type comparator (C); that analyzed verified continuous abstinence (primary variable) or others such as adherence or patient satisfaction (O).

To evaluate the results obtained from the PICO questions, priority was given to selecting the highest level of evidence that best answered the clinical question, so that finally studies with the following designs were included: meta-analysis, SLR and randomized clinical trials (RCT).

In order to increase the reliability and safety of the process, the selected articles were independently assessed by 2 authors of the study to ensure their suitability to the object of the study and the inclusion criteria. When there were doubts about the inclusion of the article, the full text of the document was reviewed and if there was still a discrepancy between the 2 authors, a third author was incorporated to arbitrate the decision of inclusion or exclusion. A secondary manual search of the bibliography of the articles that were finally included was performed. Likewise, additional articles searched in nonstandard channels (gray, invisible, unconventional, fugitive, or semi-published literature) were added[10] and, after their evaluation, were selected and documents identified in the articles collected in the search strategy were also added. The final selection of articles was done in a hierarchical manner, first selecting the SLRs that applied to each PICO question and then evaluating the RCTs (Fig. 2). Only those RCTs not included in the SLRs that provided new information were selected.

Therefore, the SLR excludes (a) opinion articles, duplicate articles, letters or editorials, (b) experimental (animal) or basic research studies, (c) clinical trials and systematic reviews that do not provide new information, (d) exclusion decision by the authors in articles that generate doubts or discrepancies, (e) articles with small sample size or absence of adequate conditions to verify smoking abstinence or absence of peer review.

The quality of the evidence was evaluated with the AMSTAR-2 (https://amstar.ca/Amstar_Checklist.php) for the SLRs and the Jadad scale[11] for the RCTs. Evidence and results tables were generated. The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system was used to rate the certainty of the estimated effects and the strength of the recommendations.

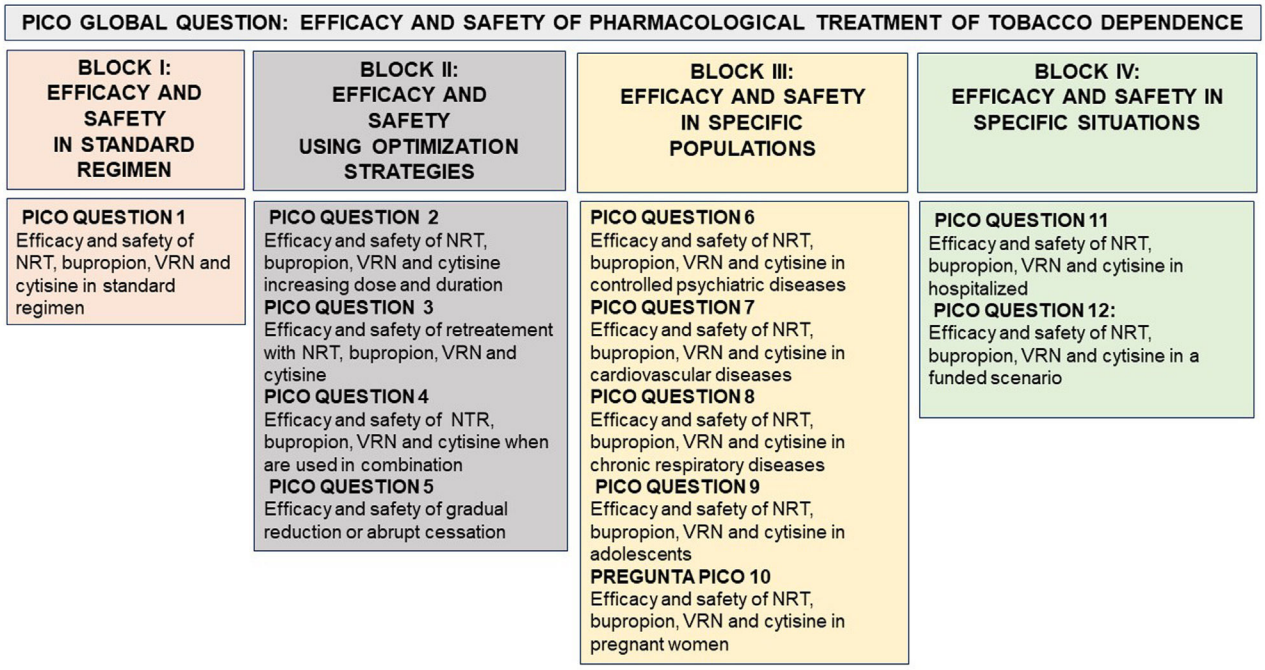


Fig. 1. Model of organization of the PICO questions based on a global PICO question (effectiveness and safety of pharmacological treatments for smoking). NRT: Nicotine replacement therapy. NRV: Varenicline. PICO or its variant PECO: Patient (Problem or Population), Intervention or Exposure, Comparison and Outcome (relevant outcome).

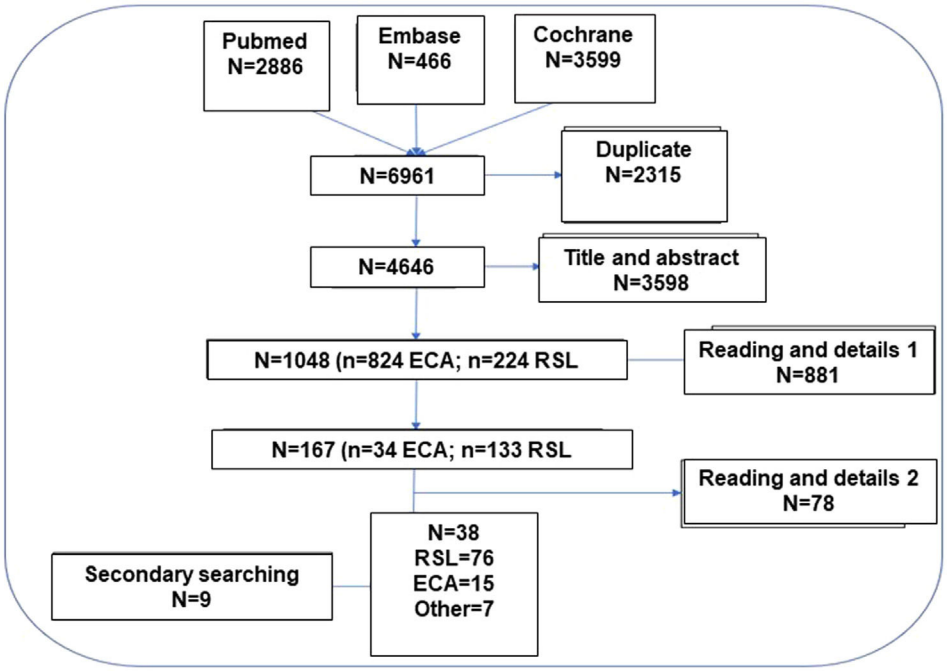


Fig. 2. Flowchart: studies inclusion.

Nominal group meetings

Three nominal group meetings were held with the experts guided by a methodologist. In the first, the objectives, scope, users of the document and the PICO questions (Population, Intervention, Comparator, Outcome) were defined in order to carry out the SLR. Data were extracted from the titles, abstracts, key words or the complete article (in some cases from the supplementary material of the document), as appropriate, and in relation to the questions of interest. Likewise, possible individual biases were assessed in each study. In the second and third meetings, the results of the SLR were discussed and the treatment algorithms and specific recommendations for the defined population subgroups were agreed upon. In order to comply with the key aspects and appropriate steps to be considered when publishing an SLR in a biomedical journal, we adhered to the PRISMA statement (Table 3MS).[8,9]

Results

PICO question 1: What is the efficacy and safety of nicotine replacement therapy (NRT), bupropion, varenicline and cytisine for the treatment of tobacco dependence?

Evidence

There are four drugs that are effective and safe for smoking cessation with level 1 scientific evidence: varenicline, NRT, bupropion and cytisine.

Varenicline, at standard doses and time, is safe and more effective than placebo. [OR: 2.83, 95% CI 2.34–3.39], level of evidence 1a.[12–16]

All types of NRT, at standard doses and time, are safe and more effective than placebo. [OR: 2.01, 95% CI 1.68–2.41], level of evidence 1a.[14–19] It should be noted that, although no clear differences in safety and efficacy have been found between the different types of NRT, combined nicotine therapy (combined NRT), that is, administration of nicotine by two different forms, has been found to be safe and more effective than administration by a single form. [OR: 1.25, 95% CI 1.15–1.36], level of evidence 1a.[14–19]

Bupropion, at standard dose and time, has been shown to be safe and more effective than placebo [OR: 1.64, 95% CI 1.52–1.77, I^2 = 15%], level of evidence 1a. It should be noted that its use causes a significant increase in mild adverse effects, but not in severe ones. [OR = 1.14, 95% CI 1.11–1.18, I^2 = 64%], level of evidence 1a-b.[14–16,18–21]

Cytisine, at standard dose and time, has been shown to be safe and more effective than placebo, [OR = 3.98, 95% CI 2.01–7.87, I^2 = 0%], level of evidence 1b.[12,13,22–25]

Fig. 3 shows the comparative efficacy data of different smoking cessation drugs in different meta-analyses. Of note, some of these studies are indirect comparisons.

Conclusions

1. Varenicline, NRT, bupropion and cytisine are safe and effective in aiding smoking cessation. Level of evidence 1a-b.
2. Bupropion is associated with a higher number of mild adverse events than placebo. Level of evidence 1a-b.
3. Comparatively between groups:
   - 3.1 All types of NRT in monotherapy are of similar efficacy. Level of evidence 1b. Combined NRT is more effective than monotherapy NRT. Level of evidence 1a.
   - 3.2 Varenicline is more effective than NRT monotherapy (level of evidence 1b), bupropion (level of evidence 1b), and cytisine (level of evidence 2a), but is not superior to combined NRT.
   - 3.3 The efficacy of NRT in monotherapy is similar to that of bupropion. Level of evidence 2a.
   - 3.4 Cytisine is more effective than NRT in monotherapy. Level of evidence 2a.

Recommendations

- Algorithms 1 and 2 (Figs. 4 and 5) show the recommendations on the use of these drugs at different doses and timing as initiation and follow-up treatment in subjects who want to quit smoking.

PICO question 2: What is the efficacy and safety in relation to the use of higher doses and/or duration of treatment with varenicline, NRT, bupropion and cytisine?

Evidence

Although there is some discordant data, most studies suggest that prolonging varenicline treatment to 6 months is followed by a higher abstinence rate,[15,16,18,26,27] level of evidence 2b-3a. The evidence is very weak with respect to increasing the dose of varenicline.[15]

In relation to NRT, higher dose patches have been found to achieve higher abstinence rates, without being associated with more safety issues, level of evidence 2a. In 24-h patches, the 21 mg dose has been shown to be the most effective [OR = 1.4, 95% CI 1.0–2.08]. In 16-h patches, the 25 mg dose is the most effective [OR = 1.19, 95% CI 1–1.41].[17]

The 4 mg chewing gum is significantly more effective than the 2 mg [OR = 1.43, 95% CI 1.12–1.83, I^2 = 67%], especially in smokers with a higher degree of dependence, level of evidence 2a.[17]

In relation to the duration of treatment with the patch, no significant differences have been found.[17]

With bupropion, no significant differences were found between 150 mg and 300 mg per day. [OR = 1.08, 95% CI 0.93–1.26, I^2 = 49%] with no differences in safety, level of evidence 1b.[21]

With cytisine there are some preliminary studies showing that the highest short-term abstinence rate was obtained with the 3 mg dose, level of evidence 2b-3a.[28,29]

Conclusions

1. Regarding NRT:
   - 1.1 Patches at higher than standard doses are more effective without causing safety problems. Level of evidence 2a.
   - 1.2 4 mg chewing gum is more effective than 2 mg and does not cause safety problems, especially in smokers with a higher degree of dependence. Level of evidence 2a.
2. With bupropion, no differences in efficacy or safety have been shown between 150 and 300 mg per day. Level of evidence 1b.
3. Cytisine could be more effective at higher doses and for a longer time without major safety problems. Level of evidence 2b-3a.
4. Varenicline could be more effective when treatment is prolonged for 24 weeks. Level of evidence 2b.

Recommendations

- Algorithms 1 and 2 (Figs. 4 and 5) show the recommendations on the use of these drugs at different doses and time as initiation and follow-up treatment in subjects who want to quit smoking.

PICO question 3: What is the efficacy and safety of first-line smoking cessation drugs when used as retreatment after a previous quit attempt with that drug?

Evidence

Retreatment with NRT consisting of using different forms of nicotine after previous use of nicotine patches has demonstrated abstinence rates of 0–6.4% with no adverse effects observed, level of evidence 3a-b.[30–32]

Retreatment with bupropion for 12 weeks was studied in a randomized clinical trial of moderate quality, showing abstinence rates at 6 and 12 months of 12 and 9% respectively, being significantly superior to placebo, level of evidence 2b-3a. Another evaluated abstinence at 6 months with repeated cycles of bupropion, being higher than 10%. No adverse effects were recorded in any of the cases.[33,34]

Retreatment with varenicline in a quality double-blind placebo-controlled RCT on nearly 500 smokers with ≥1 previous quit attempt (≥2 weeks) demonstrated a continuous abstinence rate during weeks 9–12 of 45% vs. placebo 11.8%, [OR = 7.08, 95% CI 4.34–11.55] with no serious adverse events reported, level of evidence 1b-2a.[35]

We do not have data on retreatment with cytisine.

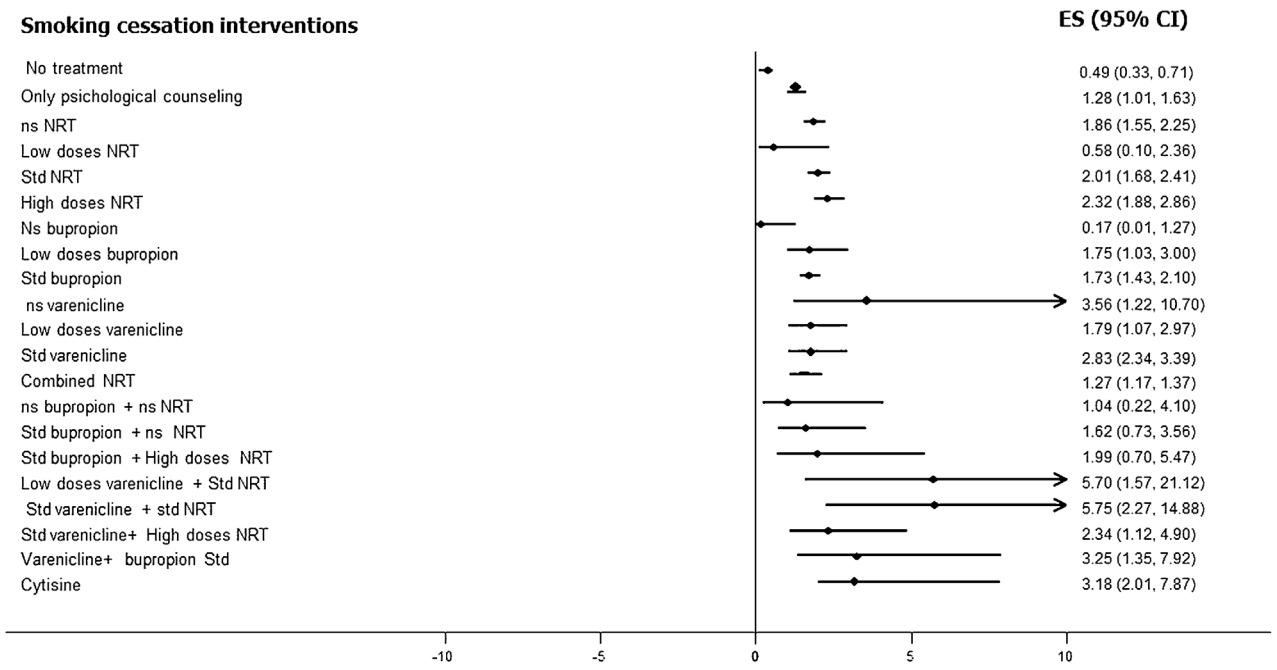


Fig. 3. Efficacy of the different drugs for smoking cessation. Analysis of comparisons indirect relationships between the different drugs and their optimization strategies.

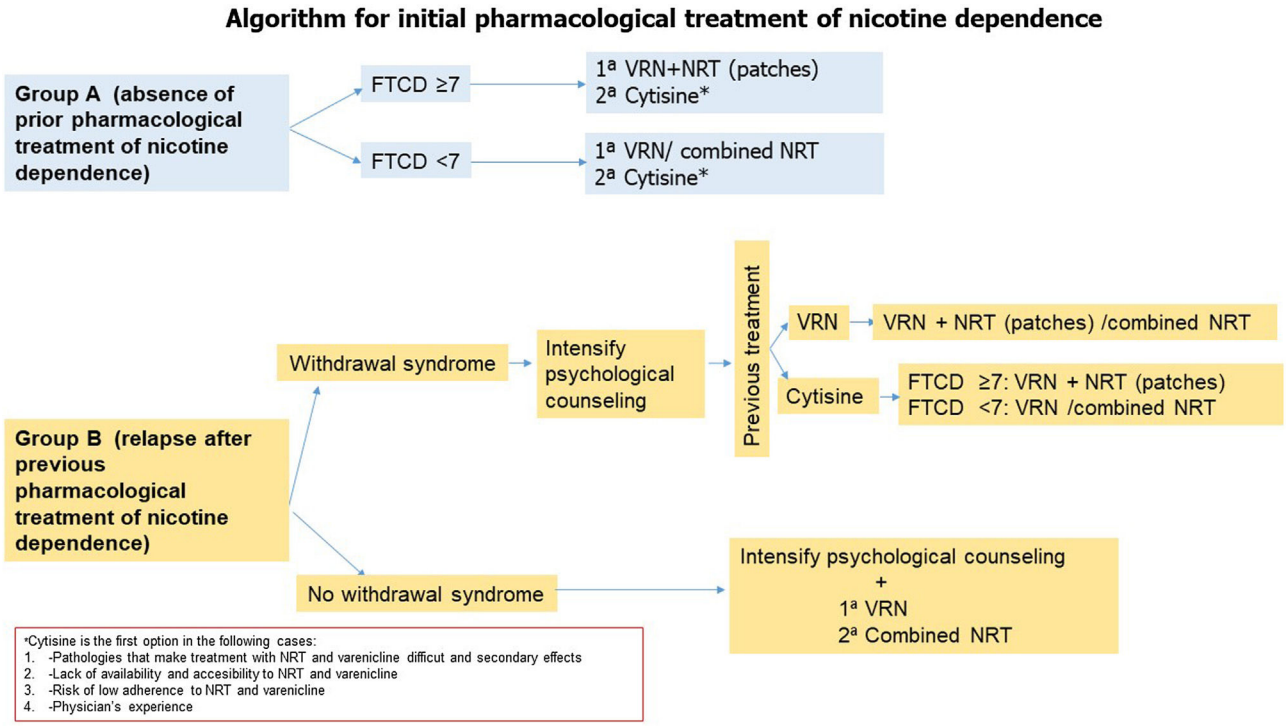


Fig. 4. Algorithm 1. In a proposal for initiation of pharmacological treatment of smoking cessation, 2 groups of smokers are distinguished: group A (smokers who have not made previous quit attempts with treatment) and group B (smokers who have made previous attempts using drugs and have relapsed). In group A smokers, in patients with non-high physical dependence (FTND < 7), the treatment of first choice is varenicline or combined nicotine replacement therapy. However, cytisine, despite presenting less scientific evidence of efficacy with respect to the previous, will be the first choice in the case of diseases in which the use of these drugs is contraindicated or in the situations shown in the figure. In patients with high nicotine dependence (FTND ≥ 7), we propose as first choice varenicline plus nicotine replacement therapy (preferably nicotine patches), and as second choice cytisine if the previously mentioned criteria are met. In group B patients if the patient has previously relapsed due to abstinence syndrome, it is recommended to intensify psychological counseling and evaluate the drug used previously. If the patient was previously treated with varenicline, it is recommended to add nicotine patches. If the patient previously used combined NRT, it is recommended to add varenicline. In case of previous treatment with cytisine, if the patient presents a high physical dependence we recommend treatment with varenicline plus nicotine patches. In case of non-high nicotine dependence, varenicline or combined NRT will be considered. In case of previous relapse in patients who have been treated with drugs not due to abstinence symptoms, psychological counseling will be intensified and the first choice will be the combination of varenicline plus nicotine patches.

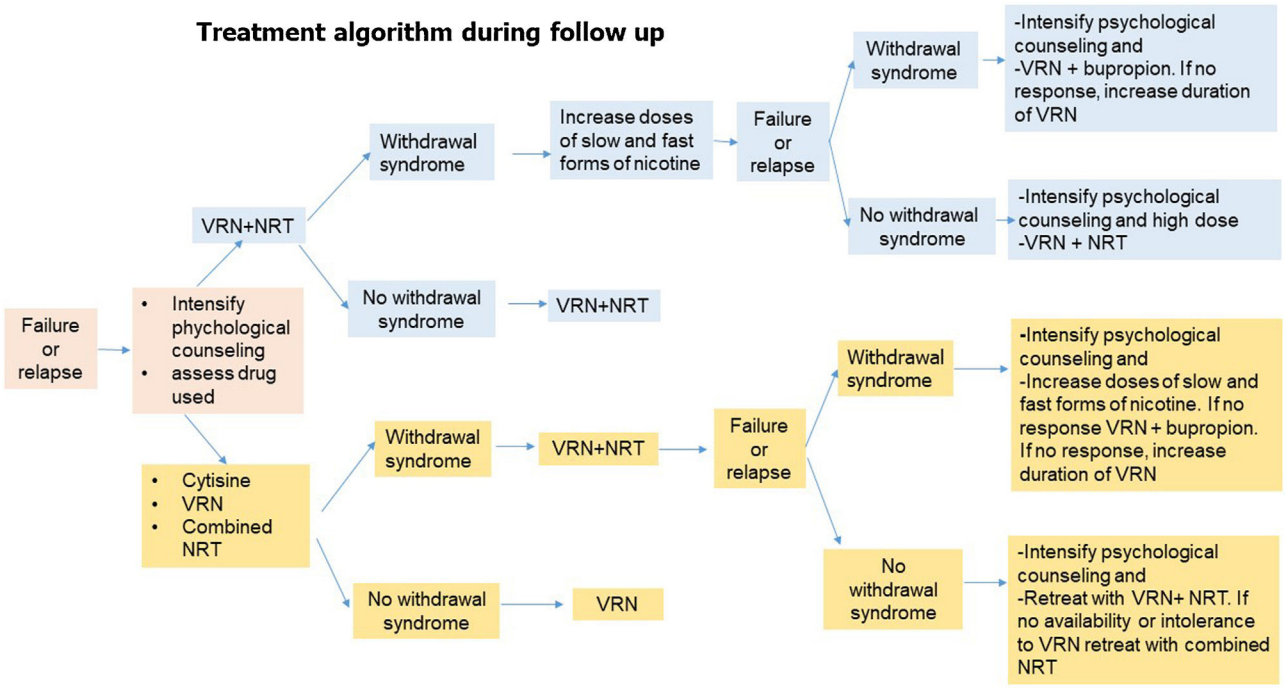


Fig. 5. Algorithm 2. During the follow-up process of smoking cessation in the event of failure or relapse, psychological treatment should be intensified, the cause of relapse and the drug used should be assessed. -If the relapse is caused by withdrawal syndrome and the patient was previously treated with varenicline plus NRT, the dose of nicotine should be increased in slow and fast forms. In case of failure or relapse as a consequence of withdrawal syndrome, despite these modifications, the combination will be changed, administering varenicline plus bupropion and if, despite this, there is no response, treatment with varenicline will be prolonged. If the patient relapses due to other causes than withdrawal syndrome, the combination of varenicline plus NRT will be repeated. -If the patient was previously treated with cytisine, varenicline or combined NRT if the cause of relapse was due to withdrawal syndrome, it is recommended to combined varenicline with NRT. If despite this combination the withdrawal syndrome persists, psychological counseling should be intensified and nicotine doses should be increased in slow and fast forms. If there is no response, a change of combination should be considered, preferably varenicline plus bupropion, and if, despite this, the patient continues to smoke, the use of varenicline should be prolonged. If the patient's relapse was not caused by withdrawal syndrome and the patient was previously treated with varenicline plus NRT, it is recommended to reinforce the combination of varenicline plus bupropion.

Conclusions

1. Retreatment with NRT and bupropion at standard dose and regimen could be effective and safe, but the magnitude of effect is small. It cannot be ruled out that at higher doses of NRT the level of efficacy is higher. Level of evidence 3a-b.
2. With the current evidence, retreatment with varenicline is effective and safe with a relevant magnitude of effect. Level of evidence 1b-2a.

Recommendations

- In patients who have previously used varenicline for more than 2 weeks and relapse, we recommend retreatment with this drug.

PICO question 4: What is the efficacy and safety of first-line smoking cessation drugs when used in combination?

Evidence

The efficacy and safety of the combination of first-line drugs (varenicline plus NRT, varenicline plus bupropion and NRT plus bupropion) is analyzed in several studies.[12–16,18,19,21,36–39] An SLR and network meta-analysis, which included 20 RCTs of moderate quality and more than 16,000 smokers, showed that compared to placebo and monotherapies, short- and long-term continuous abstinence is higher with combination treatments, without major safety issues, level of evidence 2a. The most effective combination was varenicline plus bupropion [OR = 6.08, 95% CI 3.47–10.66], which was superior to varenicline plus NRT [OR = 1.66, 95% CI 1.07–2.59] and to monotherapies.[15]

Another SLR with network meta-analysis found that compared with placebo, the greatest efficacy was obtained with standard varenicline plus standard NRT [OR = 5.75, 95% CI 2.27–14.88], followed by low-dose varenicline plus standard NRT [OR = 5.70, 95% CI 1.57–21.12]. Another SLR also demonstrates greater efficacy with varenicline plus NRT without an increased risk of serious adverse events, level of evidence 2a.[16,18] Recently, a review did not find greater efficacy when bupropion was combined with NRT or varenicline, but did find an increase in adverse events.[21] On the other hand, consensus documents are in favor of combinations in a profile of smokers with high dependence (FTND $\geq$ 7), very high smoking (>30 cigarettes/day) and previous unsuccessful quit attempts with drugs, being the combination of choice varenicline plus NRT.[39]

Conclusions

1. Great heterogeneity and complexity of the analysis of combined therapies, since indirect comparisons are necessary to obtain an overall picture of all the possibilities.
2. Combination therapy is significantly superior to placebo and monotherapies, at least in the short-medium term. Level of evidence 2a.
3. Combinations that include varenicline are superior to others. Probably the most effective is that of varenicline plus NRT. Level of evidence 2a. The magnitude of the effect is more evident in heavy smokers and in those with a higher level of dependence. Level of evidence 2a.
4. No robust evidence found for combinations with cytisine.
5. Combination has not been shown to be associated with increased risk of serious adverse events. Level of evidence 1b-2a.

Recommendations

- In patients with a higher degree of smoking and dependence, we recommend a combination of first-line drugs versus monotherapy being the combination varenicline plus NRT the most effective.

PICO question 5: What is the efficacy and safety of gradual reduction vs. abrupt cessation of smoking with the use of NRT, bupropion, varenicline and cytisine?

Evidence

Recently, in a study of 51 RCTs comparing the efficacy of gradual versus abrupt smoking cessation, no difference was found in the rate of verified continued abstinence [OR = 1.01, 95% CI 0.87–1.17, I^2 = 29%, n = 22 studies], level of evidence 1b-2a. However, in subgroup analyses, if gradual reduction was associated with pharmacological treatment, this could be more effective in achieving abstinence than abrupt cessation, although with high heterogeneity [OR = 1.68, 95% CI 1.09–2.58, I^2 = 78%, n = 11 studies], level of evidence 1b. This was observed with varenicline [OR = 1.48, 95% CI 1.16–1.9] (n = 1 study) (level of evidence 3a), and with rapid-acting NRT [OR = 2.56, 95% CI 1.93–3.39, I^2 = 0%] (n = 7 studies). There was also no difference between these strategies whether or not a fixed quit date was established, different durations of the reduction period, or with a structured cessation program [OR = 2.56, 95% CI 1.93–3.39, I^2 = 0%] (n = 7 studies), or with a structured cessation program [OR = 2.56, 95% CI 1.93–3.39, I^2 = 0%] (n = 7 studies), level of evidence 3b.

There were also no differences between these strategies with or without a fixed quit date, different lengths of the reduction period, or with or without a structured smoking reduction program.[27,40] In patients not ready to quit smoking, the evidence is similar and gradual reduction is considered a valid way to proceed.[41,42]

Recommendations

- There is insufficient evidence to consider one strategy superior to the other (NE 1b-2a).
- If tapering is coupled with pharmacological treatment (varenicline and rapid-acting NRT), higher abstinence rates would be achieved than with abrupt cessation. Level of evidence 2a.

PICO Question 6: What is the efficacy and safety of NRT, varenicline, bupropion, and cytisine in a psychiatric population?

Evidence

Several SLRs (some with meta-analyses) have been published analyzing efficacy and safety in these patients, including the most severe[1–6,43–48]; the latest review from 2022 analyzes 19 observational studies in patients with schizophrenia, bipolar disorder, and major depression.[43] The following recommendations can be drawn from the analysis of these reviews.

Recommendations

- NRT, bupropion and varenicline are effective, also in patients with more severe disease, without these treatments interfering with the course of the underlying disease. They have not been associated with serious neuropsychiatric adverse events including suicide and suicidal ideation. Level of evidence 2b-4.[6–8,48–50]
- Flexible and individualized multicomponent treatments improve outcomes, especially those associated with more intense cognitive behavioral therapy (ICBT). Level of evidence 3a-4.
- In patients with schizophrenia, the efficacy of varenicline is superior to bupropion, but similar to NRT. Level of evidence 3a.
- In patients with major depression, NRT was effective in the short term, varenicline and combinations of CBT with bupropion and NRT were effective in the long term. Level of evidence 2a-4.
- There is no evidence on efficacy and safety of cytisine.

PICO Question 7: What is the efficacy and safety of NRT, bupropion, varenicline, and cytisine in cardiovascular disease?

Evidence

In cardiovascular patients the evidence comes from the analysis of SLRs (the latest in 2021) and RCTs[12,13,51–60] with moderate quality of the studies with variability in the type and severity of diseases included.

Recommendations

- In the medium to long term, NRT, bupropion, especially in patients with stable pathology, and also varenicline (level of evidence 2a) are effective.
- In indirect comparisons, varenicline and NRT combined were superior to NRT monotherapy and bupropion. Level of evidence 3a.
- NRT, bupropion, and varenicline have not been associated with increased medium- or long-term cardiovascular adverse events in patients with cardiovascular disease. Level of evidence 2a.
- There is no evidence on efficacy and safety of cytisine.

PICO Question 8: What is the efficacy and safety of NRT, bupropion, varenicline and cytisine in patients with chronic lung disease (chronic obstructive pulmonary disease and asthma)?

Evidence

Several systematic reviews (some with meta-analysis) are analyzed.[61–76] Basically, they focus on patients with chronic obstructive pulmonary disease (COPD)[61–71] and others on subjects with asthma.[72–74] In addition, recommendations from scientific societies have been considered.[75,76]

The use of combined and/or high-dose NRT has been found to be safe and more effective than placebo in helping COPD patients to quit smoking at 6 and 12 months follow-up. [OR: 2.60, 1.29–5.24], level of evidence 1b. Data for varenicline showed similar results [OR = 3.34, 1.88–5.92], level of evidence 1b. However, for bupropion, efficacy was only found at 6-month follow-up [OR = 2.03, 1.26–3.28], level of evidence 1b.[61–71,74,75] The recommendations of the societies express the need for the association of aggressive pharmacotherapy with intense psychological counseling for the treatment of smoking cessation in smokers with COPD.[75,76]

Fewer studies are available in smokers with asthma, but both varenicline and combined NRT have been shown to be effective and safe in helping this group of subjects to quit smoking. Level of evidence 2b-3a.[72–74] No studies have been conducted with cytisine.

Recommendations

- The use of varenicline or combined NRT is recommended as the first option for the treatment of smoking in smokers with COPD. Bupropion could be used as a second option. The use of varenicline or combined NRT or NRT at high doses and/or prolongation of the use of these drugs, as well as the use of combined treatments (varenicline plus nicotine patches) together with intensified psychological counseling can be a good therapeutic option in this group of subjects.
- For asthmatic smokers, it is recommended to use combined NRT or varenicline as the first option.

Table 1
Shows the recommendations for pharmacological treatment of smoking cessation using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) system to rate the certainty of the estimated effects and the strength of the recommendations.

Cytisine (level of evidence 1b), NRT (level of evidence 1a), varenicline (level of evidence 1a) and bupropion (level of evidence 1a) have demonstrated superiority over placebo. Moderate quality of evidence. Strong grade of recommendation. Combined NRT and varenicline have been shown to be more effective than the others (level of evidence 1ab). Moderate quality of evidence. Strong grade of recommendation.
Increasing the dose or duration of NRT in the form of patches or chewing gum increases its efficacy without losing safety (level of evidence 2a). Low quality of evidence. Weak grade of recommendation. Varenicline or cytisine could be more effective by increasing dose or duration (level of evidence 2b). Low quality of evidence. Weak grade of recommendation.
The only retreatment that has increased efficacy without losing safety was varenicline (level of evidence 1b-2a). Low quality of evidence. Strong grade of recommendation.
Combinations of first-line smoking cessation drugs are more effective than monotherapy, being superior those containing varenicline (level of evidence 2a). Low quality of evidence. Strong grade of recommendation.
Gradual reduction with pharmacological treatment is as effective as abrupt cessation (level of evidence 1b 2a) Low quality of evidence. Weak grade of recommendation.
NRT, bupropion and varenicline are effective in patients with psychiatric illness. Their efficacy increases with increasing intensity of behavioral treatment (level of evidence 2b). Consistent recommendation. Low quality of evidence. Strong grade of recommendation.
Combined NRT and varenicline were superior to NRT and bupropion monotherapy in patients with cardiovascular disease (level of evidence 3a). High quality of evidence. Strong grade of recommendation.
Combined NRT and varenicline are the first choice in patients with COPD (level of evidence 1b). Moderate quality of evidence. Strong grade of recommendation.
Pharmacological treatment has not been shown to be effective in adolescents for smoking cessation (level of evidence 1b 2a). Low quality of evidence. Weak grade of recommendation.
In pregnant women, the first choice treatment is cognitive-behavioral therapy. In case of no response, nicotine gum and then nicotine patches of 15 mg 16 h (level of evidence 1b 2a). Low quality of evidence. Strong grade of recommendation.
In hospitalized patients, the treatment of first choice is combined NRT (level of evidence 1a b). Moderate quality of evidence. Strong grade of recommendation.
From a public health (social) perspective: funding of drugs for smoking treatment is cost-effective and is associated with greater abstinence (level of evidence 2a). From an individual point of view, the efficacy of treatment will depend on different factors, including the life time of each smoker; in this sense, treatment funding could be a motivational factor (level of evidence 3). High quality of evidence. Strong grade of recommendation.

PICO Question 9: What is the efficacy and safety of NRT, bupropion, varenicline and cytisine in adolescents?

Evidence

NRT is no more effective than placebo [OR = 1.11, 95% CI 0.48–2.58, I^2 = 20%], level of evidence 1b-2a) or counseling [OR = 0.15, 95% CI 0.01–2.94], level of evidence 2b[76,77] with no difference between patches and gum at 6 months. In the short term, patches (28%) are more effective than chewing gum (6%).[77]

Bupropion is not more effective than placebo [OR = 1.49, 95% CI 0.55–4.02], in monotherapy or associated with nicotine patch [OR = 1.05, 95% CI 0.41–2.69], level of evidence 2b.[78]

Varenicline is not more effective than placebo, level of evidence 1b-2a. There are no data on efficacy and safety of cytisine.[79,80]

Side effects of all treatments were mild.[77–80]

Recommendations

- Drugs are less effective for smoking cessation in adolescents.
- Cognitive-behavioral interventions should be intensified, adapted to the characteristics of their age and involving parents/legal guardians.

PICO Question 10: What is the efficacy and safety of NRT, bupropion, varenicline and cytisine in pregnant women?

Evidence

NRT is more effective than placebo or behavioral therapy in maintaining abstinence during pregnancy [OR = 1.37, 95% CI 1.08–1.74, I^2 = 34%] and postpartum [OR = 1.22, 95% CI 0.84–1.77], but not at 12 months [OR = 1.04, 95% CI 0.57–1.88], level of evidence 1b-2a.[81–84]

NRT during the first trimester is safe for the fetus, level of evidence 1b-2b.[81–85] During the 2nd and 3rd trimester it could have effects similar to tobacco exposure, level of evidence 1b-2b[82] without evidence of serious complications for the fetus (level of evidence 2a),[81,82,84,86] infant (level of evidence 2b-3a),[81] or pregnant (level of evidence 1b).[81]

Bupropion is not more effective than placebo or behavioral therapy [OR = 0.74, 95% CI 0.21–2.64], level of evidence 2a-b.[81] It may increase cardiovascular birth defects, level of evidence 4, but not miscarriage, prematurity, or low birth weight, level of evidence 2b-3a.[86–88]

Varenicline has not shown adverse effects on the fetus, level of evidence 4[86,88] Cytisine is contraindicated in pregnant women.

Recommendations

- The treatment of choice is intensive cognitive-behavioral therapy. NRT can be used if it fails,
- assessing risk–benefit, preferably during the first trimester.
- The first option is the fast-acting forms (chewing gum or tablets) and the second option is 16-h and 15 mg patches.
- Bupropion, varenicline, and cytisine should be avoided because of the limited evidence on their safety.

PICO Question 11: What is the efficacy and safety of NRT, bupropion, varenicline, and cytisine in the hospitalized patient?

Smoking is one of the main causes of disease leading to hospitalization. Cardiovascular, respiratory and tumor diseases are among the main causes of hospital admission. Different reasons support hospitalization as an ideal time to encourage smoking cessation in patients who smoke.

The published scientific evidence focuses on some SLRs with quality meta-analyses:

The 2012 Cochrane review[55] included more than 50 RCTs of heterogeneous quality, concludes that: (1) intensive cognitive behavioral therapy (ICBT) (which included intensive advice/counseling during admission and supportive contacts for at least one month after discharge) was associated with higher rates of verified continuous abstinence compared to placebo [OR: 1.37, 95% CI 1.27–1.48, I^2 = 37% (n = 25 studies)] (2) The efficacy when

adding NRT to ICBT was significantly superior to intensive intervention without the drug [OR: 1.54, 95% CI 1.34–1.79 (n = 6 studies)]. This benefit was not observed when adding varenicline or bupropion, which in the latter case also coincided with that observed by Grandi et al., 2013.[52] (Level of evidence 2a). No adverse events are reported in the subgroups of patients studied, including cardiovascular events; in this subgroup, 1 RCT showed that ICBT plus drugs is accompanied by a reduction in mortality rates in the two years following the intervention.

Subsequently, several RCTs of moderate quality have been published that have shown that varenicline is the drug that achieves the highest rate of continued abstinence at 12 months in hospitalized patients.[55,89,90]

Recommendations

- The use of NRT with NRCT in hospitalized patients with subsequent follow-up (in the first 4 weeks after discharge) is effective and safe. Level of evidence 1a-b.
- Currently, there is insufficient evidence regarding the combined use of CCT with bupropion. Level of evidence 2a. There are no studies with cytisine.
- Varenicline monotherapy is effective in hospitalized patients. Level of evidence 2b.

PICO question 12: What is the efficacy and safety of NRT, bupropion, varenicline and cytisine as a function of funding?

The scientific evidence collected in the 2017 Cochrane SLR[91] objectified that funding (full or partial) of pharmacological treatment for tobacco dependence increases verified continuous abstinence at 6 months [OR: 1.77 95% CI 1.37–2.28, I^2 = 33% (n = 9333 patients)]. Funding of smoking cessation treatment leads to more smokers making quit attempts and more of them using them in the attempt and, consequently, to more smokers quitting smoking, thereby increasing the efficiency and cost/benefit of these drugs (Table 1).[92–95]

Recommendations

- From a public health (social) perspective: the financing of drugs for the treatment of smoking cessation is cost-effective and is associated with greater abstinence. Level of evidence 2a.
- From an individual point of view, the efficacy of treatment will depend on different factors, including the life time of each smoker; in this sense, treatment financing could be a motivational factor. Level of evidence 3.

Authors' contribution

All authors contributed equally to the conception, writing, revision, and final approval of the manuscript.

Ethical aspects

This document was authorized and promoted by the Governing Boarding of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and Document Management Committee.

Financial disclosure

None of the authors have received funding.

Conflict of interests

CR-C has received honoraria for speaking engagements, sponsored courses, and participation in clinical studies from Aflofarm, GSK, Menarini, Mundipharma, Novartis, Pfizer, and Teva.

JIG-O has received honoraria for speaking, scientific consulting, clinical study participation, or publication writing for the following: Astra-Zeneca, Chiesi, Esteve, Faes, Gebro, Menarini, and Pfizer.

JAR-M has received scientific consulting and/or speaking fees from Aflofarm, Astra-Zeneca, Bial, Boehringer Ingelheim, Chiesi, GSK, Menarini, Mundipharma, Novartis, Pfizer, Rovi, and Teva.

EH-M has received fees for presentations, conferences and courses sponsored by: Astra-Zéneca, Bial, Boehringer, Chiesi, Esteve, Faes Farma, Ferrer, GSK, Mundiphasrma, Menarini, Novartis, Pfizer and Rovi.

EC-C declares that she has no conflict of interest.

JS-CM has received fees for presentations, participation in clinical studies and publications by: Aflofarm, Astra-Zeneca, Boehringer, Ferrer, GSK, Menarini, Pfizer and Rovi.

MG-R declares that he has no conflict of interest.

EP-E has received fees for presentations and collaborations for training from: Aflofarm, Bial, Chiesi, Faes, Ferrer, Novartis and Pfizer.

CAJ-R has received honoraria for presentations, participation in clinical studies and consultancy from: Aflofarm, Bial, GSK, Menarini and Pfizer.

We confirm that the manuscript has been read and approved by all the cited authors. In addition, we confirm that the order of authors that appears in the manuscript has been approved by all. On the other hand, we have given due consideration to the protection of individual property associated with this work and that there are no impediments to its publication.

We understand that the author of the correspondence is the only contact for the editorial process. We confirm that we have provided a current and correct email address, that it is accessible by the corresponding author and that it has been configured to accept email from crabcas1@gmail.com.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arbres.2023.07.024.

References

1. Tabaco. Organización Mundial de la Salud. 27 de julio de 2021. Available from: https://www.who.int/es/news-room/fact-sheets/detail/tobacco [accessed 6.12.2021].
2. Tabaco. Comisión Europea. Salud Pública. Available from: https://ec.europa.eu/health/tobacco/overview_es [accessed: 6.12.2021].
3. Gutiérrez-Abejón E, Rejas-Gutiérrez J, Criado-Espegel P, Campo-Ortega EP, Breñas-Villalón MT, Martín-Sobrino N. Impacto del consumo de tabaco sobre la mortalidad en España en el año 2012 [Smoking impact on mortality in Spain in 2012]. Med Clin (Barc). 2015;145:520–5, http://dx.doi.org/10.1016/j.medcli.2015.03.013.
4. Jiménez Ruiz CA, Barrueco Ferrero M, Solano Reina S, Torrecilla García M, Domínguez Grandal F, Díaz-Maroto Muñoz JL, et al. Recomendaciones en el abordaje diagnóstico y terapéutico del tabaquismo. Documento de consenso. Arch Bronconeumol. 2003;39:35–41, http://dx.doi.org/10.1016/S0300-2896(03)75312-5.
5. Jiménez-Ruiz CA, Riesco Miranda JA, Ramos Pinedo A, Barrueco Ferrero M, Solano Reina S, De Granda Orive JI, et al. Recomendaciones para el tratamiento farmacológico del tabaquismo. Propuestas de financiación [Recommendations for pharmacological tobacco cessation treatments: proposals for financing]. Arch Bronconeumol. 2008;44:213–9, http://dx.doi.org/10.1016/S1579-2129(09)60018-5.
6. de Higes Martínez EB, Rábade Castedo C, Jiménez-Ruiz CA. Situación actual del tratamiento del tabaquismo en España: algunas consideraciones. Prev Tab. 2021;23:127–30.
7. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. J Clin Epidemiol. 2011;64:395–400, http://dx.doi.org/10.1016/j.jclinepi.2010.09.012.

8. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6:e1000097, http://dx.doi.org/10.1371/journal.pmed.1000097.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 2009;6:e1000100, http://dx.doi.org/10.1371/journal.pmed.1000100.
10. Schöpfel J. Towards a Prague definition of grey literature. Twelfth International Conference on Grey Literature: Transparency in Grey Literature. Grey Tech Approaches to High Tech Issues. Prague, 6–7 December 2010, Dec 2010, Czech Republic. pp. 11–26. sic 00581570. Available from: https://archivesic.ccsd.cnrs.fr/sic_00581570 [accessed 20.03.23].
11. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials. 1996;17:1–12, http://dx.doi.org/10.1016/0197-2456(95)00134-4.
12. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2016;9:CD006103, http://dx.doi.org/10.1002/14651858.CD006103.pub7.
13. Livingstone-Banks J, Fanshawe TR, Thomas KH, Theodoulou A, Hajizadeh A, Hartman L, et al. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev. 2023;5:CD006103.
14. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev. 2013;2013:CD009329, http://dx.doi.org/10.1002/14651858.CD009329.pub2.
15. Guo K, Wang S, Shang X, Fenfen E, Hou L, Li J, et al. The effect of Varenicline and Bupropion on smoking cessation: a network meta-analysis of 20 randomized controlled trials. Addict Behav. 2022;131:107329, http://dx.doi.org/10.1016/j.addbeh.2022.107329.
16. Thomas KH, Dalili MN, López-López JA, Keeney E, Phillippo DM, Munafò MR, et al. Comparative clinical effectiveness and safety of tobacco cessation pharmacotherapies and electronic cigarettes: a systematic review and network meta-analysis of randomized controlled trials. Addiction. 2022;117:861–76, http://dx.doi.org/10.1111/add.15675.
17. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2019;4:CD013308, http://dx.doi.org/10.1002/14651858.CD013308.
18. Shang X, Guo K, Fenfen E, Deng X, Wang Y, Wang Z, et al. Pharmacological interventions on smoking cessation: a systematic review and network meta-analysis. Front Pharmacol. 2022;24:1012433, http://dx.doi.org/10.3389/fphar.2022.1012433.
19. Mills EJ, Wu P, Lockhart I, Thorlund K, Puhan M, Ebbert JO. Comparisons of high-dose and combination nicotine replacement therapy, varenicline, and bupropion for smoking cessation: a systematic review and multiple treatment meta-analysis. Ann Med. 2012;44:588–97, http://dx.doi.org/10.3109/07853890.2012.705016.
20. Kumar S, Kodela S, Detweiler JG, Kim KY, Detweiler MB. Bupropion-induced psychosis: folklore or a fact? A systematic review of the literature. Gen Hosp Psychiatry. 2011;33:612–7, http://dx.doi.org/10.1016/j.genhosppsych.2011.07.001.
21. Howes S, Hartmann-Boyce J, Livingstone-Banks J, Hong B, Lindson N. Antidepressants for smoking cessation. Cochrane Database Syst Rev. 2020;4:Cd000031, http://dx.doi.org/10.1002/14651858.CD000031.pub5.
22. Etter J-F. Cytisine for smoking cessation: a literature review and a meta-analysis. Arch Intern Med. 2006;166:1553–9, http://dx.doi.org/10.1001/archinte.166.15.1553.
23. Hajek P, McRobbie H, Myers K. Efficacy of cytisine in helping smokers quit: systematic review and meta-analysis. Thorax. 2013;68:1037–42, http://dx.doi.org/10.1136/thoraxjnl-2012-203035.
24. Leaviss J, Sullivan W, Ren S, Everson-Hock E, Stevenson M, Stevens JW, et al. What is the clinical effectiveness and cost-effectiveness of cytisine compared with varenicline for smoking cessation? A systematic review and economic evaluation. Health Technol Assess. 2014;18:1–120, http://dx.doi.org/10.3310/hta18330.
25. Tutka P, Vinnikov D, Courtney RJ, Benowitz NL. Cytisine for nicotine addiction treatment: a review of pharmacology, therapeutics and an update of clinical trial evidence for smoking cessation. Addiction. 2019;114:1951–69, http://dx.doi.org/10.1111/add.14721.
26. Tonstad S, Tonnesen P, Hajek P, Williams K, Billing C, Reeves K, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006;296:64–71, http://dx.doi.org/10.1001/jama.296.1.64.
27. Ebbert JO, Hughes JR, West RJ, Rennard SI, Russ C, McRae TD, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. JAMA. 2015;313:687–94, http://dx.doi.org/10.1001/jama.2015.280.
28. Nides M, Rigotti NA, Benowitz N, Clarke A, Jacobs C. A Multicenter, double-blind, randomized, placebo-controlled phase 2b trial of cytisinicline in adult smokers (the ORCA-1 trial). Nicotine Tob Res. 2021;23:1656–63, http://dx.doi.org/10.1093/ntr/ntab073.
29. Jacobs C, Fonseca M, Rigotti NA, Benowitz N, Clarke A, Cain D. A Phase I, double-blind, randomized, placebo-controlled, single dose-escalation study to evaluate the tolerability and safety of cytisinicline in adult smokers. Nicotine Tob Res. 2022, http://dx.doi.org/10.1093/ntr/ntac233.
30. Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. BMJ. 1995;311:363–6, http://dx.doi.org/10.1136/bmj.311.7001.363.
31. Tønnesen P, Nørregaard J, Säwe U, Simonsen K. Recycling with nicotine patches in smoking cessation. Addiction. 1993;88:533–9, http://dx.doi.org/10.1111/j.1360-0443.1993.tb02060.x.
32. Hughes JR, Grass JA, Pillitteri JL. Treatment resistant smokers: a pilot study of nicotine nasal spray and inhaler. J Addict Dis. 2000;19:95–100, http://dx.doi.org/10.1300/j069v19n01_08.
33. Gonzales DH, Nides MA, Ferry LH, Kustra RP, Jamerson BD, Segall N, et al. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. Clin Pharmacol Ther. 2001;69:438–44, http://dx.doi.org/10.1067/mcp.2001.115750.
34. Cupertino AP, Wick JA, Richter KP, Mussulman L, Nazir N, Ellerbeck EF. The impact of repeated cycles of pharmacotherapy on smoking cessation: a longitudinal cohort study. Arch Intern Med. 2009;169:1928–30, http://dx.doi.org/10.1001/archinternmed.2009.355.
35. Gonzales D, Hajek P, Pliamm L, Nackaerts K, Tseng LJ, McRae TD, et al. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. Clin Pharmacol Ther. 2014;96:390–6, http://dx.doi.org/10.1038/clpt.2014.124.
36. Windle SB, Filion KB, Mancini JG, Adye-White L, Joseph L, Gore GC, et al. Combination therapies for smoking cessation: a hierarchical bayesian meta-analysis. Am J Prev Med. 2016;51:1060–71, http://dx.doi.org/10.1016/j.amepre.2016.07.011.
37. Zhong Z, Zhao S, Zhao Y, Xia S. Combination therapy of varenicline and bupropion in smoking cessation: a meta-analysis of the randomized controlled trials. Compr Psychiatry. 2019;95:152125, http://dx.doi.org/10.1016/j.comppsych.2019.152125.
38. Vogeler T, McClain C, Evoy KE. Combination bupropion SR and varenicline for smoking cessation: a systematic review. Am J Drug Alcohol Abuse. 2016;42:129–39, http://dx.doi.org/10.3109/00952990.2015.1117480.
39. Leone FT, Zhang Y, Evers-Casey S, Evins AE, Eakin MN, Fathi J, et al. Initiating pharmacologic treatment in tobacco-dependent adults. An official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2020;202:e5–31, http://dx.doi.org/10.1164/rccm.202005-1982ST.
40. Lindson N, Klemperer E, Hong B, Ordóñez-Mena JM, Aveyard P. Smoking reduction interventions for smoking cessation. Cochrane Database Syst Rev. 2019;9:CD013183, http://dx.doi.org/10.1002/14651858.cd013183.pub2.
41. Ali A, Kaplan CM, Derefinko KJ, Klesges RC. Smoking cessation for smokers not ready t quit: meta-analysis and cost-effectiveness analysis. Am J Prev Med. 2018;55:253–62, http://dx.doi.org/10.1016/j.amepre.2018.04.021.
42. Asfar T, Ebbert JO, Klesges RC, Relyea GE. Do smoking reduction interventions promote cessation in smokers not ready to quit? Addict Behav. 2011;36:764–8, http://dx.doi.org/10.1016/j.addbeh.2011.02.003.
43. Fornaro M, Carvalho AF, De Prisco M, Mondin AM, Billeci M, Selby P, et al. The prevalence, odds, predictors, and management of tobacco use disorder or nicotine dependence among people with severe mental illness: systematic review and meta-analysis. Neurosci Biobehav Rev. 2022;132:289–303, http://dx.doi.org/10.1016/j.neubiorev.2021.11.039.
44. Peckham E, Brabyn S, Cook L, Tew G, Gilbody S. Smoking cessation in severe mental ill health: what works? An updated systematic review and meta-analysis. BMC Psychiatry. 2017;17:252, http://dx.doi.org/10.1186/s12888-017-1419-7.
45. Pinho S, Rocha V, Vieira-Coelho MA. Effectiveness of multimodal interventions focused on smoking cessation in patients with schizophrenia: a systematic review. Schizophr Res. 2021;231:145–53, http://dx.doi.org/10.1016/j.schres.2021.03.012.
46. Siskind DJ, Wu BT, Wong TT, Firth J, Kisely S. Pharmacological interventions for smoking cessation among people with schizophrenia spectrum disorders: a systematic review, meta-analysis, and network meta-analysis. Lancet Psychiatry. 2020;7:762–74, http://dx.doi.org/10.1016/s2215-0366(20)30261-3.
47. Aldi GA, Bertoli G, Ferraro F, Pezzuto A, Cosci F. Effectiveness of pharmacological or psychological interventions for smoking cessation in smokers with major depression or depressive symptoms: a systematic review of the literature. Subst Abus. 2018;39:289–306, http://dx.doi.org/10.1080/08897077.2018.1439802.
48. Ahmed S, Virani S, Kotapati VP, Bachu R, Adnan M, Khan AM, et al. Efficacy and safety of varenicline for smoking cessation in schizophrenia: a meta-analysis. Front Psychiatry. 2018;9:428, http://dx.doi.org/10.3389/fpsyt.2018.00428.
49. Wightman DS, Foster VJ, Krishen A, Richard NE, Modell JG. Meta-analysis of suicidality in placebo-controlled clinical trials of adults taking bupropion. Prim Care Companion J Clin Psychiatry. 2010;12:e1–8, http://dx.doi.org/10.4088/pcc.09m00894blu.
50. Evins AE, West R, Benowitz NL, Russ C, Lawrence D, McRae T, et al. Efficacy and safety of pharmacotherapeutic smoking cessation aids in schizophrenia spectrum disorders: subgroup analysis of EAGLES. Psychiatr Serv. 2021;72:7–15, http://dx.doi.org/10.1176/appi.ps.202000032.
51. Cardiac adverse effects of nicotine replacement therapy. Prescrire Int. 2015;24:292–3.
52. Grandi SM, Shimony A, Eisenberg MJ. Bupropion for smoking cessation in patients hospitalized with cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. Can J Cardiol. 2013;29:1704–11, http://dx.doi.org/10.1016/j.cjca.2013.09.014.
53. Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. Circulation. 2014;129:28–41, http://dx.doi.org/10.1161/circulationaha.113.003961.
54. Pipe AL. Systematic review and meta-analysis: network meta-analysis demonstrates the safety of pharmacotherapy for smoking

cessation in cardiovascular patients. Evid Based Med. 2014;19:193, http://dx.doi.org/10.1136/eb-2014-110030.
55. Rigotti NA, Clair C, Munafò MR, Stead LF. Interventions for smoking cessation in hospitalised patients. Cochrane Database Syst Rev. 2012;5:CD001837, http://dx.doi.org/10.1002/14651858.cd001837.pub3.
56. Sposito AC, Bonilha I, Luchiari B, Benchimol A, Hohl A, Moura F, et al. Cardiovascular safety of naltrexone and bupropion therapy: systematic review and meta-analyses. Obes Rev. 2021;22:e13224, http://dx.doi.org/10.1111/obr.13224.
57. Sterling LH, Windle SB, Filion KB, Touma L, Eisenberg MJ. Varenicline and adverse cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. J Am Heart Assoc. 2016;5, http://dx.doi.org/10.1161/jaha.115.002849.
58. Suissa K, Larivière J, Eisenberg MJ, Eberg M, Gore GC, Grad R, et al. Efficacy and safety of smoking cessation interventions in patients with cardiovascular disease: a network metaanalysis of randomized controlled trials. Circ Cardiovasc Qual Outcomes. 2017;10:e002458, http://dx.doi.org/10.1161/circoutcomes.115.002458.
59. Ware JH, Vetrovec GW, Miller AB, Van Tosh A, Gaffney M, Yunis C, et al. Cardiovascular safety of varenicline: patient-level meta-analysis of randomized, blinded, placebo-controlled trials. Am J Ther. 2013;20:235–46, http://dx.doi.org/10.1097/mjt.0b013e31828455b.
60. Benowitz NL, Pipe A, West R, Hays JT, Tonstad S, McRae T, et al. Cardiovascular safety of varenicline, bupropion, and nicotine patch in smokers: a randomized clinical trial. JAMA Intern Med. 2018;178:622–31, http://dx.doi.org/10.1001/jamainternmed.2018.0397.
61. Strassmann R, Bausch B, Spaar A, Kleijnen J, Braendli O, Puhan MA. Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. Eur Respir J. 2009;34:634–40, http://dx.doi.org/10.1183/09031936.00167708.
62. Tsiapa G, Gkiozos I, Souliotis K, Syrigos K. Review: smoking cessation strategies in patients with lung disease. In Vivo. 2013;27:171–6.
63. van der Meer RM, Wagena E, Ostelo RWJG, Jacobs AJE, van Schayck OCP. Smoking cessation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2003;2016, http://dx.doi.org/10.1002/14651858.cd002999.
64. van Eerd E, van der Meer RM, Reda AA, van Schayck CP, Kotz D. Smoking cessation in smokers with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2013;2013, http://dx.doi.org/10.1002/14651858.cd010744.pub2.
65. van Eerd EAM, van der Meer RM, van Schayck OCP, Kotz D. Smoking cessation for people with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2016;2016:CD010744, http://dx.doi.org/10.1002/14651858.cd010744.pub2.
66. Wagena EJ, van der Meer RM, Ostelo RJWG, Jacobs JE, van Schayck CP. The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: results from a systematic review. Respir Med. 2004;98:805–15, http://dx.doi.org/10.1016/j.rmed.2004.06.001.
67. Wagena EJ, Van Der Meer RM, Ostelo RJWG, Jacobs JE, Van Schayck CP. The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: results from a systematic review. Respir Med COPD Update. 2005;1:29–39, http://dx.doi.org/10.1016/j.rmed.2004.06.001.
68. Zarghami M, Taghizadeh F, Sharifpour A, Alipour A. Efficacy of guided self-change for smoking cessation in chronic obstructive pulmonary disease patients: a randomized controlled clinical trial. Tob Induc Dis. 2019;17:90, http://dx.doi.org/10.18332/tid/114227.
69. Ellerbeck EF, Nollen N, Hutcheson TD, Phadnis M, Fitzgerald SA, Vacek J, et al. Effect of long-term nicotine replacement therapy vs standard smoking cessation for smokers with chronic lung disease: a randomized clinical trial. JAMA Netw Open. 2018;1:e181843, http://dx.doi.org/10.1001/jamanetworkopen.2018.1843.
70. Qin R, Liu Z, Zhou X, Cheng A, Cui Z, Li J, et al. Adherence and efficacy of smoking cessation treatment among patients with COPD in China. Int J Chron Obstruct Pulmon Dis. 2021;16:1203–14, http://dx.doi.org/10.2147/copd.s301579.
71. Le Mao R, Tromeur C, Paleiron N, Sanchez O, Gagnadoux F, Jouneau S, et al. Effect of early initiation of varenicline on smoking cessation in COPD patients admitted for exacerbation: the save randomized clinical trial. COPD. 2020;17:7–14, http://dx.doi.org/10.1080/15412555.2019.1703928.
72. Tønnesen P, Pisinger C, Hvidberg S, Wennike P, Bremann L, Westin A, et al. Effects of smoking cessation and reduction in asthmatics. Nicotine Tob Res. 2005;7:139–48, http://dx.doi.org/10.1080/14622200412331328411.
73. Gratziou Ch, Florou A, Ischaki E, Eleftheriou K, Sachlas A, Bersimis S, et al. Smoking cessation effectiveness in smokers with COPD and asthma under real life conditions. Respir Med. 2014;108:577–83, http://dx.doi.org/10.1016/j.rmed.2014.01.007.
74. Westergaard CG, Porsbjerg C, Backer V. The effect of Varenicline on smoking cessation in a group of young asthma patients. Respir Med. 2015;109:1416–22, http://dx.doi.org/10.1016/j.rmed.2015.07.017.
75. Jiménez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, van Schayck CP, Hajek P, et al. Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J. 2015;46:61–79, http://dx.doi.org/10.1183/09031936.00092614.
76. Jiménez-Ruiz CA, Riesco Miranda JA, Altet Gómez N, Lorza Blasco JJ, Signes-Costa Miñana J, Solano Reina S, et al. Tratamiento del tabaquismo en fumadores con EPOC. Arch Bronconeumol. 2013;49:354–63, http://dx.doi.org/10.1016/j.arbres.2013.02.005.
77. Fanshawe TR, Halliwell W, Lindson N, Aveyard P, Livingstone-Banks J, Hartmann-Boyce J. Tobacco cessation interventions for young people. Cochrane Database Syst Rev. 2017;11:CD003289, http://dx.doi.org/10.1002/14651858.cd003289.pub6.
78. Kim Y, Myung S-K, Jeon Y-J, Lee E-H, Park C-H, Seo HG, et al. Effectiveness of pharmacologic therapy for smoking cessation in adolescent smokers: meta-analysis of randomized controlled trials. Am J Health Syst Pharm. 2011;68:219–26, http://dx.doi.org/10.2146/ajhp100296.
79. Gray KM, Baker NL, McClure EA, Tomko RL, Squeglia LM, Saladin ME, et al. Efficacy and safety of varenicline for adolescent smoking cessation: a randomized clinical trial. JAMA Pediatr. 2019;173:1146–53, http://dx.doi.org/10.1001/jamapediatrics.2019.3553.
80. Gray KM, Rubinstein ML, Prochaska JJ, DuBrava SJ, Holstein AR, Samuels L, et al. High-dose and low-dose varenicline for smoking cessation in adolescents: a randomised, placebo-controlled trial. Lancet Child Adolesc Health. 2020;4:837–45, http://dx.doi.org/10.1016/s2352-4642(20)30243-1.
81. Claire R, Chamberlain C, Davey M-A, Cooper SE, Berlin I, Leonardi-Bee J, et al. Pharmacological interventions for promoting smoking cessation during pregnancy. Cochrane Database Syst Rev. 2020;3:CD010078, http://dx.doi.org/10.1002/14651858.cd010078.pub3.
82. Grangé G, Berlin I, Bretelle F, Bertholdt C, Berveiller P, Blanc J, et al. Smoking and smoking cessation in pregnancy. Synthesis of a systematic review. J Gynecol Obstet Hum Reprod. 2020;49:101847, http://dx.doi.org/10.1016/j.jogoh.2020.101847.
83. Blanc J, Tosello B, Ekblad MO, Berlin I, Netter A. Nicotine replacement therapy during pregnancy and child health outcomes: a systematic review. Int J Environ Res Public Health. 2021;18, http://dx.doi.org/10.3390/ijerph18084004.
84. Taylor L, Claire R, Campbell K, Coleman-Haynes T, Leonardi-Bee J, Chamberlain C, et al. Fetal safety of nicotine replacement therapy in pregnancy: systematic review and meta-analysis. Addiction. 2021;116:239–77, http://dx.doi.org/10.1111/add.15185.
85. Coleman T, Chamberlain C, Cooper S, Leonardi-Bee J. Efficacy and safety of nicotine replacement therapy for smoking cessation in pregnancy: systematic review and meta-analysis. Addiction. 2011;106:52–61, http://dx.doi.org/10.1111/j.1360-0443.2010.03179.x.
86. Patnode CD, Henderson JT, Coppola EL, Melnikow J, Durbin S, Thomas RG. Interventions for tobacco cessation in adults, including pregnant persons: updated evidence report and systematic review for the US preventive services task force. JAMA. 2021;325:280–98, http://dx.doi.org/10.1001/jama.2020.23541.
87. Hendrick V, Suri R, Gitlin MJ, Ortiz-Portillo E. Bupropion use during pregnancy: a systematic review. Prim Care Companion CNS Disord. 2017;19:17r02160, http://dx.doi.org/10.4088/pcc.17r02160.
88. Turner E, Jones M, Vaz LR, Coleman T. Systematic review and meta-analysis to assess the safety of bupropion and varenicline in pregnancy. Nicotine Tob Res. 2019;21:1001–10, http://dx.doi.org/10.1093/ntr/nty055.
89. Franck C, Filion KB, Eisenberg MJ. Smoking cessation in patients with acute coronary syndrome. Am J Cardiol. 2018;121:1105–11, http://dx.doi.org/10.1016/j.amjcard.2018.01.017.
90. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, et al. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. Circulation. 2016;133:21–30, http://dx.doi.org/10.1161/circulationaha.115.019634.
91. van den Brand FA, Nagelhout GE, Reda AA, Winkens B, Evers S, Kotz D, et al. Healthcare financing systems for increasing the use of tobacco dependence treatment. Cochrane Database Syst Rev. 2017;9:Cd004305, http://dx.doi.org/10.1002/14651858.cd004305.pub5.
92. van den Brand FA, Candel M, Nagelhout GE, Winkens B, van Schayck CP. How financial incentives increase smoking cessation: a two-level path analysis. Nicotine Tob Res. 2021;23:99–106, http://dx.doi.org/10.1093/ntr/ntaa024.
93. van den Brand FA, Magnée T, de Haan-Bouma L, Barendregt C, Chavannes NH, van Schayck OCP, et al. Implementation of financial incentives for successful smoking cessation in real-life company settings: a qualitative needs assessment among employers. Int J Environ Res Public Health. 2019;16, http://dx.doi.org/10.3390/ijerph16245135.
94. van den Brand FA, Nagelhout GE, Hummel K, Willemsen MC, McNeill A, van Schayck OCP. Does free or lower cost smoking cessation medication stimulate quitting? Findings from the International Tobacco Control (ITC) Netherlands and UK Surveys. Tob Control. 2019;28 Suppl. 1:s61–7, http://dx.doi.org/10.1136/tobaccocontrol-2017-054023.
95. van den Brand FA, Nagelhout GE, Winkens B, Chavannes NH, van Schayck OCP, Evers S. Cost-effectiveness and cost-utility analysis of a work-place smoking cessation intervention with and without financial incentives. Addiction. 2020;115:534–45, http://dx.doi.org/10.1111/add.14861.