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

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Review

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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-analysis[15] 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 ponto-geniculo-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 study[18] 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 (ISCD) 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 (ISCD 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

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(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]

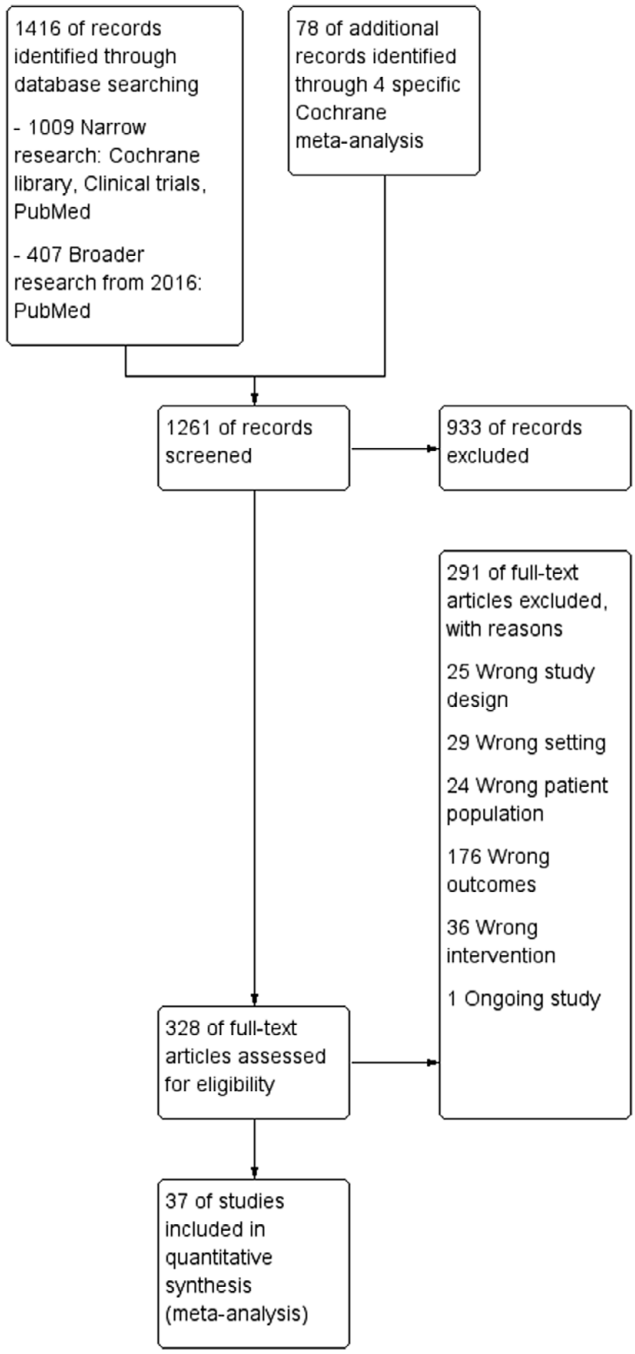

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

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 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]

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Table 1. Characteristics of Included Studies

Author Year Country	Population	Intervention (participants)	Duration of intervention: Follow-up—weeks	Control (participants)	Primary outcome criteria	Funding source
Ahluwalia *et al.*[39] United States	600	Bupropion (300)	7:26	Placebo (300)	Prolonged abstinence (+exhaled CO)	National cancer Institute GSK for treatment
Anthenelli *et al.* [40] 16 contries	3989 (Non-psychiatric cohort)	Varenicline (990) Bupropion (989) NRT (1006)	12:24	Placebo	Moderate/severe AEs (composite measure) Continuous abstinence (+exhaled CO)	Pfizer GSK
Aubin *et al.*[41] Europe, United States	746	Varenicline (376)	10–12: 52	NRT patch (370)	Continuous abstinence (+exhaled CO)	Pfizer
Ayeward *et al.*[42] United Kingdom	1792	NRT (880)	4:52	Behavioral intervention (860)	Continuous abstinence (+exhaled CO)	Institutional funding
Baker *et al.*[43] United Kingdom	1086	Varenicline (424)	12: 52	- NRT patch (241) - NRT patch + oral (421)	7 DPP (+exhaled CO)	National Heart, Lung, and Blood Institute
Bolliger *et al.*[44] Latin American, African and middle East Contries	583	Varenicline (390)	12: 24	Placebo (198)	Continuous abstinence (+exhaled CO)	Pfizer
Cinciripini *et al.*[45] United States	294	Varenicline (86) Bupropion (102)	12:24	Placebo (106)	Prolonged Abstinence (+exhaled CO)	National Institute on Drug Abuse (Dr Cinciripini) and by Cancer Center Support Grant
Dalsgarð *et al.*[46] Europe	335	Bupropion (221)	7:	Placebo (114)	Continuous Abstinence (+exhaled CO)	GSK
Ebbert *et al.*[47] United States	52	NRT patch 42 mg (25)	8: 26	Placebo (27)	7 DPP (+urine anabasine concentration)	Pfizer Inc, National Institutes of Health, GlaxoSmithKline
Ebbert *et al.*[48] United States	1510	Varenicline (760)	24:52	Placebo	Continuous abstinence (+exhaled CO)	Pfizer
Ebbert *et al.*[49] United States	93	Varenicline (45)	12: 26	Placebo (48)	7 DPP (+exhaled CO)	Pfizer
Fagerström *et al.*[50] Norway, Sweden	431	Varenicline (218)	12: 26	Placebo (213)	Continuous abstinence (+salivary cotinine)	Pfizer
Fossati *et al.*[51] Italia	593	Bupropion (400)	7:52	Placebo (193)	Continuous abstinence (+exhaled CO)	Mario Negri Institute GlaxoSmithKline provided an unconditional grant
Gonzales *et al.*[52] United States	861	Varenicline (275)	12: 52	- Bupropion (329) - Placebo (257)	Continuous abstinence (+exhaled CO)	Pfizer
Gonzales *et al.*[53] Europe, Australia, North America	494	Varenicline (249)	12: 52	Placebo (245)	7 DPP and continuous abstinence (+exhaled CO)	Pfizer, McNeil, GlaxoSmithKline, Queen Mary university
Haggsträm *et al.*[54] Brazil	156	Bupropion (53)	8: 26	Placebo (51) Nortriptyline (52)	Continuous abstinence (+exhaled CO)	No information
Holt *et al.*[55] New Zealand	134	Bupropion (88)	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: Follow-up—weeks	Control (participants)	Primary outcome criteria	Funding source
Hurt *et al.*[56] United States	240	NRT (120)	8:52	*Placebo (120)*	Continuous abstinence (+exhaled CO)	Lederle Laboratories, NY
Jorenby *et al.*[57] United States	889	Bupropion (243)	9: 52	- NRT patch (243) - *Bupropion + NRT patch (244)* - Placebo (159)	7 DPP abstinence (+exhaled CO)	Glaxo Wellcome
Jorenby *et al.*[58] United States	1023	Varenicline (343)	12: 52	- Bupropion (340) - Placebo (340)	Continuous abstinence (+exhaled CO)	Pfizer
Lerman *et al.*[59] Canada	1246	NRT (418) Varenicline (420)	11: 52	Placebo (408)	7-day PP at 12 months	Pfizer Inc. provided varenicline and placebo pills at no cost Institutional funding
Mc Carthy *et al.*[60] United States	463	Bupropion (229)	8: 52	Placebo (234)	7 DPP abstinence (+exhaled CO)	National cancer institute Placebo provided by GSK
Niaura *et al.*[61] United States	312	Varenicline (157)	12: 52	Placebo (155)	Continuous abstinence (+exhaled CO)	Pfizer
Nides *et al.*[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	- Bupropion (126) - Placebo (123)	Continuous abstinence (+exhaled CO)	Pfizer
Oncken *et al.*[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	Placebo (121)	Continuous abstinence (+exhaled CO + dosage)	Pfizer
Rennard *et al.*[64] United States	659	Varenicline (5486)	12: 24	Placebo (165)	Continuous abstinence (+exhaled CO)	Pfizer
Richmond *et al.*[65] Australia	315	NRT patch + CBT (158)	10: 26	Placebo +CBT (157)	7 DPP and continuous abstinence (+exhaled CO)	Public: Prince of Wales Hospital, Sidney
Rigotti *et al.*[66] United States	714	Varenicline (355)	12: 52	Placebo (359)	Continuous abstinence (+exhaled CO)	Pfizer
Rovina *et al.*[67] Greece	205	Bupropion (169)	19: 52	Placebo (36)	Continuous abstinence (+exhaled CO)	not specified
Sachs *et al.*[68] United States	220	NRT patch (113)	18: 52	Placebo (107)	Abstinence since the previous study visit (+exhaled CO)	US Public Health service, Parke davis
Tonnesen *et al.*[69] Denmark	710	Bupropion (527)	7: 52	Placebo (180)	7 DPP (+exhaled CO)	GSK

Table 1. *Continued*

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

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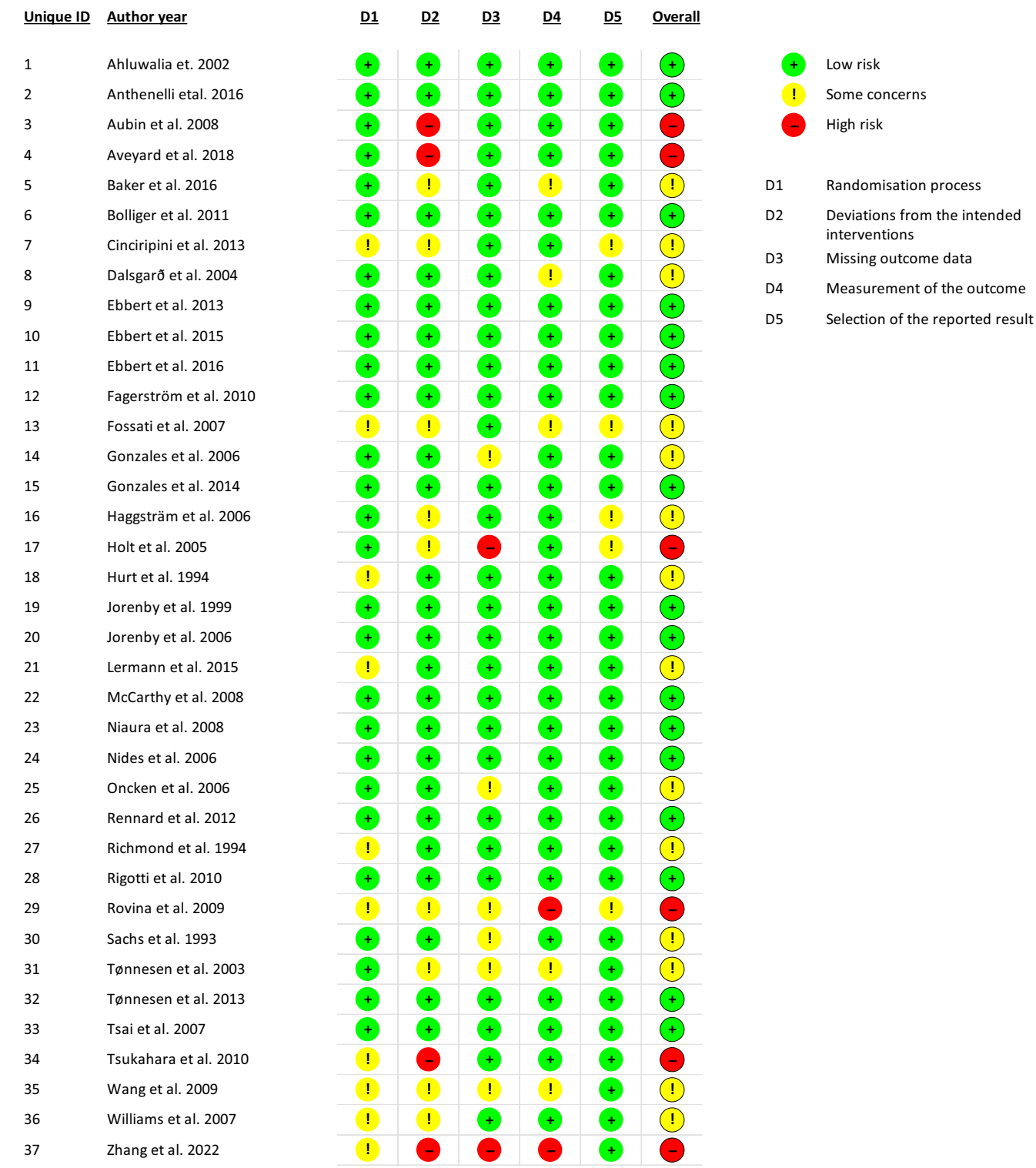

Figure 2. Risk of bias of studies.

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

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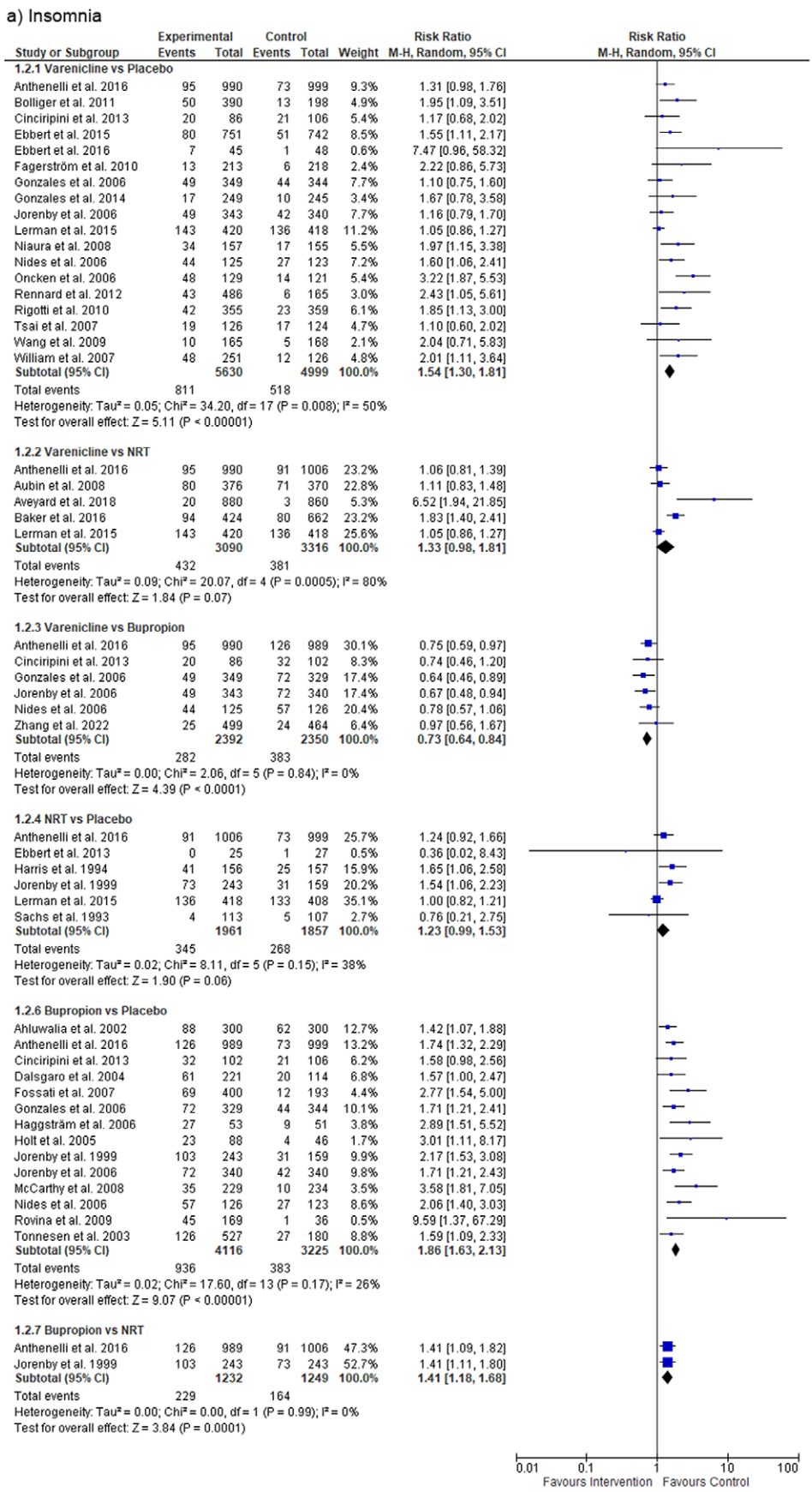

Figure 3. Pairwise comparisons for smoking cessation interventions for insomnia and parasomnia.

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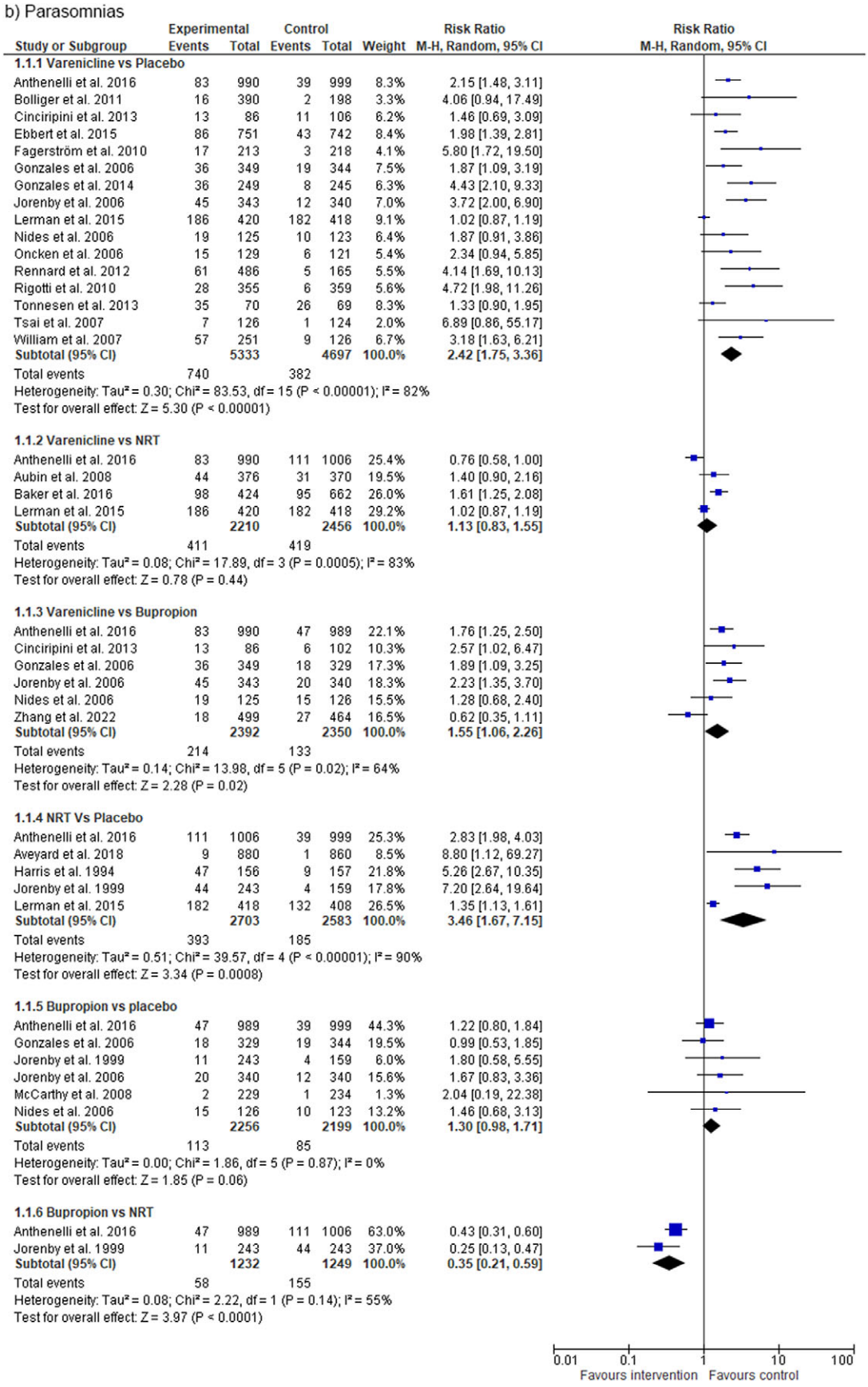

Figure 3. Continued

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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 parasomnia[86]

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 ISCD 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 NRT[94] 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

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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.

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