

Insomnia and parasomnia induced by validated smoking cessation pharmacotherapies and electronic cigarettes: a network meta-analysis

Review

Cite this article: Vanderkam P, Pomes C, Dzeraviashka P, Castera P, Jaafari N, and Lafay-Chebassier C (2024). Insomnia and parasomnia induced by validated smoking cessation pharmacotherapies and electronic cigarettes: a network meta-analysis. *CNS Spectrums* 29(2), 96–108.
<https://doi.org/10.1017/S1092852924000087>

Received: 31 August 2023


Accepted: 21 February 2024

Keywords:

Smoking cessation methods; electronic cigarette; sleep disorders; insomnia; parasomnia; network meta-analysis

Corresponding author:

Paul Vanderkam;
 Email: paul.vanderkam@u-bordeaux.fr

Paul Vanderkam^{1,2,3} , Charlotte Pomes⁴, Palina Dzeraviashka³, Philippe Castera³, Nematollah Jaafari² and Claire Lafay-Chebassier^{1,5}

¹Université de Poitiers, INSERM, U-1084, Laboratoire de Neurosciences Expérimentales et Cliniques, Poitiers, France, ²Unité de Recherche Clinique Intersectorielle en Psychiatrie, Centre Hospitalier Henri Laborit, Poitiers, France, ³Department of General Practice, University of Bordeaux, Bordeaux, France, ⁴Department of General Practice, University of Poitiers, Poitiers, France and ⁵CHU de Poitiers, Service de Pharmacologie Clinique et Vigilances, Poitiers, France

Abstract

We aim to assess the relationship between validated smoking cessation pharmacotherapies and electronic cigarettes (e-cigarettes) and insomnia and parasomnia using a systematic review and a network meta-analysis. A systematic search was performed until August 2022 in the following databases: PUBMED, COCHRANE, CLINICALTRIAL. Randomized controlled studies against placebo or validated therapeutic smoking cessation methods and e-cigarettes in adult smokers without unstable or psychiatric comorbidity were included. The primary outcome was the presence of “insomnia” and “parasomnia.” A total of 1261 studies were selected. Thirty-seven studies were included in the quantitative analysis (34 for insomnia and 23 for parasomnia). The reported interventions were varenicline (23 studies), nicotine replacement therapy (NRT, 10 studies), bupropion (15 studies). No studies on e-cigarettes were included. Bayesian analyses found that insomnia and parasomnia are more frequent with smoking cessation therapies than placebo except for bupropion. Insomnia was less frequent with nicotine substitutes but more frequent with bupropion than the over pharmacotherapies. Parasomnia are less frequent with bupropion but more frequent with varenicline than the over pharmacotherapies. Validated smoking cessation pharmacotherapies can induce sleep disturbances with different degrees of frequency. Our network meta-analysis shows a more favorable profile of nicotine substitutes for insomnia and bupropion for parasomnia. It seems essential to systematize the assessment of sleep disturbances in the initiation of smoking cessation treatment. This could help professionals to personalize the choice of treatment according to sleep parameters of each patient. Considering co-addictions, broadening the populations studied and standardizing the measurement are additional avenues for future research.

Key points

Validated smoking cessation pharmacotherapies and e-cigarettes can induce sleep disturbances with different degrees of frequency.

Our network meta-analysis shows a more favorable profile of nicotine substitutes for insomnia and bupropion for parasomnia.

It seems essential to systematize the assessment of sleep disturbances in the initiation of smoking cessation treatment. This could help professionals to personalize the choice of treatment according to sleep parameters of each patient.

Introduction

Tobacco has a very detrimental impact on public health, killing up to 50% of its users.¹ Its consumption causes a complex dependence and has multiple harmful consequences, with various neoplastic, cardiovascular, and respiratory diseases, inflicting a high cost on society.^{1–3} Despite declining smoking prevalence in many countries, there are disparities among vulnerable patients, young people, and women.^{4–7}

Current treatment ranges from minimal counselling to pharmacological treatments and cognitive behavioral therapies (CBT). Validated pharmacotherapies include nicotine replacement therapy (NRT), varenicline, and bupropion.⁸ They increase the chances of smoking cessation,^{9,10} but many studies show a high relapse rate in the long term.^{11,12} Electronic cigarettes (e-cigarettes) are also part of the emerging smoking cessation methods since the 2010s, with frequent use among smokers.^{13,14} A recent meta-analysis¹⁵ reported a significant

efficacy of the electronic cigarette with nicotine versus placebo in terms of cessation and reduction after 6–12 months, but its safety is highly debated due to insufficient good-quality randomized controlled trials.

There is an important variability in treatment response, and one current challenge is to identify the causes of treatment failure to move toward personalized management. For example, evidence suggests that sleep disorders can be important for smoking cessation.¹⁶

First, cigarette smoking can alter sleep architecture, and current smokers experience greater difficulty initiating and maintaining sleep.^{17–21} Acute nicotine intake from cigarette smoking stimulates the release of key neurotransmitters that regulate sleep architecture. In animal studies, nicotine stimulates serotonin release in the dorsal raphe nucleus, which contribute to suppressing the pontogeniculo-occipital spike of the last stage of sleep and the rapid eye movement (REM) sleep, which is important for memory and spatial consolidation.^{22–24} Other studies have shown a dose-dependent effect of nicotine on REM sleep: a lower dose stimulates REM sleep, while a higher one suppresses it and reduces sleep time.²⁵ Saint Mleux et al. found that nicotine inhibits key regions implicated in promoting sleep via activation of norepinephrine release.²⁴ In humans, the Zhang study¹⁸ shows that smokers have a longer stage 1 sleep phase and a higher percentage of stage 2 sleep (light sleep), decreasing sleep quality. Other studies reported that smokers are more vulnerable to longer sleep latency, more awakening, and a shorter sleep time.^{25,26}

Second, sleep disorders are an important part of withdrawal symptoms.^{19–21,27} For example, 42% of smokers report insomnia during abstinence,²⁸ and sleep disturbances increase following smoking cessation. Most of these disorders disappear after three months. For smoking cessation outcomes, smokers with prior sleep disorders have shown a lower success in later smoking cessation attempts. Moreover, sleep quality at the beginning of the cessation attempt predicted relapse.²⁶

Third, sleep disorders are important side effects of validated pharmacotherapies. In a meta-analysis, up to 10% of participants treated with NRT reportedly experience insomnia that can persist more than 12 weeks after stopping.²⁵ At the beginning of smoking cessation treatments, up to 50% of smokers report sleep disturbance. According to Paterson et al.²⁶, 4–21% of sleep disorders with bupropion and up to 46% of varenicline-seeking smokers reported difficulty sleeping and abnormal dreams.

To our knowledge, no recent meta-analysis or systematic review on sleep disturbances and smoking cessation treatment exists. Due to the limitations of existing systematic reviews and the emergence of new cessation methods, an update on this topic seems necessary, and more precisely on the occurrence of insomnia and parasomnia. Indeed, according to the International Classification of Sleep Disorders (ICSD) 3,²⁹ sleep disorders commonly reported in smoking cessation studies can be classified as insomnia (difficulty to initiating and maintaining sleep) and parasomnia (abnormal dreams, nightmare). Using a systematic review and network meta-analysis, we aim to evaluate the insomnia and parasomnia induced by validated smoking cessation pharmacotherapies and e-cigarettes.

Network meta-analysis allows a comparison of several health interventions for a given indication. It combines direct evidence (treatments compared two by two) with indirect evidence (treatments compared via a common comparator).^{30,31} This analysis allows for a more accurate estimate and can establish a relative ranking between treatments for the desired endpoint.³²

Materials and methods

We conducted a systematic review following the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) guidelines.³³

Research strategy

The databases Cochrane Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov, and PubMed were consulted until 11 of august 2022 after a first exploratory research. We used the International Classification of Sleep Disorders (ICSD 3) and MedRa classification to define our research strategy.^{29,34}

The keywords used are divided into two parts:

1. #1 For smoking cessation methods:
 - a. MeSH: Tobacco use cessation devices, Electronic nicotine delivery systems, Electronic nicotine delivery device, Varenicline, Bupropion, Electronic cigarettes, Smoking cessation agents
 - b. Non-MeSH: Nicotine replacement therapy, e-cigarettes
2. #2 For sleep disorders:
 - a. MeSH: Sleep-wake disorders, Sleep apnea syndromes, Parasomnia, Restless legs syndrome, Sleep initiation and maintenance disorders, Dyssomnias, Insomnia, Disorders of initiating and maintaining sleep
 - b. Non-MeSH: Sleep disorders, abnormal dreams, sleep disturbance

A manual search was conducted: We selected Cochrane reviews which reported sleep outcomes from 4 meta-analysis on NRT (2016 update), varenicline (2018 update), bupropion (2020 update), and electronic cigarettes (2021 update).

Then, we used two research equations:

- A PubMed broader research from 2016 (date of the latest Cochrane update) to 08/11/2022: #1 AND Smoking Cessation, Filter: Randomised controlled trial
- A narrow specific research: #1 AND #2

Data selection

We included English-language literature randomized controlled trials double-blind, single-blind, or open-label.

The eligibility criteria following the PICO model (Patient/Population, Intervention, Comparison, Outcomes) were:

- Patient/Population: adult smokers (men and women over 18) without unstable comorbidity and without pregnancy. Patients with psychiatric or addiction comorbidities were excluded.
- Intervention: validated therapeutic smoking cessation methods and the electronic cigarette with a duration of at least 1 month.
- Comparison: active, placebo, or no treatment interventions.
- Outcomes: The primary outcome is determined by the presence of insomnia and/or parasomnia (including abnormal dreams and vivid dreams).

Screening and data extraction

Two authors (CP, PV) independently screened the titles and abstracts of search hits to select studies of interest and reviewed the full text with the Covidence software.³⁵ Disagreements were resolved by discussions between the authors and with a third view

(CL). Information on methodology, participants, interventions, and outcome measures was collected by CP on Excel spreadsheets and cross-checked by PV and CL. If the outcomes measures were not prespecified in the studies, the authors searched on the side effects reported in the full texts.

Evaluation of the quality of studies

The risk of bias was assessed using the Cochrane collaboration risk of bias (RoB 2) tool.³⁶ We assessed the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of reported results (with respect to prespecified analysis), and overall bias. Judgments of risk were classified as low, high, or of some concern.

Quantitative analysis

We used the “Meta insight V 3.19” website using the WinBUGS tool and Revman 5.4 software.^{37,38} Analyses were stratified for each outcome criterion and by intervention.

We used a Mantel–Haenszel (MH) method for pairwise analysis with a random-effect model. The results are presented as relative risk (RR) for binary variables with a 95% confidence interval.

To obtain a significant result, we chose a p-value <0.05 and a confidence interval not including 1. A relative risk greater than 1 indicates a negative effect on sleep. Heterogeneity was assessed using the I² statistic. An I² estimate of >50% corresponds to substantial heterogeneity, moderate heterogeneity to 25–50%, and low heterogeneity when it is <25%.

For the network meta-analysis, we used a Bayesian method. The different interventions and placebo mapping were represented by a network plot for the two analyses.

Transitivity was maintained by selecting studies with similar indications for the interventions, for example, smoking cessation.

The consistency of the network, corresponding to the absence of disagreement between the results of the direct and indirect comparisons, was assessed by a global inconsistency test.

The analysis was not preregistered, and the results should be considered exploratory.

Results

Selection of studies

We identified 1261 articles using our search strategy. After removing duplicates and screening titles and abstracts, 328 full texts were assessed for eligibility. Two hundred ninety-one studies were excluded mainly for lack of outcome data or inappropriate study design, setting, and wrong outcomes. Finally, 37 studies were selected for the quantitative analysis (Figure 1).^{39–75}

Characteristics and quality of the studies

Table 1 shows the characteristics of each study. They date from 1993 to 2022. Participants were smokers with no comorbidity or psychiatric history.

The interventions found were varenicline (23 studies), bupropion (15 studies), and nicotine replacement therapy (10 studies). No studies on electronic cigarettes could be included in the quantitative analysis. Comparators were placebo (28 studies), active treatment (nine studies) or behavioral therapy (one study). Eight trials used three or more arms (Table 1). Intervention duration

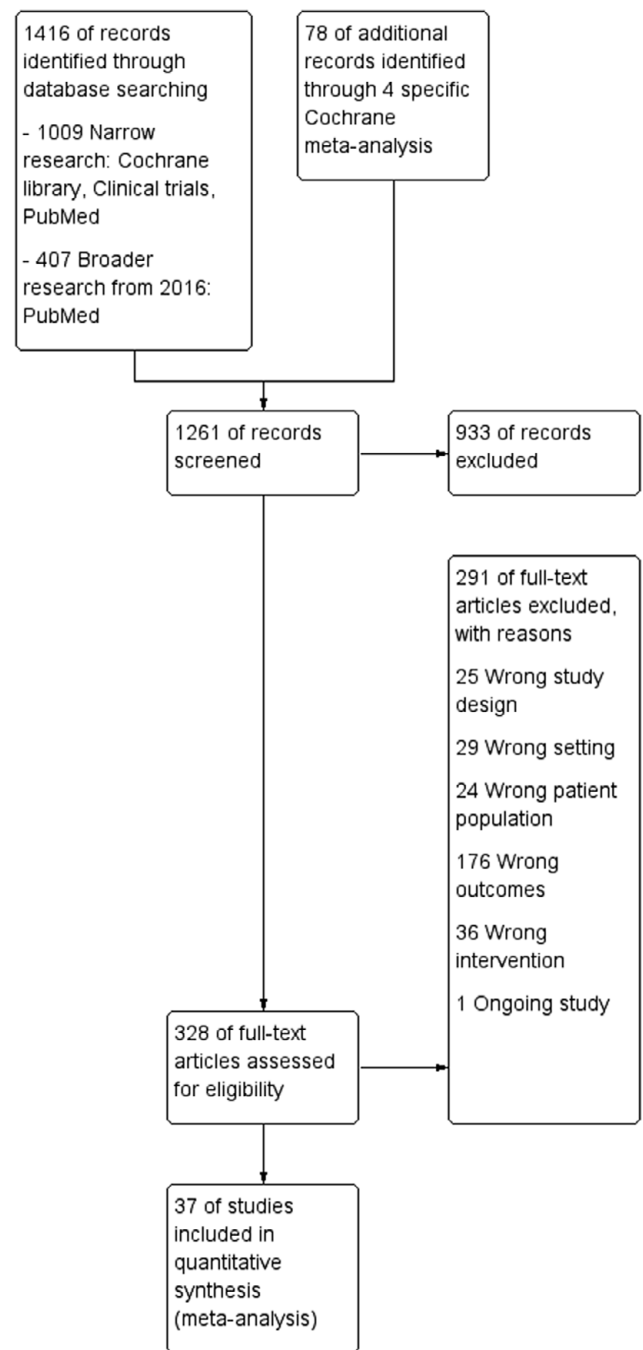


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

ranged from 4 weeks (prior to quit date) to 18 weeks post-quit date. Follow-up times ranged from 12 to 52 weeks. Most of the studies have the same endpoint of smoking abstinence with different parameters (7-day point prevalence or continuous abstinence, confirmed by exhaled CO, saliva cotinine, or urinary anabasine concentration), and two studies use a primary outcome focus on adverse effect.^{40,74} The full text analysis identified insomnia outcomes in 34 studies and parasomnia in 23. Twenty-two studies reported both of the outcomes.

Of the 37 studies, 18 were classified as low risk of bias, 13 as some concerns risk, and six as high risk (Figure 2).³¹

Table 1. Characteristics of Included Studies

| Author Year Country | Population | Intervention (participants) | Duration of intervention: | | Control (participants) | Primary outcome criteria | Funding source |
|---|------------|--|---------------------------|-----------------|---|--|---|
| | | | Follow-up—weeks | Follow-up—weeks | | | |
| Ahluwalia <i>et al.</i> ³⁹ United States | 600 | Bupropion (300) | 7:26 | 7:26 | Placebo (300) | Prolonged abstinence (+exhaled CO) | National cancer Institute GSK for treatment |
| Anthenelli <i>et al.</i> ⁴⁰ 16 countries (Non-psychiatric cohort) | 3989 | Varenicline (990) Bupropion (989) NRT (1006) | 12:24 | 12:24 | Placebo | Moderate/severe AEs (composite measure) Continuous abstinence (+exhaled CO) | Pfizer GSK |
| Aubin <i>et al.</i> ⁴¹ Europe, United States | 746 | Varenicline (376) | 10–12: 52 | 10–12: 52 | NRT patch (370) | Continuous abstinence (+exhaled CO) | Pfizer |
| Ayeward <i>et al.</i> ⁴² United Kingdom | 1792 | NRT (880) | 4:52 | 4:52 | Behavioral intervention (860) | Continuous abstinence (+exhaled CO) | Institutional funding |
| Baker <i>et al.</i> ⁴³ United Kingdom | 1086 | Varenicline (424) | 12: 52 | 12: 52 | - NRT patch (241) - NRT patch + oral (421) | 7 DPP (+exhaled CO) | National Heart, Lung, and Blood Institute |
| Bolliger <i>et al.</i> ⁴⁴ Latin American, African and middle East Countries | 583 | Varenicline (390) | 12: 24 | 12: 24 | Placebo (198) | Continuous abstinence (+exhaled CO) | Pfizer |
| Cinciripini <i>et al.</i> ⁴⁵ United States | 294 | Varenicline (86) Bupropion (102) | 12:24 | 12:24 | Placebo (106) | Prolonged Abstinence (+exhaled CO) | National Institute on Drug Abuse (Dr Cinciripini) and by Cancer Center Support Grant |
| Dalsgaard <i>et al.</i> ⁴⁶ Europe | 335 | Bupropion (221) | 7: | 7: | Placebo (114) | Continuous Abstinence (+exhaled CO) | GSK |
| Ebbert <i>et al.</i> ⁴⁷ United States | 52 | NRT patch 42 mg (25) | 8: 26 | 8: 26 | Placebo (27) | 7 DPP (+urine anabasine concentration) | Pfizer Inc, National Institutes of Health, GlaxoSmithKline |
| Ebbert <i>et al.</i> ⁴⁸ United States | 1510 | Varenicline (760) | 24:52 | 24:52 | Placebo | Continuous abstinence (+exhaled CO) | Pfizer |
| Ebbert <i>et al.</i> ⁴⁹ United States | 93 | Varenicline (45) | 12: 26 | 12: 26 | Placebo (48) | 7 DPP (+exhaled CO) | Pfizer |
| Fagerström <i>et al.</i> ⁵⁰ Norway, Sweden | 431 | Varenicline (218) | 12: 26 | 12: 26 | Placebo (213) | Continuous abstinence (+salivary cotinine) | Pfizer |
| Fossati <i>et al.</i> ⁵¹ Italia | 593 | Bupropion (400) | 7:52 | 7:52 | Placebo (193) | Continuous abstinence (+exhaled CO) | Mario Negri Institute GlaxoSmithKline provided an unconditional grant |
| Gonzales <i>et al.</i> ⁵² United States | 861 | Varenicline (275) | 12: 52 | 12: 52 | - Bupropion (329) - Placebo (257) | Continuous abstinence (+exhaled CO) | Pfizer |
| Gonzales <i>et al.</i> ⁵³ Europe, Australia, North America | 494 | Varenicline (249) | 12: 52 | 12: 52 | Placebo (245) | 7 DPP and continuous abstinence (+exhaled CO) | Pfizer, McNeil, GlaxoSmithKline, Queen Mary university |
| Haggström <i>et al.</i> ⁵⁴ Brazil | 156 | Bupropion (53) | 8: 26 | 8: 26 | Placebo (51) Nortriptyline (52) | Continuous abstinence (+exhaled CO) | No information |
| Holt <i>et al.</i> ⁵⁵ New Zealand | 134 | Bupropion (88) | 7:52 | 7:52 | Placebo (46) | Continuous abstinence (+exhaled CO) | Medical Research Institute of New Zealand have all received research grants from GlaxoSmithKline and Novartis |

Table 1. Continued

| Author | Year | Country | Population | Intervention (participants) | Duration of intervention: | | Control (participants) | Primary outcome criteria | Funding source |
|--------------------------------------|------|---------------|------------|--|---------------------------|-----------------|---|---|--|
| | | | | | Follow-up—weeks | Follow-up—weeks | | | |
| Hurt <i>et al.</i> ⁵⁶ | | United States | 240 | NRT (120) | 8:52 | 8:52 | Placebo (120) | Continuous abstinence (+exhaled CO) | Lederle Laboratories, NY |
| Jorenby <i>et al.</i> ⁵⁷ | | United States | 889 | Bupropion (243) | 9:52 | 9:52 | - NRT patch (243) - Bupropion + NRT patch (244) - Placebo (159) | 7 DPP abstinence (+exhaled CO) | Glaxo Wellcome |
| Jorenby <i>et al.</i> ⁵⁸ | | United States | 1023 | Varenicline (343) | 12:52 | 12:52 | - Bupropion (340) - Placebo (340) | Continuous abstinence (+exhaled CO) | Pfizer |
| Lerman <i>et al.</i> ⁵⁹ | | Canada | 1246 | NRT (418) Varenicline (420) | 11:52 | 11:52 | Placebo (408) | 7-day PP at 12 months | Pfizer Inc. provided varenicline and placebo pills at no cost Institutional funding |
| McCarthy <i>et al.</i> ⁶⁰ | | United States | 463 | Bupropion (229) | 8:52 | 8:52 | Placebo (234) | 7 DPP abstinence (+exhaled CO) | National cancer institute Placebo provided by GSK |
| Niaura <i>et al.</i> ⁶¹ | | United States | 312 | Varenicline (157) | 12:52 | 12:52 | Placebo (155) | Continuous abstinence (+exhaled CO) | Pfizer |
| Nides <i>et al.</i> ⁶² | | United States | 626 | - Varenicline 0.3 mg (126) - Varenicline 1 mg (126) - Varenicline 2 mg 6 weeks then Placebo 1 week (125) | 7:52 | 7:52 | - Bupropion (126) - Placebo (123) | Continuous abstinence (+exhaled CO) | Pfizer |
| Oncken <i>et al.</i> ⁶³ | | United States | 627 | - Varenicline 1 mg untitrated (124) - Varenicline 1 mg titrated (129) - Varenicline 2 mg untitrated (124) - Varenicline 2 mg titrated (129) | 12:52 | 12:52 | Placebo (121) | Continuous abstinence (+exhaled CO + dosage) | Pfizer |
| Rennard <i>et al.</i> ⁶⁴ | | United States | 659 | Varenicline (5486) | 12:24 | 12:24 | Placebo (165) | Continuous abstinence (+exhaled CO) | Pfizer |
| Richmond <i>et al.</i> ⁶⁵ | | Australia | 315 | NRT patch + CBT (158) | 10:26 | 10:26 | Placebo +CBT (157) | 7 DPP and continuous abstinence (+exhaled CO) | Public: Prince of Wales Hospital, Sidney |
| Rigotti <i>et al.</i> ⁶⁶ | | United States | 714 | Varenicline (355) | 12:52 | 12:52 | Placebo (359) | Continuous abstinence (+exhaled CO) | Pfizer |
| Rovina <i>et al.</i> ⁶⁷ | | Greece | 205 | Bupropion (169) | 19:52 | 19:52 | Placebo (36) | Continuous abstinence (+exhaled CO) | not specified |
| Sachs <i>et al.</i> ⁶⁸ | | United States | 220 | NRT patch (113) | 18:52 | 18:52 | Placebo (107) | Abstinence since the previous study visit (+exhaled CO) | US Public Health service, Parke Davis |
| Tonnesen <i>et al.</i> ⁶⁹ | | Denmark | 710 | Bupropion (527) | 7:52 | 7:52 | Placebo (180) | 7 DPP (+exhaled CO) | GSK |

Table 1. Continued

| Author | Year | Country | Population | Intervention (participants) | Follow-up—weeks | Control (participants) | Primary outcome criteria | Funding source | Duration of intervention: | |
|---------------------------------------|------|------------------|------------|-----------------------------|-----------------|------------------------|---|-----------------------|-----------------------------|------------------------|
| | | | | | | | | | Intervention (participants) | Control (participants) |
| Tonnesen <i>et al.</i> ⁷⁰ | | Denmark | 139 | Varenicline (70) | 12: 52 | Placebo (69) | 7 DPP (+exhaled CO, plasma cotinine and body weight) | Grants + Pfizer | | |
| Tsuhakara <i>et al.</i> ⁷¹ | | Japan | 35 | Varenicline (16) | 12: 24 | NRT (16) | Continuous abstinence (+exhaled CO) | Institutional funding | | |
| Tsai <i>et al.</i> ⁷² | | Korea and Taiwan | 250 | Varenicline (126) | 12: 24 | Placebo (124) | Continuous abstinence (+exhaled CO) | Pfizer | | |
| Wang <i>et al.</i> ⁷³ | | China | 333 | Varenicline (165) | 12: 24 | Placebo (168) | Continuous abstinence (+exhaled CO) | Pfizer | | |
| Williams <i>et al.</i> ⁷⁴ | | United States | 377 | Varenicline (251) | 52: 53 | Placebo (126) | Adverse events | Pfizer | | |
| Zhang <i>et al.</i> ⁷⁵ | | Canada | 964 | Varenicline (499) | 12: 52 | Bupropion (465) | 7 DPP | Pfizer Grant | | |

In blue: Interventions not included in the analysis. Abbreviations: CBT, cognitive behavioral therapies; NRT, nicotine replacement therapy; 7 DPP, 7 day point prevalence abstinence.

Data analysis

Pairwise meta-analysis (direct comparisons)

For the analysis focused on the outcome “Insomnia,” 34 studies were included.

Subgroup effects analysis (Figure 3) showed that insomnia was significantly more frequent with varenicline (RR: 1.54 [1.30–1.81]) and bupropion (RR: 1.86 [1.63–2.13]) than with placebo. On the other hand, varenicline is significantly less responsible for insomnia than bupropion (RR: 0.73 [0.64–0.84]). Bupropion caused insomnia significantly more frequently than NRT (RR: 1.41 [1.18–1.68]). Other comparisons are non-significant. There was substantial heterogeneity in two comparisons: varenicline versus (vs) placebo, varenicline vs NRT. Bupropion vs placebo and NRT vs placebo resulted in moderate heterogeneity. Varenicline vs bupropion and bupropion vs NRT are homogeneous (Figure 3).

For the analysis focused on the endpoint “Parasomnia,” 23 studies were included.

The analysis of subgroup effects (Figure 3) shows that varenicline and NRT caused significantly more parasomnia than placebo (RR: 2.42 [1.75–3.36] and RR: 3.46 [1.67–7.15], respectively). However, the subgroups effects of bupropion vs placebo and varenicline vs NRT were not significant. Parasomnia were significantly more frequent with varenicline compared to bupropion (RR: 1.55 [1.06–2.26]). Parasomnia were less frequent with bupropion than with NRT comparing them directly (RR: 0.35 [0.21–0.59]). The varenicline vs placebo comparison showed substantial heterogeneity, and only one comparison had low heterogeneity: bupropion vs placebo (Figure 3).

Network meta-analysis (Indirect comparisons)

The network structures with “Insomnia” and “Parasomnia” outcomes are available in the supplementary material file (Supplementary Figure S1).

For insomnia, Table 2 shows the results based on a Bayesian network meta-analysis. The cessation methods significantly increased the risk of insomnia. NRT was significantly less harmful to insomnia than bupropion and varenicline (RR: 0.62 [0.49–0.76] and RR 0.79 [0.64–0.95]). Varenicline had a lower risk of insomnia than bupropion (RR:0.78 [0.66–0.92]) (Table 2). In the ranking probability analysis, placebo and NRT had better profiles (Supplementary Figure S2).

The Bayesian method reveals that bupropion caused significantly less parasomnia than NRT (RR: 0.52 [0.32–0.82]) and varenicline (RR: 0.59 [0.41–0.86]). Comparisons between varenicline and NRT were not significant (Table 3). The rank probability analysis shows a better profile of bupropion than varenicline and NRT (Supplementary Figure S3).

Coherence analysis

A consistency analysis is performed by comparing the values of the direct and indirect comparisons (Supplementary Tables S1 and S2). A p-value greater than 0.05 means that there is no statistically significant difference. Here, all the comparisons for insomnia have a p-value greater than 0.05; the results are therefore consistent.

For parasomnia analysis, two comparisons are inconsistent: NRT vs varenicline, and bupropion vs placebo.

Discussion

This network meta-analysis is based on 37 studies with 25 011 patients randomly assigned to five different interventions or

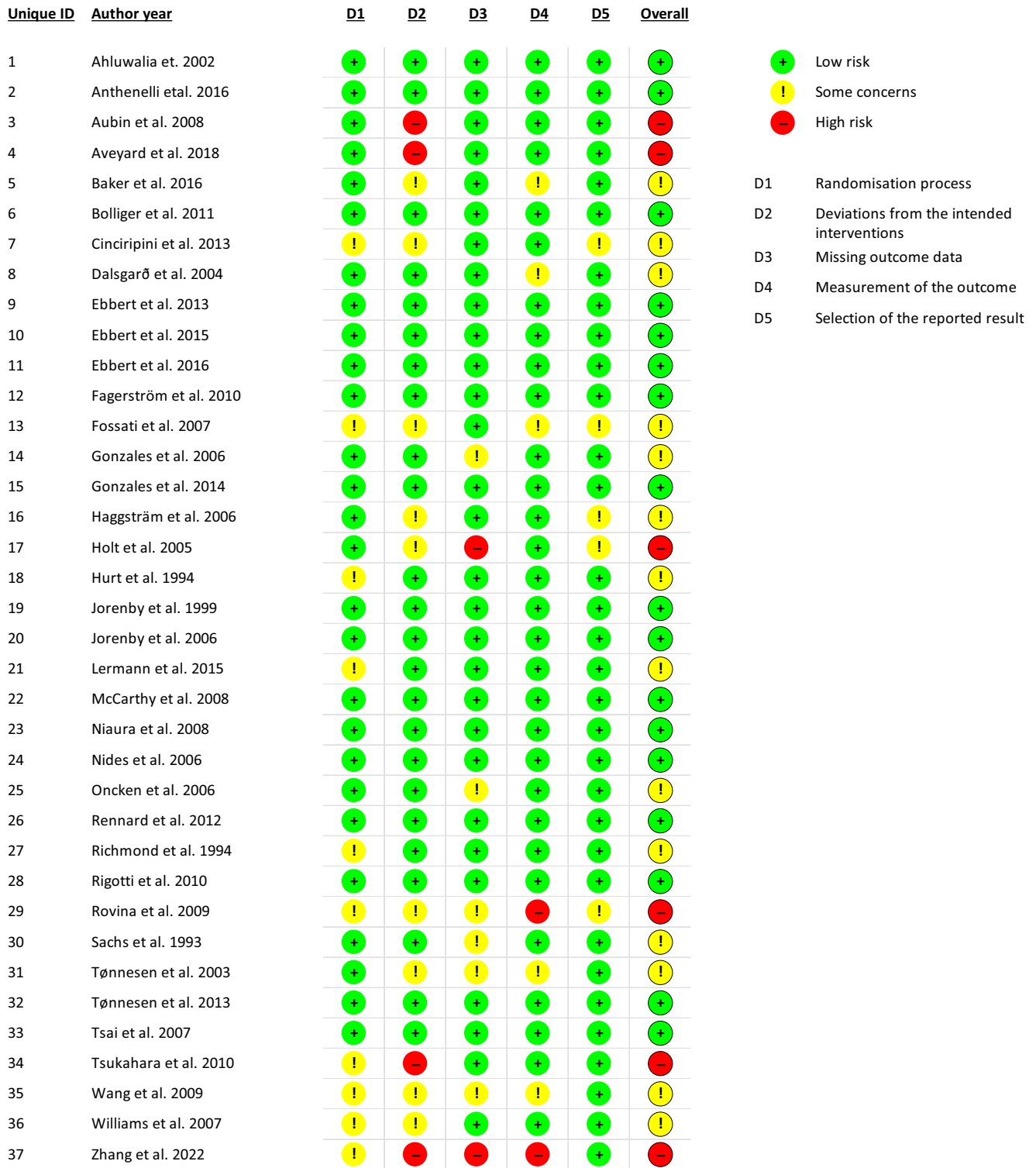


Figure 2. Risk of bias of studies.

placebo for smoking cessation. The original study confirms that insomnia and parasomnia are more frequent with smoking cessation therapies than with placebo except bupropion. There is a more favorable profile of NRT for insomnia and bupropion for parasomnia than with other smoking cessation treatments. Network meta-analysis is a validated and recognized systematic scientific method. Its value is based on a good level of evidence.^{31,32,76,77}

To our knowledge, it is the first network meta-analysis on the topic of insomnia and parasomnia induced by pharmacotherapies for smoking cessation with a ranking of the different smoking cessation methods to guide the choice of treatment.

For NRT, in non-smokers, transdermal nicotine intake reduced REM sleep with a complete recuperation after stopping. In smokers, Gourlay et al.⁷⁸ found that sleep disorders with NRT

a) Insomnia

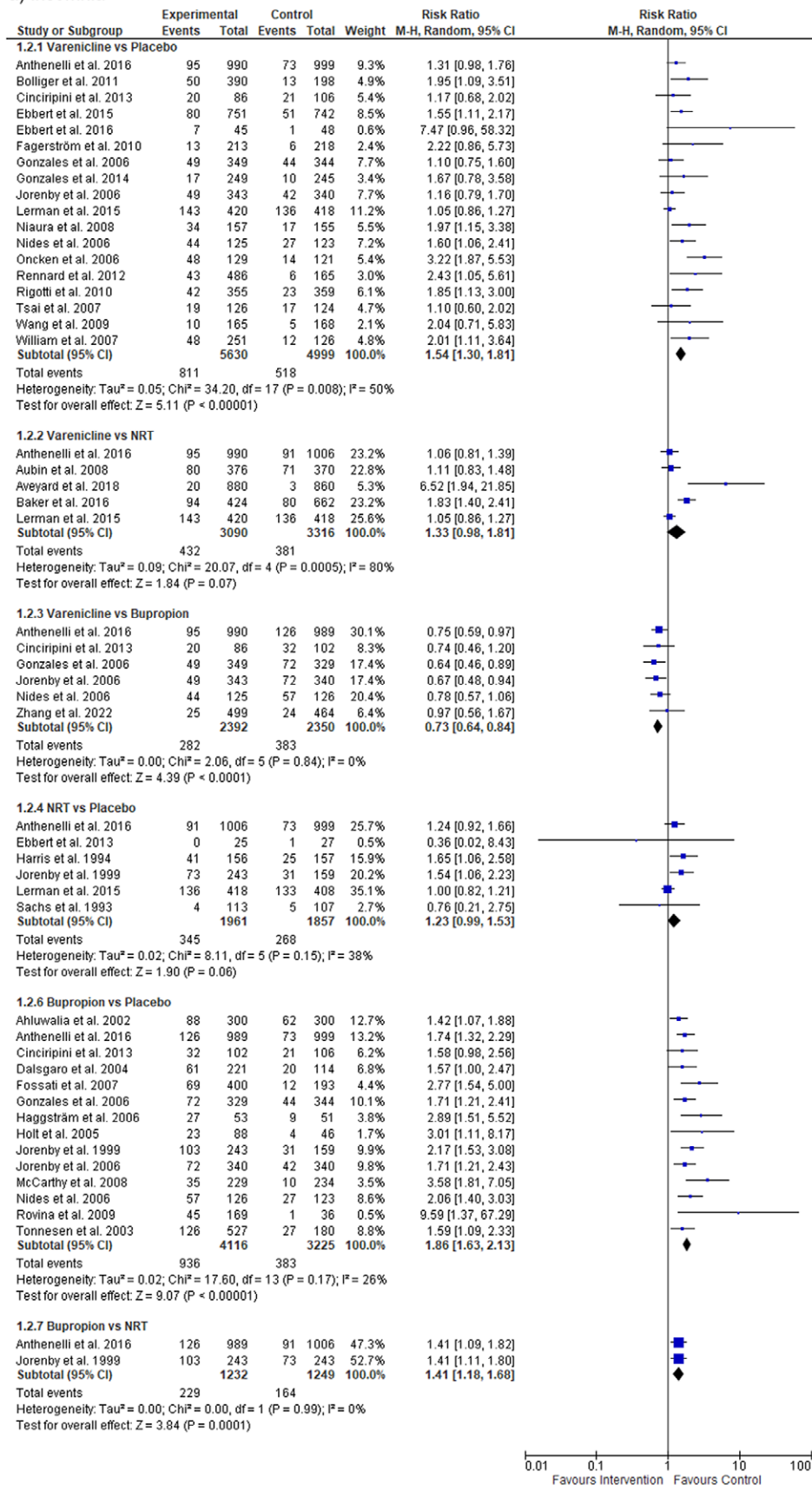


Figure 3. Pairwise comparisons for smoking cessation interventions for insomnia and parasomnia.

b) Parasomnias

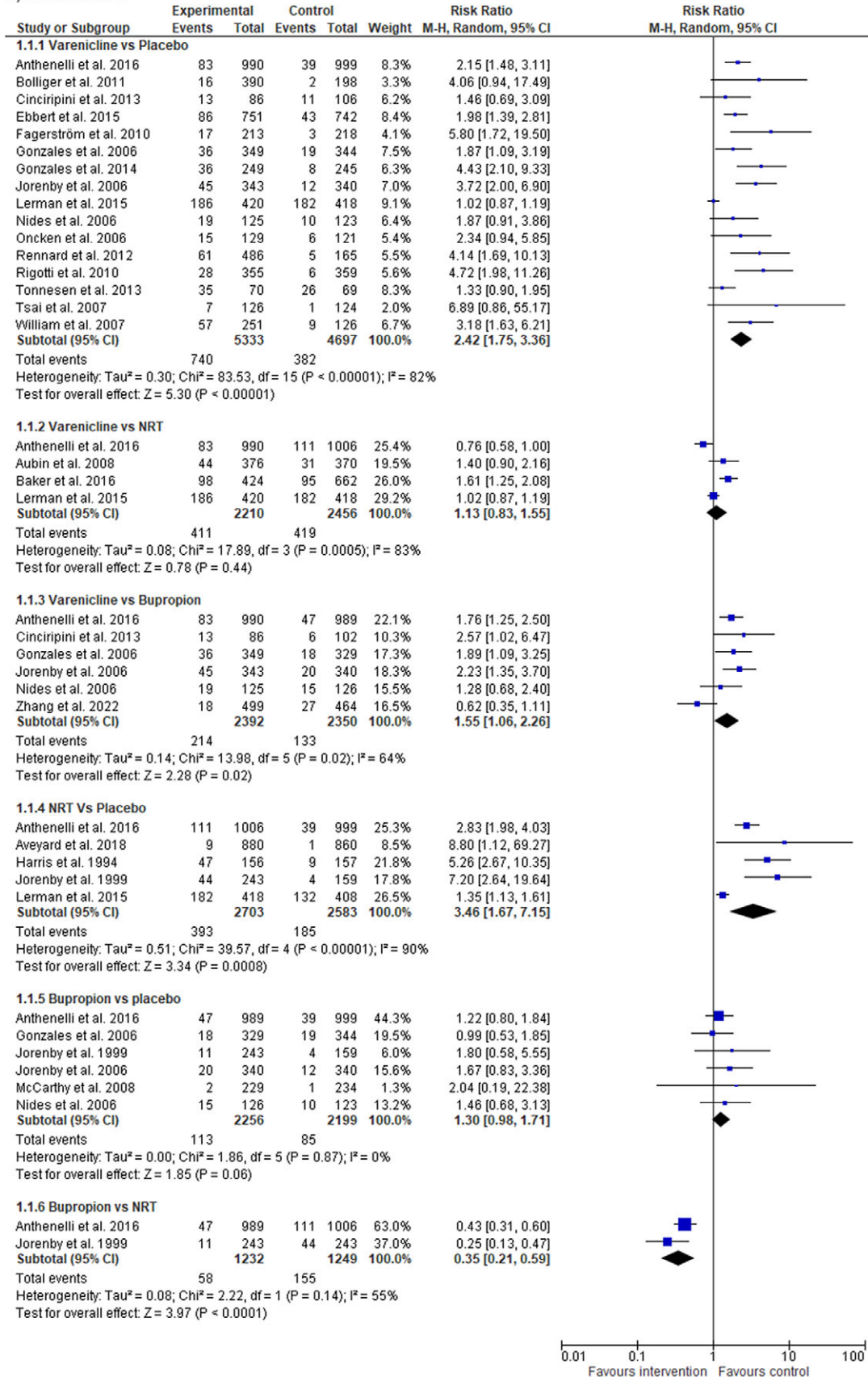


Figure 3. Continued

Table 2. Comparisons of Smoking Cessation Interventions for Insomnia (Bayesian Method)

| | | | |
|-------------------|--------------------------|--------------------------|--------------------------|
| Bupropion | 0.62 (0.49, 0.76) | 0.5 (0.42, 0.57) | 0.78 (0.66, 0.92) |
| 1.62 (1.32, 2.04) | NRT | 0.81 (0.66, 0.99) | 1.27 (1.05, 1.56) |
| 2.01 (1.74, 2.36) | 1.24 (1.01, 1.51) | Placebo | 1.57 (1.37, 1.83) |
| 1.28 (1.08, 1.52) | 0.79 (0.64, 0.95) | 0.64 (0.55, 0.73) | Varenicline |

In the lower left triangle, comparisons should be read from left to right. In the upper right triangle, comparisons should be read from right to left (that is treatment 1 versus treatment 2). Significant values are in bold (confidence interval not including 1).

Table 3. Comparisons of Smoking Cessation Interventions for Parasomnia (Bayesian Method)

| | | | |
|--------------------------|--------------------------|--------------------------|-------------------------|
| Bupropion | 1.93 (1.21, 3.12) | 0.68 (0.45, 1) | 1.7 (1.16, 2.47) |
| 0.52 (0.32, 0.82) | NRT | 0.35 (0.23, 0.52) | 0.88 (0.59, 1.28) |
| 1.47 (1, 2.21) | 2.83 (1.94, 4.35) | Placebo | 2.49 (1.92, 3.3) |
| 0.59 (0.41, 0.86) | 1.14 (0.78, 1.7) | 0.4 (0.3, 0.52) | Varenicline |

In the lower left triangle, comparisons should be read from left to right. In the upper right triangle, Comparisons should be read from right to left (that is treatment 1 versus treatment 2). Significant values are in bold (confidence interval not including 1).

are correlated to the severity of nicotine dependence and are more frequent in women. Frederickson found a correlation between plasma cotinine levels and the severity of sleep disorders.⁷⁹ In withdrawal periods, NRT increases arousal and reduces sleep time.^{25,80} According to Vasquez et al., transdermal nicotine can disrupt, like cigarette smoking, the PGO activity in cats.⁸¹ The time administration is important to consider: The 16 h nicotine patch reduces parasomnia but contributes to a night craving related to a fall in nicotine concentration. Compared to 16 h nicotine patch, there is less microarousal and an increase of the REM period with 24-hr nicotine patches.^{82,83}

In our study, varenicline increases the number of awakenings and reports of parasomnia compared to bupropion. This effect for varenicline is confirmed by polysomnographic studies.^{84,85} For bupropion, the effects on sleep architecture are unclear, with few studies available. These two drugs have different actions. Bupropion is an antidepressant and acts by inhibiting the dopamine reuptake in the brain reward center. As a partial agonist of alpha4-beta2 nicotinic acetylcholine receptors, varenicline stimulates dopamine release and blocks the action of nicotine cigarette intake. The important rate of sleep disorders frequency with varenicline in our study can be linked to a nicotinic disturbance and dopamine dysregulation, which can be implied in parasomnia⁸⁶

However, our study has limitations. First, we define the selection criteria, including healthy smokers without comorbidity and those who were not hospitalized. This choice allows us to avoid confounding factors that can affect sleep quality and increase insomnia and parasomnia.^{87–89} Nevertheless, smoking cessation in patients with comorbidities, particularly psychiatric or co-addictions, remains a public health issue. A network meta-analysis including these different selection criteria would be interesting to carry out.

Second, some cessation methods are more extensively analyzed and have had longer follow-up periods, while others are understudied. For example, the results reported for nicotine substitutes or varenicline are numerous, while no studies on electronic cigarettes could be included in our analysis. Most of them do not report sleep disturbances or do so in an imprecise manner. In addition, studies on smoking cessation are not systematically published, making their inclusion and integration problematic. This

difference in data availability could potentially create a selective reporting and publication bias.

Most of the studies analyzed were sponsored by the manufacturers of varenicline and nicotine replacement products. Previous work on nicotine replacement therapies has shown that industry-sponsored trials are significantly more likely to have favorable results than independent trials.⁹⁰ However, most of the studies reviewed here are of high-quality evidence (randomized controlled trials) and have a low risk of bias.

There is also heterogeneity in the definitions of sleep disorders. Insomnias are usually explored in withdrawal scales such as the Minnesota Tobacco Withdrawal Scale (MNWS),⁹¹ and parasomnias are mainly reported as abnormal and vivid dreams in the side effects reported. These outcomes were mainly not prespecified in most of the studies and were extracted in the side effects reported. This constitutes a selection bias. We used the definitions for the ICSD 3,²⁹ other sleep dimensions could not be extracted.

However, using a single coding scheme for future randomized trials would provide consistency of outcome and limit this measurement bias. For example, these future trials could use a standardized questionnaire such as the Insomnia Severity Index (ISI) or the Pittsburgh Sleep Quality Index (PSQI).^{92,93} A systematic collection of sleep disorders in future studies would reduce the inconsistencies between direct and indirect estimates. Nevertheless, our study's transitivity was respected, strengthening our analysis. Indeed, we selected only studies with an identical intervention indication: smoking cessation.

It seems difficult to distinguish sleep disorders related to withdrawal symptoms from the side effects of pharmacological treatment. However, the persistent disturbances observed in patients on NRT⁹⁴ and our results have shown a higher frequency of sleep disturbances with pharmacological treatments compared to placebo. This effect suggests specific mechanisms, but little is known in the literature and could not explain the difference highlighted in this meta-analysis.

If smoking cessation is a factor for improving sleep health, poor sleep quality can reduce the success of cessation.⁹⁵ Attention to sleep patterns before starting treatment and considering the side effects on sleep associated with smoking cessation therapy are

relevant to increasing smoking cessation probability.^{96–98} Thus, health professionals could promote sleep hygiene measures and adjust dosages to prevent the onset or worsening of sleep disorders. Informing the patient of the links between smoking cessation and sleep health would make it possible to include them in the choice of method and thus make them an actor in the abstinence process.

Conclusion

In conclusion, validated smoking cessation pharmacotherapies can induce sleep disturbances with different degrees of frequency. Our network meta-analysis shows a more favorable profile of nicotine substitutes for insomnia and bupropion for parasomnia. However, our results are qualified by the presence of inconsistencies. These are probably due to a lack of homogeneity in the selected studies and data analysis of specific interventions.

Our study is innovative and deals with a current problem. Current management is increasingly aimed at refractory and anxious smokers who often suffer from sleep disorders. Network meta-analysis—an emerging, validated and recognized method applied to these issues—contributes to scientific research.

Systematizing the assessment of sleep disorders in the initiation of smoking cessation seems essential. This could help health professionals in supervising smoking patients to adapt their practice. Furthermore, considering co-addictions, broadening the populations studied (such as patients with psychiatric comorbidities), and standardizing the measurement are additional avenues for future research on this subject.

Supplementary material. The supplementary material for this article can be found at <http://doi.org/10.1017/S1092852924000087>.

Author contribution. Conceptualization: C.P., P.D., P.V.; Formal analysis: C.P., P.V.; Writing – original draft: C.P., C.L., N.J., P.D., P.C., P.V.; Writing – review & editing: C.P., C.L., N.J., P.D., P.C., P.V.; Supervision: C.L., N.J.; Validation: C.L., P.C.; Visualization: C.L.; Methodology: P.V.

Financial support. This research did not receive grants from any funding agency in the public, commercial, or not-for-profit sectors.

Disclosure. The authors declare none.

References

1. Tobacco. World Health Organization. [Internet]. <https://www.who.int/fr/news-room/fact-sheets/detail/tobacco>.
2. World Health Organization, Management of Substance Abuse Team, World Health Organization. Global Status Report on Alcohol and Health; 2018. http://www.who.int/substance_abuse/publications/global_alcohol_report/en/.
3. Degenhardt L, Charlson F, Ferrari A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry*. 2018;**5**(12):987–1012.
4. Perriot J, Underner M, Peiffer G. Smoking cessation in “difficult smokers”. *Revue des maladies respiratoires*. 2012;**29**(4):448–461.
5. Vijayaraghavan M, Schroeder SA, Kushel M. The effectiveness of tobacco control policies on vulnerable populations in the USA: a review. *Postgrad Med J*. 2016;**92**(1093):670–676.
6. Jamal A, Phillips E, Gentzke AS, et al. Current cigarette smoking among adults — United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;**67**(2):53–59.
7. Piper ME, Cook JW, Schlam TR, et al. Gender, race, and education differences in abstinence rates among participants in two randomized smoking cessation trials. *Nicotine Tob Res*. 2010;**12**(6):647–657.
8. Cahill K, Stevens S, Lancaster T. Pharmacological treatments for smoking cessation. *JAMA*. 2014;**311**(2):193–194. doi:10.1001/jama.2013.283787.
9. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev*. 2018;**5**(5):CD000146. doi:10.1002/14651858.CD000146.pub5.
10. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev*. 2016;**2016**(5):CD006103. doi:10.1002/14651858.CD006103.pub7.
11. Marlatt GA, Donovan DM, eds. *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors*. 2nd ed. New York: Guilford Press; 2005.
12. Yeomans K, Payne KA, Marton JP, et al. Smoking, smoking cessation and smoking relapse patterns: a web-based survey of current and former smokers in the US. *Int J Clin Pract*. 2011;**65**(10):1043–1054.
13. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. *Addiction*. 2016; **111**(11):2032–2040.
14. Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. *Tob Control*. 2018;**27**(1):18–25.
15. Hartmann-Boyce J, McRobbie H, Butler AR, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2021;**4**(4):CD010216.
16. Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;**49**:57–71.
17. Gibson M, Munafò MR, Taylor AE, Treur JL. Evidence for genetic correlations and bidirectional, causal effects between smoking and sleep behaviors. *Nicotine Tob Res*. 2018;**21**(6):731–738.
18. Zhang L, Samet J, Caffo B, Punjabi NM. Cigarette smoking and nocturnal sleep architecture. *Am J Epidemiol*. 2006;**164**(6):529–537.
19. Boakye D, Wyse CA, Morales-Celis CA, et al. Tobacco exposure and sleep disturbance in 498 208 UK Biobank participants. *J Public Health (Oxf)*. 2018;**40**(3):517–526.
20. Liao Y, Xie L, Chen X, et al. Sleep quality in cigarette smokers and non-smokers: findings from the general population in central China. *BMC Public Health*. 2019;**19**(1):808
21. Peters EN, Fucito LM, Novosad C, Toll BA, O'Malley SS. Effect of night smoking, sleep disturbance, and their co-occurrence on smoking outcomes. *Psychol Addict Behav*. 2011;**25**(2):312–319.
22. Guzmán-Marín R, Alam MN, Mihailescu S, Szymusiak R, McGinty D, Drucker-Colín R. Subcutaneous administration of nicotine changes dorsal raphe serotonergic neurons discharge rate during REM sleep. *Brain Res*. 2001;**888**(2):321–325.
23. Mihailescu S, Guzmán-Marín R, Drucker-Colín R. Nicotine stimulation of dorsal raphe neurons: effects on laterodorsal and pedunculopontine neurons. *Eur Neuropsychopharmacol*. 2001;**11**(5):359–366.
24. Saint-Mleux B. Nicotinic enhancement of the noradrenergic inhibition of sleep-promoting neurons in the ventrolateral preoptic area. *J Neurosci*. 2004;**24**(1):63–67.
25. Jaehne A, Loessl B, Bärkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. *Sleep Med Rev*. 2009;**13**(5):363–377.
26. Patterson F, Grandner MA, Malone SK, Rizzo A, Davey A, Edwards DG. Sleep as a target for optimized response to smoking cessation treatment. *Nicotine Tob Res*. 2017;**21**(2):139–148.
27. Ashare RL, Lerman C, Tyndale RF, et al. Sleep disturbance during smoking cessation: withdrawal or side effect of treatment? *J Smok Cessat*. 2017;**12**(2):63–70.
28. Cummings KM, Giovino G, Jaén CR, Emrich LJ. Reports of smoking withdrawal symptoms over a 21 day period of abstinence. *Addict Behav*. 1985;**10**(4):373–381.
29. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest*. 2014;**146**(5):1387–1394. doi:10.1378/chest.14-0970.

30. Salanti G, Higgins JPT, Ades AE, Ioannidis JPA. Evaluation of networks of randomized trials. *Stat Methods Med Res.* 2008;**17**(3):279–301.
31. Riley RD, Jackson D, Salanti G, et al. Multivariate and network meta-analysis of multiple outcomes and multiple treatments: rationale, concepts, and examples. *BMJ.* 2017;**358**:j3932.
32. Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol.* 2011;**64**(2):163–171. doi:10.1016/j.jclinepi.2010.03.016.
33. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;**6**(7):e1000097. doi:10.1371/journal.pmed.1000097.
34. Medical Dictionary for Regulatory Activities Terminology (MedDRA) - Sleep disorders and disturbances - Classes | NCBO BioPortal [Internet]. <https://bioportal.bioontology.org/ontologies/MEDDRA?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMEDDRA%2F10040991>. Accessed October 25, 2022.
35. Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia [Internet]. www.covidence.org.
36. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019;**366**:l4898.
37. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: an interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. *Res Syn Meth.* 2019;**10**(4):569–581.
38. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.
39. Ahluwalia JS, Harris KJ, Catley D, Okuyemi KS, Mayo MS. Sustained-release bupropion for smoking cessation in African Americans: a randomized controlled trial. *JAMA.* 2002;**288**(4):468–474.
40. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. *Lancet.* 2016;**387**(10037):2507–2520.
41. Aubin H-J, Bobak A, Britton JR, Oncken C, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. *Thorax.* 2008;**63**(8):717–724.
42. Aveyard P, Lindson N, Tearne S, et al. Nicotine preloading for smoking cessation: the preloading RCT. *Health Technol Assess.* 2018;**22**(41):1–84.
43. Baker TB, Piper ME, Stein JH, et al. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 weeks: a randomized clinical trial. *JAMA.* 2016;**315**(4):371–379.
44. Bolliger CT, Issa JS, Posadas-Valay R, et al. Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2011;**33**(4):465–477.
45. Cinciripini PM, Robinson JD, Karam-Hage M. Effects of varenicline and bupropion sustained-release use plus intensive smoking cessation counseling on prolonged abstinence from smoking and on depression, negative affect, and other symptoms of nicotine withdrawal. *JAMA Psychiatry.* 2013;**70**(5):33.
46. Dalsgarð ÓJ, Hansen N-CG, Søres-Petersen U, et al. A multicenter, randomized, double-blind, placebo-controlled, 6-month trial of bupropion hydrochloride sustained-release tablets as an aid to smoking cessation in hospital employees. *Nicotine Tob Res.* 2004;**6**(1):55–61.
47. Ebbert JO, Croghan IT, Hurt RT, Schroeder DR, Hays JT. Varenicline for smoking cessation in light smokers. *Nicotine Tob Res.* 2016;**18**(10):2031–2035.
48. Ebbert JO, Croghan IT, Schroeder DR, Hurt RD. A randomized phase II clinical trial of high-dose nicotine patch therapy for smokeless tobacco users. *Nicotine Tob Res.* 2013;**15**(12):2037–2044.
49. Ebbert JO, Hughes JR, West RJ, et al. Effect of varenicline on smoking cessation through smoking reduction: a randomized clinical trial. *JAMA.* 2015;**313**(7):687–694.
50. Fagerström K, Gilljam H, Metcalfe M, Tonstad S, Messig M. Stopping smokeless tobacco with varenicline: randomised double blind placebo controlled trial. *BMJ.* 2010;**341**:c6549.
51. Fossati R, Apolone G, Negri E, et al. A double-blind, placebo-controlled, randomized trial of bupropion for smoking cessation in primary care. *Arch Intern Med.* 2007;**167**(16):1791–1797.
52. Gonzales D, Hajek P, Pliamm L, 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**(3):390–396. doi:10.1038/clpt.2014.124.
53. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an α 4 β 2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA.* 2006;**296**(1):47–55.
54. Haggström FM, Chatkin JM, Sussenbach-Vaz E, Cesari DH, Fam CF, Fritscher CC. A controlled trial of nortriptyline, sustained-release bupropion and placebo for smoking cessation: preliminary results. *Pulm Pharmacol Ther.* 2006;**19**(3):205–209.
55. Holt S, Timu-Parata C, Ryder-Lewis S, Weatherall M, Beasley R. Efficacy of bupropion in the indigenous Maori population in New Zealand. *Thorax.* 2005;**60**(2):120–123.
56. Hurt RD, Dale LC, Fredrickson PA, et al. Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up. One-year outcome and percentage of nicotine replacement. *JAMA.* 1994;**271**(8):595–600.
57. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an α 4 β 2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA.* 2006;**296**(1):56–63.
58. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med.* 1999;**340**(9):685–691.
59. Lerman C, Schnoll RA, Hawk LW, et al. Use of the nicotine metabolite ratio as a genetically informed biomarker of response to nicotine patch or varenicline for smoking cessation: a randomised, double-blind placebo-controlled trial. *Lancet Respir Med.* 2015;**3**(2):131–138. doi:10.1016/S2213-2600(14)70294-2.
60. McCarthy DE, Piasecki TM, Lawrence DL, et al. A randomized controlled clinical trial of bupropion SR and individual smoking cessation counseling. *Nicotine Tob Res.* 2008;**10**(4):717–729.
61. Niaura R, Hays JT, Jorenby DE, et al. The efficacy and safety of varenicline for smoking cessation using a flexible dosing strategy in adult smokers: a randomized controlled trial. *Curr Med Res Opin.* 2008;**24**(7):1931–1941.
62. Nides M. Smoking cessation with varenicline, a selective α 4 β 2 nicotinic receptor partial agonist: results from a 7-week, randomized, placebo- and bupropion-controlled trial with 1-year follow-up. *Arch Intern Med.* 2006;**166**(15):1561.
63. Oncken C, Gonzales D, Nides M, et al. Efficacy and safety of the novel selective nicotinic acetylcholine receptor partial agonist, varenicline, for smoking cessation. *Arch Intern Med.* 2006;**166**(15):1571–1577.
64. Rennard S, Hughes J, Cinciripini PM, et al. A randomized placebo-controlled trial of varenicline for smoking cessation allowing flexible quit dates. *Nicotine Tob Res.* 2012;**14**(3):343–350.
65. Richmond RL, Harris K, de Almeida Neto A. The transdermal nicotine patch: results of a randomised placebo-controlled trial. *Med J Aust.* 1994;**161**(2):130–135.
66. Rigotti NA, Pipe AL, Benowitz NL, Arteaga C, Garza D, Tonstad S. Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease. *Circulation.* 2010;**121**(2):221–229.
67. Rovina N, Nikoloutsou I, Katsani G, et al. Effectiveness of pharmacotherapy and behavioral interventions for smoking cessation in actual clinical practice. *Ther Adv Respir Dis.* 2009;**3**(6):279–287.
68. Sachs DPL, Säwe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med.* 1993;**153**(16):1881–1890.
69. Tonnesen P, Mikkelsen K. Varenicline to stop long-term nicotine replacement use: a double-blind, randomized, placebo-controlled trial. *Nicotine Tob Res.* 2013;**15**(2):419–427.
70. Tonnesen P, Tonstad S, Hjalmarsen A, et al. A multicentre, randomized, double-blind, placebo-controlled, 1-year study of bupropion SR for smoking cessation. *J Intern Med.* 2003;**254**(2):184–192.
71. Tsai S-T, Cho H-J, Cheng H-S, et al. A randomized, placebo-controlled trial of varenicline, a selective α 4 β 2 nicotinic acetylcholine receptor partial

- agonist, as a new therapy for smoking cessation in Asian smokers. *Clin Ther.* 2007;**29**(6):1027–1039.
72. Tsukahara H, Noda K, Saku K. A randomized controlled open comparative trial of varenicline vs nicotine patch in adult smokers - efficacy, safety and withdrawal symptoms (the VN-SEESAW study). *Circ J.* 2010;**74**(4):771–778.
 73. Wang C, Xiao D, Chan KPW, Pothirat C, Garza D, Davies S. Varenicline for smoking cessation: a placebo-controlled, randomized study. *Respirology.* 2009;**14**(3):384–392.
 74. Williams JM, Anthenelli RM, Morris CD, et al. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry.* 2012;**73**(5):16746.
 75. Zhang H, Mansoursadeghi-Gilan T, Hussain S, et al. Evaluating the effectiveness of bupropion and varenicline for smoking cessation using an internet-based delivery system: a pragmatic randomized controlled trial (MATCH study). *Drug Alcohol Depend.* 2022;**232**:109312.
 76. Li B-Z, Threapleton DE, Wang J-Y, et al. Comparative effectiveness and tolerance of treatments for *Helicobacter pylori*: systematic review and network meta-analysis. *BMJ.* 2015;**351**:h4052.
 77. Panikker S, Lord J, Jarman JWE, et al. Outcomes and costs of left atrial appendage closure from randomized controlled trial and real-world experience relative to oral anticoagulation. *Eur Heart J.* 2016;**37**(46):3470–3482.
 78. Gourlay SG, Forbes A, Marriner T, McNeil JJ. Predictors and timing of adverse experiences during transdermal nicotine therapy. *Drug Saf.* 1999;**20**(6):545–555.
 79. Fredrickson PA, Hurt RD, Lee GM, et al. High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels. *Psychopharmacology (Berl).* 1995;**122**(3):215–222.
 80. Wolter TD, Hauri PJ, Schroeder DR, et al. Effects of 24-hr nicotine replacement on sleep and daytime activity during smoking cessation. *Prev Med.* 1996;**25**(5):601–610.
 81. Vazquez J, Guzmán-Marín R, Salín-Pascual RJ, Drucker-Colín R. Transdermal nicotine on sleep and PGO spikes. *Brain Res.* 1996;**737**(1–2):317–320.
 82. Page F, Coleman G, Conduit R. The effect of transdermal nicotine patches on sleep and dreams. *Physiol Behav.* 2006;**88**(4–5):425–432.
 83. Staner L, Luthringer R, Dupont C, Aubin H, Lagrue G. Sleep effects of a 24-h versus a 16-h nicotine patch: a polysomnographic study during smoking cessation. *Sleep Med.* 2006;**7**(2):147–154.
 84. West R, Baker CL, Cappelleri JC, Bushmakin AG. Effect of varenicline and bupropion SR on craving, nicotine withdrawal symptoms, and rewarding effects of smoking during a quit attempt. *Psychopharmacology.* 2008;**197**(3):371–377.
 85. Pataka A, Frantzidis C, Nday C, et al. Polysomnographic changes after varenicline administration for smoking cessation. *ERJ Open Res.* 2019;**5**(3):156.
 86. Happe S, Berger K, On Behalf of the FAQT Study Investigators. The association of dopamine agonists with daytime sleepiness, sleep problems and quality of life in patients with Parkinson's disease. *J Neurol.* 2001;**248**(12):1062–1067.
 87. Chakravorty S, Chaudhary NS, Brower KJ. Alcohol dependence and its relationship with insomnia and other sleep disorders. *Alcohol Clin Exp Res.* 2016;**40**(11):2271–2282.
 88. Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. *Sleep Med Rev.* 2008;**12**(5):381–389.
 89. Lewis DA. Sleep in patients with asthma and chronic obstructive pulmonary disease. *Curr Opin Pulm Med.* 2001;**7**(2):105–112.
 90. Etter J-F, Burri M, Stapleton J. The impact of pharmaceutical company funding on results of randomised trials of nicotine replacement therapy for smoking cessation: a meta-analysis. *Addiction.* 2007;**102**(5):815–822.
 91. Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. *Arch Gen Psychiatry.* 1986;**43**(3):289–294. doi:10.1001/archpsyc.1986.01800030107013.
 92. Morin CM. *Insomnia: Psychological assessment and management.* Vol. xvii. New York, NY: Guilford Press; 1993:238.
 93. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989;**28**(2):193–213.
 94. Mills EJ, Wu P, Lockhart I, Wilson K, Ebbert JO. Adverse events associated with nicotine replacement therapy (NRT) for smoking cessation. A systematic review and meta-analysis of one hundred and twenty studies involving 177,390 individuals. *Tob Induced Dis.* 2010;**8**(1):8.
 95. Short NA, Mathes BM, Gibby B, Oglesby ME, Zvolensky MJ, Schmidt NB. Insomnia symptoms as a risk factor for cessation failure following smoking treatment. *Addict Res Theory.* 2017;**25**(1):17–23.
 96. Dörner TE, Tröstl A, Womastek I, Groman E. Predictors of short-term success in smoking cessation in relation to attendance at a smoking cessation program. *Nicotine Tob Res.* 2011;**13**(11):1068–1075.
 97. Peltier MR, Lee J, Ma P, Businelle MS, Kendzor DE. The influence of sleep quality on smoking cessation in socioeconomically disadvantaged adults. *Addict Behav.* 2017;**66**:7–12.
 98. Okun ML, Levine MD, Patricia H, Perkins KA, Marcus MD. Subjective sleep disturbance during a smoking cessation program: associations with relapse. *Addict Behav.* 2011;**36**:861–864.