www.cambridge.org/cns

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

© The Author(s), 2024. Published by Cambridge University Press.



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

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 dosedependent 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 (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 end-point.³²

97

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
 - 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

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

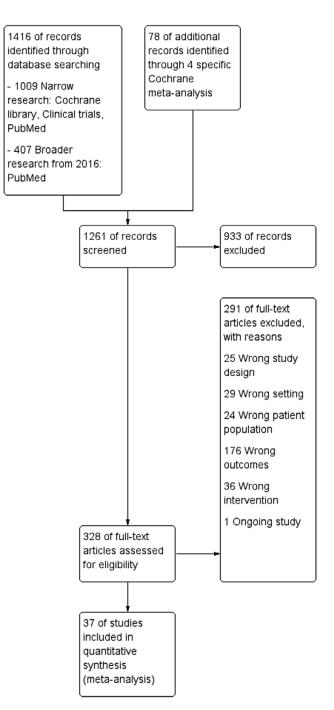


Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

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

Author Year Country	Population	Intervention (participants)	Duration of intervention: Follow-up—weeks	Control (participants)	Primary outcome criteria	Funding source
Ahluwalia <i>et al.</i> ³⁹ United States	600	Bupropion (300)	7:26	Placebo (300)	Prolonged abstinence (+exhaled CO)	National cancer Institute GSK for treatment
Anthenelli <i>et al.</i> 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 <i>et al.</i> ⁴¹ Europe, United States	746	Varenicline (376)	10–12: 52	NRT patch (370)	Continuous abstinence (+exhaled CO)	Pfizer
Ayeward <i>et al.</i> ⁴² United Kingdom	1792	NRT (880)	4:52	Behavioral intervention (860)	Continuous abstinence (+exhaled CO)	Institutional funding
Baker <i>et al.</i> 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 <i>et al.</i> ⁴⁴ Latin American, African and middle East Contries	583	Varenicline (390)	12: 24	Placebo (198)	Continuous abstinence (+exhaled CO)	Pfizer
Cinciripini <i>et al.</i> 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 <i>et al.</i> 46 Europe	335	Bupropion (221)	7:	Placebo (114)	Continuous Abstinence (+exhaled CO)	GSK
Ebbert <i>et al.</i> 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 <i>et al.</i> 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 <i>et al.</i> ⁵⁰ Norway, Sweden	431	Varenicline (218)	12: 26	Placebo (213)	Continuous abstinence (+salivary cotinine)	Pfizer
Fossati <i>et al.</i> ⁵¹ Italia	593	Bupropion (400)	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	- Bupropion (329) - Placebo (257)	Continuous abstinence (+exhaled CO)	Pfizer
Gonzales <i>et al.</i> 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 <i>et al.</i> ⁵⁴ Brazil	156	Bupropion (53)	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	Placebo (46)	Continuous abstinence (+exhaled CO)	Medical Research Institute of New Zealand have all received research grants from GlaxoSmithKline and Novartis

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
Hurt <i>et al.</i> ⁵⁶ United States	240	NRT (120)	8:52	Placebo (120)	Continuous abstinence (+exhaled CO)	Lederle Laboratories, NY
Jorenby <i>et al.⁵⁷</i> United States	889	Bupropion (243)	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	- Bupropion (340) - Placebo (340)	Continuous abstinence (+exhaled CO)	Pfizer
Lerman <i>et al.</i> 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 <i>et al.</i> 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 <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	- 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	Placebo (121)	Continuous abstinence (+exhaled CO + dosage)	Pfizer
Rennard <i>et al</i> . ⁶⁴ United States	659	Varenicline (5486)	12: 24	Placebo (165)	Continuous abstinence (+exhaled CO)	Pfizer
Richmond <i>et al.</i> 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 <i>et al.</i> ⁶⁶ United States	714	Varenicline (355)	12: 52	Placebo (359)	Continuous abstinence (+exhaled CO)	Pfizer
Rovina <i>et al.</i> 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 <i>et al</i> . ⁶⁹ Denmark	710	Bupropion (527)	7: 52	Placebo (180)	7 DPP (+exhaled CO)	GSK

CNS	Spectrums
-----	-----------

Continued

			Duration of intervention:			
Author Year Country	Population	Intervention (participants) Follow-up-weeks Control (participants)	Follow-up—weeks	Control (participants)	Primary outcome criteria	Funding source
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	Institutional funding
Tsai <i>et al.</i> 72 Korea and Taiwan	250	Varenicline (126)	12: 24	Placebo (124)	Continuous abstinence (+exhaled CO)	Pfizer
Wang et <i>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 et <i>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.	analysis. therapies; NRT, nicotin	e replacement therapy; 7 DPP, 7 da	y point prevalence abstir	nence.		

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

<u>Unique ID</u>	Author year	<u>D1</u>	<u>D2</u>	<u>D3</u>	<u>D4</u>	<u>D5</u>
1	Ahluwalia et. 2002	+	+	+	+	+
2	Anthenelli etal. 2016	+	+	+	+	+
3	Aubin et al. 2008	+	-	+	+	+
4	Aveyard et al. 2018	+	-	+	+	+
5	Baker et al. 2016	+	!	+	!	+
6	Bolliger et al. 2011	+	+	+	+	+
7	Cinciripini et al. 2013	!	!	+	+	!
8	Dalsgarð et al. 2004	+	+	+	!	+
9	Ebbert et al. 2013	+	+	+	+	+
10	Ebbert et al. 2015	+	+	+	+	+
11	Ebbert et al. 2016	+	+	+	+	+
12	Fagerström et al. 2010	+	+	+	+	+
13	Fossati et al. 2007	!	!	+	!	!
14	Gonzales et al. 2006	+	+	!	+	+
15	Gonzales et al. 2014	+	+	+	+	+
16	Haggsträm et al. 2006	+	!	+	+	!
17	Holt et al. 2005	+	!	-	+	!
18	Hurt et al. 1994	!	+	+	+	+
19	Jorenby et al. 1999	+	+	+	+	+
20	Jorenby et al. 2006	+	+	+	+	+
21	Lermann et al. 2015	!	+	+	+	+
22	McCarthy et al. 2008	+	+	+	+	+
23	Niaura et al. 2008	+	+	+	+	+
24	Nides et al. 2006	+	+	+	+	+
25	Oncken et al. 2006	+	+	!	+	+
26	Rennard et al. 2012	+	+	+	+	+
27	Richmond et al. 1994	!	+	+	+	+
28	Rigotti et al. 2010	+	+	+	+	+
29	Rovina et al. 2009	!	!	!	-	!
30	Sachs et al. 1993	+	+	!	+	+
31	Tønnesen et al. 2003	+	!	!	!	+
32	Tønnesen et al. 2013	+	+	+	+	+
33	Tsai et al. 2007	+	+	+	+	+
34	Tsukahara et al. 2010	!	-	+	+	+
35	Wang et al. 2009	!	!	!	!	+
36	Williams et al. 2007	!	!	+	+	+
37	Zhang et al. 2022	!	-	-	-	+

P. Vanderkam et al.

•	Low risk					
!	Some concerns					
•	High risk					
D1	Randomisation process					
D2	Deviations from the intended interventions					
D3	Missing outcome data					
D4	Measurement of the outcome					
D5	Selection of the reported result					

Overall

+ +

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

Dependent of Loging of	a) Insomnia							
1.2.1 Variations vs Placebo 7 99 9.5 1.31 D.95 1.76 Bellger at 2011 300 31 196 4.5% 1.35 1.00 5.00 Company at 2011 300 31 196 4.5% 1.35 1.00 5.10 Elever (at 2.001 21 10 5.6 1.35 1.00 5.71 Elever (at 2.006 349 4.4 4.4 7.7% 1.10 0.71, 4.00 Concasts at 1.2006 349 4.4 1.7% 1.10 0.75, 5.01 Concasts at 1.2006 4.10 1.21 1.45 1.55, 0.05, 7.3 Concasts at 1.2006 4.10 1.21 1.45 1.55, 0.05, 7.3 Nilse at 1.2001 4.2 2.55 1.37, 1.05, 0.5, 7.3 1.37, 1.05, 0.05, 7.3 Nilse at 1.2001 4.2 2.55 1.27, 0.00, 0.00, 7.5, 0.57 1.27, 0.00, 0.00, 7.5, 0.57 Tail works 5.00 1.10, 0.00, 7.1 1.05, 0.00, 7.5, 0.57 1.05, 0.00, 7.5, 0.57 Tail works 4.20	Study or Subgroup					Weight		
Archmenent et al. 2016 6 9 90 73 999 93% 13 199 93% 13% 13 19 0.95, 179 Checking et al. 2013 20 88 21 106 5.4% 137 10.83, 511 Checking et al. 2013 20 88 21 106 5.4% 137 10.83, 511 Checking et al. 2010 13 213 16 218 2.4% 12210.06, 523 Checking et al. 2016 43 244 124 2340 7.7% 1.106 (0.75, 5.60 Checking et al. 2016 17 244 10 2.45 3.4% 137 10.78, 358 Checking et al. 2016 17 244 10 2.45 3.4% 137 10.78, 358 Checking et al. 2016 17 244 121 5.4% 3221 187, 553 Checking et al. 2016 12 3 14 121 5.4% 3221 187, 553 Checking et al. 2016 14 2340 7.7% 1.106 (0.75, 5.60 Checking et al. 2016 14 2340 7.7% 1.106 (0.75, 5.60 Checking et al. 2016 14 2340 7.7% 1.106 (0.75, 5.60 Checking et al. 2016 14 121 5.4% 3221 187, 553 Checking et al. 2016 14 121 5.4% 3221 187, 553 Checking et al. 2016 14 121 5.4% 3221 187, 553 Checking et al. 2016 14 121 5.4% 3221 187, 553 Checking et al. 2016 14 123 549 12 12 18 4.8% 1221 11, 13, 100 Checking et al. 2016 14 120 51 14 121 5.4% 3221 187, 553 Checking et al. 2016 14 120 51 14 121 5.4% 3221 187, 583 Checking et al. 2016 14 120 51 14 121 5.4% 3221 187, 15, 331 Checking et al. 2016 14 120 51 14 120 54% 120 1000 12.2% 1.101 180, 148 Checking et al. 2016 14 120 51 14 120 54% 120 1000 12.2% 1.101 180, 148 Checking et al. 2016 14 120 50 13 14 100 62 2.2% 1.051 140, 241 Checking et al. 2016 14 120 50 13 14 120 56% 122 2.2% 1.051 140, 241 Checking et al. 2016 14 120 50 13 14 120 50 14 120 50% 1420 140 140 140 140 140 140 140 140 140 14			Total	Lvents	Total	Weight	m-n, Random, 55% Cr	M-H, Kandoli, 55% Cl
Cincerimp et al. 2013 20 86 21 106 6.4% 1.17 [0.52, 202 Elever et al. 2016 7 43 1 40 0.5% 7.47 [0.66, 60.32] Elever et al. 2016 17 43 1 40 0.5% 7.47 [0.66, 60.32] Provinces et al. 2014 17 2.49 10 2.45 3.4% 1.47 [0.75, 5.60] Occurs et al. 2016 19 24 23 42 23 40 7.7% 1.156 [0.67, 17.0] Lerman et al. 2006 49 123 14 121 5.4% 221 [0.75, 5.60] Occurs et al. 2016 19 123 14 121 5.4% 221 [0.75, 5.60] Occurs et al. 2016 19 123 14 121 5.4% 221 [0.75, 5.60] Chemonal et al. 2016 19 123 14 121 5.4% 221 [0.75, 5.60] Figett et al. 2010 42 2355 23 339 6.1% 1.356 [0.8, 1.27] Name et al. 2006 49 123 14 121 5.4% 221 [0.75, 5.60] Figett et al. 2010 42 2355 23 339 6.1% 1.356 [0.8, 1.40] Name et al. 2006 49 123 14 121 5.4% 221 [0.75, 5.60] Figett et al. 2010 42 2355 23 339 6.1% 1.356 [0.8, 1.40] Name et al. 2007 49 125 12 123 2.4% 221 [0.11, 3.64] Stotbal 2057 (0.5, 5.62] Figett et al. 2010 7 40 2050 (1.77) Total events 811 518 Heterogenety. Turk = 0.00; Chr = 2.07, d = 1.07 = 0.0005; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.00000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.0000; P = 00% Test for overall etcl. 2 - 5.1 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 5.1 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 1.3 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 1.3 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 1.3 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 1.3 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 1.3 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 1.3 07 + 0.000; P = 0.0% Test for overall etcl. 2 - 1.3 07 + 0.000; P = 0.000; P = 0.0% Test for overall etcl.			990	73	999	9.3%	1.31 [0.98, 1.76]	
Eber et al. 2015 60 74 91 94 742 85% 1.36 (11, 2, 17) Fageration et al. 2010 13 213 6 218 24% 2.22 (28, 6, 573) Fageration et al. 2010 13 213 6 218 24% 2.22 (28, 6, 573) Constants et al. 2016 14 248 2.23 (28, 776) 1.16 (0.74, 176) Loremon et al. 2016 14 248 2.24% 2.24% 2.22 (28, 6, 573) Loremon et al. 2016 14 248 2.24% 2.24	Bolliger et al. 2011	50	390	13	198	4.9%	1.95 [1.09, 3.51]	
Elbert et al. 2016 7 45 1 40 0.6% 7 1/27 [0.95, 69.23 Gonzales et al. 2010 49 244 44 344 7.7% 11.00 0.75, 160 Gonzales et al. 2010 49 244 44 344 7.7% 11.00 0.75, 160 Gonzales et al. 2010 49 243 419 128 414 128 11.05 0.86, 173 Gonzales et al. 2010 49 243 419 128 418 1128 11.05 0.86, 173 Niles et al. 2000 44 125 27 123 7.2% 1560 10.05, 241 Oncente et al. 2000 19 165 5 168 2.1% 2.04 0.77, 5.83 Remand et al. 2012 43 488 6 185 3.0% 2.23 11.05, 5.81 Remand et al. 2012 43 488 6 185 3.0% 2.23 11.05, 5.81 Remand et al. 2012 43 488 6 185 3.0% 2.23 11.05, 5.81 Remand et al. 2017 49 251 12 128 448 20 17% 11.06 0.75, 15.83 Statical et al. 2017 49 251 12 128 4.20 499 10.0.0% 1.24 11.30, 1.81 Table et al. 2017 49 251 12 128 4.20 49 210 2.2% 1.81 11.08, 2.14 Data levels 5 11 2.20 40 77, 5.83 Wang et al. 2008 80 378 77 370 2.2.8% 1.11 10.82, 1.43 Statical et al. 2012 80 378 77 370 2.2.8% 1.11 10.82, 1.43 Statical et al. 2015 149 420 138 418 2.26% 1.05 (0.81, 1.39 Autor et al. 2015 149 420 138 418 2.26% 1.05 (0.81, 1.39 Autor et al. 2015 149 420 138 418 2.26% 1.05 (0.81, 1.39 Autor et al. 2015 149 420 138 418 2.26% 1.05 (0.83, 1.27) Table remits 41.2016 04 242 33 31 Table remits 41.2016 04 242 33 Table remit et al. 2016 04 343 77 233 01.7% 1.05 (0.83, 1.41) Table remits 41.2016 04 242 33 Table remit et al. 2016 04 343 77 233 01.7% 10.00 00.00 07, 1.60% 1.33 (0.84, 0.84) Autor et al. 2015 149 420 138 418 2.26% 1.05 (0.83, 1.41) Table remit et al. 2016 04 343 77 233 01.7% 10.00 07.5 (0.59, 0.57) Table remit et al. 2016 04 343 77 233 01.7% 1.05 (0.84, 1.30) Concise et al. 2000 07 7 0.00 07 12 0.00 07.7 (0.97, 1.09 0.00 07.7 (0.93, 0.64, 0.27) Table remit et al. 2016 04 343 07 233 01.7% 1.05 (0.84, 0.26) Table remit et al. 2016 07 30 09 25.7% 1.24 (0.97, 1.58, 0.36) Table remit et al. 2016 07 30 09 25.7% 1.24 (0.97, 1.58, 0.36) Table remit et al. 2016 07 6 30 31 29 200 12.7% 1.24 (0.97, 1.58, 0.36) Table remit et al. 2010 07 73 340 4.45 1.7% 330 0.02, 4.13 (0.90, 2.45) Table remit et al. 2010 07 7	Cinciripini et al. 2013	20	86	21	106	5.4%	1.17 [0.68, 2.02]	
Fageration et al. 2010 13 213 6 218 2.4% 2.22 (0.06, 5.73) Gonzales et al. 2014 17 248 10 245 3.4% 1.57 (0.7, 3.56) Gonzales et al. 2014 17 248 10 245 3.4% 1.57 (0.7, 3.56) Gonzales et al. 2016 17 248 10 245 3.4% 1.57 (0.7, 3.56) Gonzales et al. 2016 18 13 143 218 113, 147 (0.7, 3.56) Gonzales et al. 2006 48 129 14 121 5.4% 3.22 (0.7, 7.56) Gonzales et al. 2010 12 43 646 185 3.23 3.89 6.1% 1.38 (0.15, 6.1) Figure et al. 2010 12 43 646 185 3.23 3.89 6.1% 1.38 (0.15, 6.1) Figure et al. 2010 14 12 15 113 147 (1.7, 8.1) Gonzales et al. 2010 15 113 14 (1.7, 7.1) Figure et al. 2010 148 2.59 112 128 4.2% 2.20 (1.1, 1.3, 6.0) William via 1.2007 148 2.59 112 128 4.2% 2.20 (1.1, 1.3, 6.0) Total events 11 618 Heterogenety, Tau* 0.05, Chr = 3.20, d. et 1.70 = 0.0000; P = 0.0% Test for overal effect 22 = 5.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test for overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test overal effect 22 = 3.1 (P = 0.0000); P = 0.0% Test overal effect 22 = 3.0 (P = 0.0); P = 0.0% Test overal effect 23 = 3.0 (P = 0.0); P = 0.0% Test overal effect 24 = 3.0 (P = 0.0); P = 0.0% Test overal effect 24 = 3.0 (P = 0.0); P = 0.0% Test overal effect 24 = 3.0 (P = 0.0); P = 0.0% Test overal effect 24 = 3.0 (P = 0.0); P = 0.0% Test overal effect 24 = 0.0 (P = 0.0); P = 0.0% Test overal effect 24 = 0.0 (P = 0.0); P = 0.0% Test overal effect 24 = 0.0 (P = 0.0); P = 0.0% Test overal effect 24 = 0.0 (P = 0.0); P = 0.0% Test overal effect 24 = 0.0 (P = 0.0); P = 0.0%								
Oricitade et al. 2000 40 94 944 7.7% 1.100 7.75, 1.60 Oricitade et al. 2006 40 343 42 340 7.7% 1.106 0.75, 1.50 Jornam et al. 2006 44 125 17 125 1.55 0.55, 1.20 Jornam et al. 2006 44 125 127 125 1.56 0.77, 1.55 Nices et al. 2006 44 125 127 123 1.26 0.55, 613 Removed et al. 2017 12 126 1.56 0.25, 613 0.55, 613 0.55, 613 Removed et al. 2007 10 128 1.75 1.50 0.25, 653 0.25, 613 0.44 1.56 0.25, 613 0.25, 614, 713 0.2								
Oracales et al. 2014 17 249 10 245 344% 1.57<								
Joeneby et al. 2006 # 49 43 42 340 7.7% 1.16 [0.72; 1.70] Naure stal. 2005 34 157 17 185 6.5% 1.377 1.26 1.25 (1.56 3.16) Naure stal. 2006 44 123 27 123 7.27 124 1.26 1.165 (0.58 1.27) Naure stal. 2012 44 148 16 125 6.9% 2.241 105 6.61 The stal. 2017 14 128 148 16 125 6.9% 2.241 105 6.61 The stal. 2017 14 128 148 16 125 6.9% 2.241 105 6.61 The stal. 2007 14 128 17 124 4.7% 1.10 1.06 0.202 William et al. 2007 49 251 12 128 4.8% 2.201 11.1 3.40 The stal. 2007 49 251 12 128 4.8% 2.201 11.1 3.40 The stal. 2007 49 251 12 128 4.8% 2.201 11.1 3.40 The stal. 2007 49 251 12 128 4.8% 2.201 11.1 3.40 The stal. 2007 49 251 12 128 4.8% 2.201 11.1 3.40 The stal. 2007 49 251 12 128 4.8% 2.201 11.1 3.40 The stal. 2007 49 251 12 128 4.8% 2.201 11.1 3.40 The stal. 2015 44 4.24 89 082 2.22% 1.41 10.05, 1.49 The stal 2016 44 123 16 16 12 2.0% 1.33 (0.68 1, 139 The stal. 2015 44 4.24 89 082 2.22% 1.43 (1.40, 0.88 1, 129 The stal. 2015 44 4.24 89 082 2.22% 1.43 (1.40, 0.88 1, 129 The stal. 2015 44 4.24 89 082 2.22% 1.43 (1.40, 2.41) The stal. 2015 44 4.24 89 082 2.22% 1.43 (1.40, 2.41) The stal. 2015 44 4.24 89 082 2.22% 1.43 (1.40, 2.41) The stal. 2015 44 4.24 89 082 2.22% 1.43 (1.40, 2.41) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 2.43) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 2.43) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.44 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.47 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.40 (1.40, 0.56) The stal. 2016 49 3.43 77 3.40 7.74 & 0.40 (1.40, 0.57) The stal. 2016 49 3.43 77 3.40 7.74 & 0.40 (1.40, 0.52) The stal. 2016 49 3.43 77 3.40 7.74 & 0.40 (1.40, 0.52) The stal. 2016 49 1.20 2.20 11.20 8.								
Lemma et al. 2016 142 42 00 136 418 112% 1.06 [0.85, 1.27] Nies et al. 2006 44 125 127 123 72% 1.60 [1.06, 2.41] Orchest al. 2001 44 125 127 123 72% 1.60 [1.06, 2.41] Orchest al. 2001 44 125 127 123 72% 1.60 [1.06, 2.41] Orchest al. 2001 44 125 127 123 72% 1.60 [1.06, 2.01] Wang et al. 2001 45 15 18 12% 2.44 83 2.51 [1.2, 1.53 1 Viana et al. 2007 44 2.51 12 12.64 4.88 2.51 [1.1, 3.64 1.53 1 Viana et al. 2007 45 2.51 12 12.12 4.88 2.51 [1.1, 3.64 1.53 1 Viana et al. 2007 45 2.51 12 12.12 4.88 2.51 [1.1, 3.64 1.53 1 Viana et al. 2008 80 376 71 370 22.8% 1.54 [1.3, 91 [1.1, 3.64 1.53 1] Viana et al. 2008 80 376 71 370 22.8% 1.54 [1.3, 91 [1.1, 3.64 1.53 1] Viana et al. 2016 91 91 006 2.22.2% 1.53 [1.4, 0.2, 4.1 12 [1.5, 1.49 1.53 1] Viana et al. 2016 91 91 006 2.22.8% 1.54 [1.4, 0.4, 1.1 2] Jubic viant 64 2.55 [1.6 - 0.0001) Table vents 42 331 1.54 [1.4, 0.4, 1.1 2] Jubic value (1.5, 0.5, 0.1 - 2.0, 0.5 - 2.0, 0.5 - 2.0, 1.53 [1.4, 0.4, 1.1 2] Jubic value (1.5, 0.5, 0.1 - 2.0, 0.5 - 2.0, 0.5 - 2.0, 0.5 - 0.5								_ _ _
Naura et al. 2006 34 157 17 155 55% 1.27 [1.15, 3.39] Misura et al. 2006 44 123 14 121 54% 3.22 [1.87, 5.53] Remand et al. 2010 42 356 27 328 1.00 (1.68, 2.41) Remand et al. 2010 42 356 27 328 0.1% 1.35 (1.05, 5.61) William et al. 2007 49 2.51 12 126 4.6% 2.01 (1.1, 3.84] Subtotal (55C) 01 550 4 499 0.00.9% 1.54 (1.30, 1.84] Subtotal (55C) 01 550 4 499 0.00.9% 1.54 (1.30, 1.84] Subtotal (55C) 01 550 4 499 0.00.9% 1.54 (1.30, 1.84] L22 Varancialmer value 42, 2.51 17 ($P = 0.00.00$); $P = 50\%$ Test for overail effect 22 = 51 17 ($P = 0.00.00$); $P = 50\%$ Test for overail effect 22 = 51 07 1 370 02 228 5 1.10 (1.10, 83, 1.46] Lermin et al. 2016 42 086 3 76 11 370 2288 1.10 (1.10, 83, 1.46] Lermin et al. 2015 44 240 136 222 223 1.33 (1.06, 2.17) Subtotal (55C) 147 2.20, 7, ff = 4 ($P = 0.0005$); $P = 00\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 00\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 00\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 00\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 00\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 00\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 00\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.84 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.80 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.80 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.80 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.80 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.80 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 1.80 ($P = 0.0005$); $P = 0\%$ Test for overail effect 22 = 0.00 ($P = 0.000$; $P = 0.000$; $P = 0.000$								+
Nies et al. 2006 44 125 27 123 7.2% 1.60 10.6, 2.41 1 Sheen et al. 2012 43 446 6 163 30% 2.43 10.5, 5.61 1.3, 5.03 1.45 11.3, 5.04 1.45 11.3, 5.04 1.45 11.3, 5.04 1.45 11.3, 5.04 1.45 11.3, 5.04 1.45 11.3, 5.04 1.45 11								_ _
Remark of al. 2012 43 486 6 195 30% 2.43 [10.65, 681] Tasi et al. 2007 19 126 17 124 47% 1.10 [10.00, 2.02] Tasi et al. 2007 9 221 12 38 48% 2.01 [1.11, 3.84] William et al. 2007 9 221 12 38 48% 2.01 [1.11, 3.84] William et al. 2007 9 221 12 38 48% 2.01 [1.11, 3.84] Hencognemb, Tasi = 0.05, 0.06 = 3.20, of = 17, $P = 0.000$; $P = 50\%$. Test for overall effect 2.2 5.11 ($P = 0.000$; $P = 50\%$. Test for overall effect 2.2 1.01 ($P = 0.000$; $P = 0.000$; $P = 50\%$. Test for overall effect 2.2 1.02 ($P = 0.000$; $P = 0.000$; $P = 50\%$. Test for overall effect 2.2 1.04 ($P = 0.000$; $P = 0.000$; $P = 0.000$, $P = 0.0000$, $P = 0.000$, $P = 0.0000$, $P = 0.00000$, $P = 0.0000$, $P = 0.0000$	Nides et al. 2006	44	125	27	123	7.2%		- - -
Right at 12010 42 355 23 359 61% 1.85 [1.13, 0.00] Wang et al. 2000 10 165 5 168 21% 2.04 (8.71, 5.83) Wang et al. 2000 10 165 5 168 21% 2.04 (8.71, 5.83) Wang et al. 2000 10 165 5 168 21% 2.04 (8.71, 5.83) Wang et al. 2000 10 165 5 168 21% 2.04 (8.71, 13, 8.4) Heterogreent, Tart=0.65, 0 and +17/P = 0.006); P = 50% Feat for overall effect Z = 5.11 ($P = 0.006$; P = 0.006; P = 50% Feat for overall effect Z = 5.11 ($P = 0.006$; P = 0.006; P = 50% Feat for overall effect Z = 5.11 ($P = 0.006$; P = 0.006; P = 50% Feat for overall effect Z = 5.11 ($P = 0.006$; P = 0.006; P = 50% Feat for overall effect Z = 0.07, of = 4 ($P = 0.006$; P = 00% Ease real 2.016 9 90 90 91 1006 23.22% 1.33 [1.40, 2.41] L2.2 Variant et al. 2016 94 424 90 682 23.2% 1.33 [1.40, 2.41] L2.2 Variant et al. 2016 94 424 90 682 23.2% 1.33 [1.40, 2.41] Ease real 2.016 90 G; ChP = 2.00, 07, F = 6 ($P = 0.0005$; P = 60% Teal for overall effect Z = 1.84 ($P = 0.07$) Teal events 2.00 40 3440 71 23.29 10.2 8.3% 0.75 [0.56, 0.97] Chick equal teal. 2016 94 93.3 11.25 92.65 1.05 [0.64, 0.84] Unremote tal. 2016 94 91 1006 72 999 25.7% 1.24 [0.82, 1.80] East et al. 2016 91 1006 72 999 25.7% 1.24 [0.82, 1.80] L2.2 Variancillar vs Burcpacion Heterogreent, Tau ² = 0.00; ChP = 2.06, df = 5 ($P = 0.0005$; P = 0% Teal for overall effect Z = 4.3 ($P = 0.0005$); P = 0% Teal for overall effect Z = 4.3 ($P = 0.0005$); P = 0% Teal for overall effect Z = 4.3 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 1.94 ($P = 0.0005$); P = 0% Teal for overall effect Z = 0 1.17, P = 2.66 Teal for overa	Oncken et al. 2006	48	129	14	121	5.4%	3.22 [1.87, 5.53]	
Tai di al 2007 19 126 17 124 47% 1.10 0.00, 202 William et 12,007 49 231 12 126 42% 2.01 (1.11, 5.84) Subtola (19%-C) 6 65.00 499 00.00, 15.21% 2.24 (0.17, 5.83) 2.01 (1.11, 5.84) Subtola (19%-C) 6 65.00 0.00, 17 - 50%, 1.06 (0.81, 1.39) William et 12, 2016 49 99 00 11 006 23.2% 1.105 (0.81, 1.39) William et 12, 2016 99 900 91 1006 23.2% 1.05 (0.83, 1.48) Subtola (19%-C) 3000 33 60 5.3% 6.52 (1.94, 2.18) Subtola (19%-C) 40 0000; 12.22% 1.11, 18, 14.81 Larman et 12, 2015 143 420 136 418 256% 1.05 (0.8, 1.81) Total events 41.2016 09 000 20, 7f = 40, 0000; P = 80%, 1.55 (0.8, 1.81) Total events 41.2016 000 000 33 61 00.04% 1.33 (0.89, 1.81) Total events 42.2 0.00 44 92 239 11.4% 0.64 (0.46, 1.20) Subtola (19%-C) 2.2392 2.239 10.23% 0.75 (0.58, 0.97) Withered it at, 2016 49 349 72 329 17.4% 0.67 (0.48, 0.94) Vities et 12, 2016 44 125 57 126 20.4% 0.75 (0.58, 0.97) Withered it at, 2016 49 349 72 329 17.4% 0.64 (0.46, 1.20) Subtola (19%-C) 2.2392 2.239 100.0% 0.33 (1.67, 0.58, 0.67) Subtola (19%-C) 2.2392 2.239 100.0% 0.75 (0.58, 0.67) Withered it at, 2016 49 349 72 329 17.4% 0.67 (0.58, 0.67) Subtola (19%-C) 2.2392 2.239 100.0% 0.73 (0.8, 0.44) Subtola (19%-C) 2.2392 2.239 100.0% 0.73 (0.8, 0.44) Subtola (19%-C) 2.2392 2.239 100.0% 0.73 (0.8, 0.48) Subtola (19%-C) 2.2392 2.239 100.24 1.24 (1.08, 1.81) Subtola (19%-C) 1.26 (1.9, 0.80) Subtola (19%-C) 1.26 (1.9, 0.90) Subtola (1.11, 1.12, 241) Subtola (19%-C) 2.2392 2.250 100.0% 1.27 (1.14, 1.10, 1.82) Subtola (19%-C) 2.2392 2.251 10.24 (1.11, 1.12, 241) Subtola (19%-C) 2.2392 2.227 128 6.5% 2.061 (1.11, 1.11, 1.20) Subtola (19%-C) 2.2392 2.228 1.27 (1.14, 1.10, 2.13) Subtola (19%-C) 2.2392 2.228 1.27 (1.14, 1.10, 2.13) Subtola (19%-C) 2.2392 2.228 1.24 (1.10, 1.12, 2.13) Subtola (19%-C) 2.2392 1.27 (1.12, 2.13) Subtola (Rennard et al. 2012	43	486	6	165	3.0%	2.43 [1.05, 5.61]	
Weing et al. 2000 10 165 5 168 21% 2.04 ($17, 16, 83$) Minima et al. 2007 40 251 12 126 48% 2.01 ($11, 13, 64$) 1.54 ($13, 0, 1.61$) 1.52 Variancian events 811 518 1.54 ($13, 0, 1.61$) 1.52 Variancian events 811 518 1.52 ($13, 0, 1.61$) 1.52 Variancian events 811 518 1.52 ($13, 0, 1.61$) 1.52 Variancian events 811 518 1.52 ($13, 0, 1.61$) 1.52 Variancian events 811 518 1.52 ($13, 0, 1.61$) 1.52 Variancian events 811 518 1.52 ($13, 0, 1.61$) 1.52 Variancian events 811 518 1.52 ($13, 0, 1.61$) 1.52 Variancian events 810 1.52 ($13, 0, 1.61$) 1.52 Variancian events 810 1.52 ($13, 0, 1.61$) 1.52 Variancian events 810 1.52 ($13, 0, 1.61$) 1.53 ($13, 0, 1.61$) 1.53 ($13, 0, 1.61$) 1.54 ($13, 0, 1.61$) 1.55 ($15, 1.61$) 1.53 ($15, 0, 1.61$) 1.53 ($10, 0, 1.61$) 1.54 ($14, 0, 1.62$) 1.55 ($15, 0, 0, 0, 7$) 1.53 ($10, 0, 1.61$) 1.54 ($13, 0, 1.61$) 1.55 ($15, 0, 0, 0, 7$) 1.53 ($10, 0, 1.61$) 1.54 ($13, 0, 1.61$) 1.54 ($13, 0, 1.61$) 1.55 ($15, 0, 0, 0, 7$) 1.55 ($15, 0, 0, 2, 7$								
William et al. 2007 4 8 251 12 122 4 48% Statistical (25% C) 5 13 5 14 5 15 5 14 5 15 5								_
Subtola (95% C) 5530 499 100.0% 1.54 (1.30, 1.81) Heterogenelly: Tat" = 0.05; (h ² = 34.20, df = 17 (P = 0.008); F = 50%; Factor overall effect 2 = 5.11 (P < 0.0001) 1.2.2 Varencine vs NKT Winner at .2006 95 09 99 19 1006 23.2% 1.10 (8.0.1, 1.38) Heterogenelly: Tat" = 0.02; (h ² = 2.0.7, df = 4.0 P = 0.0005); F = 80%; Factor overall effect 2 = 1.81 (P < 0.0005); F = 80%; Test for overall effect 2 = 1.81 (P < 0.0005); F = 80%; Test for overall effect 2 = 1.81 (P < 0.0005); F = 80%; Test for overall effect 2 = 1.84 (P = 0.0005); F = 80%; Test for overall effect 2 = 1.84 (P = 0.0005); F = 80%; Test for overall effect 2 = 1.84 (P = 0.0005); F = 80%; Test for overall effect 2 = 1.84 (P = 0.0005); F = 80%; Test for overall effect 2 = 1.84 (P = 0.0005); F = 80%; Test for overall effect 2 = 1.84 (P = 0.0005); F = 0.84, F = 0.05; Test for overall effect 2 = 1.84 (P = 0.0005); F = 80%; Test for overall effect 2 = 1.84 (P = 0.0005); F = 0.84, F = 0.05, F = 0.15, F = 0.84, F								
Total events 811 518 Herrograme(T, Tur) = 0.05, Ch ² = 2.13, Ch ² = 0.00, Ch ² =		48		12				
Helerogenety: Tar = 0.05; Ch ² = 34.20, df = 17 ($\ell = 0.008$); $\ell = 508$, Testfor overall effect $Z = 5.11$ ($\ell = 0.008$); $\ell = 508$, Testfor overall effect $Z = 5.11$ ($\ell = 0.008$); $\ell = 508$, tarticle vs. NIT Anthenell et al. 2016 95 (90 91 1006 23.2% 1.06 [0.81, 1.39] Anthenell et al. 2018 94 94 97 228 1.111 [0.83, 1.48] Subtoal (95% C) 340 94 3.366 5.38 0.521 94, 21.85] Subtoal (95% C) 3409 1.3316 100.06 1.33 (9.08, 1.81] Toal events 4.22 381 Helerogenety: Tar = 0.00; Ch ² = 20.07, df = 4 ($\ell = 0.0005$); $\ell = 908$, Testfor overall effect $Z = 1.84$ ($\ell = 0.07$) Tal events 2.20 84 3.2 2.28 10.06 1.33 (0.68, 0.81] Toal events 2.20 8.3 10.7 (df = 4 ($\ell = 0.0005$); $\ell = 0.00$, Testfor overall effect $Z = 1.84$ ($\ell = 0.0005$); $\ell = 0.80$, $\ell = 0.80$		011	5050	610	4999	100.0%	1.54 [1.50, 1.61]	•
Test for overall effect: $Z = 5.11$ ($P < 0.0001$) 1.2.2 Varencicine vs NRT when ell at 2.006 90 976 71 370 22.8k 1.06 [0.81, 1.39] 1.11 [0.83, 1.48] When et 2.008 90 93 90 65 53% 6.52 [1.9, 2.185] 1.31 [1.40, 2.11] 1.32 [0.96, 1.27] Total version 1.2.3 [0.96, 1.21] 1.2.3 [0.96, 1.21] 1.2.4 [0.92, 1.66] 1.2.4 [0.97, 1.06] 1.2.5 [0.96, 0.97] 1.2.4 [0.97, 1.06] 1.2.4 [0.97, 1.06] 1.2.4 [0.97, 1.06] 1.2.4 [0.97, 1.06] 1.2.4 [0.97, 1.06] 1.2.4 [0.97, 1.06] 1.2.5 [0.96, 2.98] 1.2.4 [0.97, 1.95, 1.00] 1.2.5 [0.96, 2.98] 1.2.6 [0.96, 2.98] 1.2.6 [0.96, 2.98] 1.2.6 [0.96, 2.98] 1.2.6 [0.96, 2.98] 1.2.7 [0.96, 2.98] 1.			1 20 df		- 0 000	V- IZ - 600	ĸ	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $					- 0.000), I== 505	10	
where let al 2016 9 5 980 91 1006 23.2% 1 06 [0.81, 1.39] ways of al. 2018 20 880 3 860 5.3% 552 [1.94, 21.86] baser et al. 2016 94 424 80 662 23.2% 111 [10.81, 1.48] terms et al. 2015 143 420 136 418 25.6% 1.05 [0.86, 1.27] subtoal (95% (C) 3 300 3316 100.0% 1 133 [0.86, 1.27] baser et al. 2016 95 900 126 989 30.1% where list 2006 44 343 72 329 17.4% 0.67 [0.46, 0.39] biorchip et al. 2006 44 343 72 329 17.4% 0.67 [0.46, 0.39] biorchip et al. 2006 44 343 72 329 17.4% 0.67 [0.46, 0.39] biorchip et al. 2006 44 343 72 329 17.4% 0.67 [0.46, 0.39] biorchip et al. 2006 44 343 72 320 10.0% biorchip et al. 2006 44 125 57 125 20.4% 0.67 [0.46, 0.39] biorchip et al. 2006 44 1325 57 15.3% 1.24 [0.82, 1.66] biorchip et al. 2013 0 25 1 27 0.3% cost al. 2010 Chi = 2.06, dr = 5 (P = 0.46, P = 0% Fest for overall effect $Z = 1.39 (P - 0.0001)$ 12.4 NRT vs Placebo subtoal (9% C) 2 53 000 12.7% biorchip et al. 2013 0 25 1 27 0.3% biorchip et al. 2013 0 22 1 0.06 63 5.1% biorchip et al. 2013 0 22 1 0.05 (1.23 0.02, 8.43) test for overall effect $Z = 1.30 (P - 0.000)$ 12.4 NRT vs Placebo biovenite et al. 2017 132 102 2.1 106 6.3% 159 [0.80, 2.56] biorchip et al. 2016 72 33 04 44 410.1% 155 [1.06, 2.23] biorchip et al. 2016 72 33 04 44 10.1% 159 [1.08, 2.56] biorchip et al. 2007 69 400 12 139 4.4% 159 [1.08, 2.56] biorchip et al. 2006 77 53 9 51 3.3% 289 [151, 553, 3.06] biorchip et al. 2006 77 53 9 51 3.3% biorchip (9% C) 2 4116 128 989 73 99% 232 100.0% 1.44 [1.14, 1.46, 1.50] biorchip et al. 2006 77 53 9 51 3.3% biorchip (9% C) 2 43 73 243 52.7% 1.44 [1.08, 1.37] biorchip et al. 2006 77 53 9 51 3.3% biorchip et al. 2006 77 53 9 51 3.3% biorchip et al. 2006 77 53 9 51 3.3%	restion overall ellect. Z -	3.11 (r S	0.00001	,				
Anheneli et al. 2016 95 980 911 1006 72.2% 1 0.60 [0.81, 1.39] Aveyard et al. 2018 20 880 3 860 5.3% 6.52 [1.94, 21.65] Bearer et al. 2016 142 424 80 662 23.2% 1.38 [1.40, 2.41] Lerman et al. 2015 143 420 136 418 2.56% 1.05 [1.06, 1.27] Subtotal (95% C) 4 3309 3 381 100.0% 1.33 [0.98, 1.81] Total events 432 3381 Heterogeneity: Tau" = 0.09; Ch" = 2.07; df = 4 (P = 0.0005); P = 0%. Test for overall effect Z = 1.44 (P = 0.07) 1.2.3 Varencicine vs Bupropion Anheneli et al. 2016 95 980 126 989 30.1% 0.75 [0.50, 0.67] Christipher et al. 2016 95 980 126 989 30.1% 0.75 [0.50, 0.67] Christipher et al. 2016 95 980 126 989 30.1% 0.75 [0.57] 0.59] Christipher et al. 2016 95 980 126 989 30.1% 0.75 [0.57] 0.59] Christipher et al. 2016 94 125 57 126 20.4% 0.79 [0.57] 1.67] Zhang et al. 2006 44 125 57 128 20.4% 0.79 [0.57] 1.67] Subtotal (95% C) 2.299 24 480 4% 0.79 [0.57] 1.67] Subtotal (95% C) 2.299 24 33 15 20.2% 1.56] [1.57] Total events 282 383 Heterogeneity: Tau" = 0.00; Ch" = 2.06, df = 5 (P = 0.46); P = 0% Test for overall effect Z = 4.39 (P < 0.0001) 1.2.4 NRT vs Placebo Anheneli et al. 2016 91 1006 73 999 25.7% 1.24 [0.82, 1.66] Lerman et al. 2015 138 418 133 408 35.1% 1.00 [0.82, 1.21] Lerman et al. 2015 138 418 133 408 35.1% 1.00 [0.82, 1.21] Lerman et al. 2015 139 418 133 408 35.1% 1.00 [0.82, 1.21] Lerman et al. 2015 139 418 133 408 35.1% 1.00 [0.82, 1.21] Lerman et al. 2016 128 989 73 999 13.2% 1.74 [1.32, 2.29] Total events 222 318 44 44 10.1% 1.71 [1.21, 2.41] Heterogeneity: Tau" = 0.02; Ch" = 1.26, gf = 5 (P = 0.15); P = 38% Test for overall effect Z = 1.90 (P = 0.00) 1.2.6 Bupropion vs Placebo Anheneli et al. 2016 122 29 300 62 300 12.7% 1.42 [1.07, 1.88] Anheneli et al. 2016 122 308 44 44 10.1% 1.71 [1.21, 2.41] Heterogeneity: Tau" = 0.02; Ch" = 1.76, gf = 1.39; P = 0.47; P = 38% Test for overall effect Z = 1.90 (P = 0.00) 1.2.6 Bupropion vs Placebo Anheneli et al. 2006 77 3.99 13.2% 1.74 [1.07, 1.88] Anheneli et al. 2006 77 3.99 13.3% 1.71 [1.21, 2.41] Heterogeneity: T	1.2.2 Varenicline vs NRT	Г						
Aubin et al. 2008 80 376 71 370 228% 1.111 [03] 1.46 Weyerd et al. 2016 94 424 80 662 32% 55% 5521.94, 21.05 Baker et al. 2016 94 424 80 662 23.2% 1.38 [14.0, 2.41] Lemma et al. 2015 143 420 136 418 256% 1.05 [0.6, 1.27] Subtotal (95% C) 3090 3316 100.0% 1.33 [0.98, 1.81] Total events 432 381 Heterogenety: Tar"= 0.00; Ch"= 2.07; df = 4 (P = 0.0005); P = 00% Test for overall effect Z = 1.84 (P = 0.0005); T = 00% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.94 (P = 0.0005); T = 0.94); P = 0% Test for overall effect Z = 1.91 (P = 0.94); P = 0% Test for overall effect Z = 1.91 (P = 0.94); P = 0% Test for overall effect Z = 1.91 (P = 0.94); P = 0% Test for overall effect Z = 1.91 (P = 0.94); P = 0% Test for overall effect Z = 1.91 (P = 0.95); P = 38% Test for overall effect Z = 1.91 (P = 0.92); P = 0% Test for overall effect Z = 1.91 (P = 0.92); P = 0% Test for overall effect Z = 1.91 (P = 0.90); P = 0% Test for overall effect Z = 0.02 (P = 0.15); P = 38% Test for overall effect Z = 0.10 (P = 0.00); 127 %; 1.42 [1.07, 1.88] Automether tal 2.005 6 72 329 41 324 527 %; 1.42 [1.00, 1.82] Automether tal 2.006 6 72 329 41 324 527 %; 1.42 [1.00, 1.82] Automether tal 2.006 72 329 41 324 327 85 328 1111 11 157 12 Defender tal 2.006 72 122 72 13 8.6% 328 1111 11 157 12 Defender tal 2.006 72 423 37 12 428 5100.006; 1.44 111, 111, 110, 130 140 Total events 33 32 100 243 57 32 43 57 %; 1.41 [1.09, 1.82] Automether tal 2.006 77 128 0.00			990	91	1006	23.2%	1.06 [0.81, 1.39]	+
weysard tal. 2018 20 800 3 960 5.3% 6 52 (1.94, 2): 65 Barker et al. 2015 142 424 80 662 23.2% 138 (1.40, 2.41) Lerman et al. 2015 143 420 136 418 25.6% 1.05 [0.68, 1.27] 1.33 [0.98, 1.81] Total events 432 381 Heterogeneity: Tarue 20.07, df = 4 (P = 0.0005); F = 80% Test for overall effect Z = 1.84 (P = 0.07) 12.3 Varencicline vs Burpropion Anthenell et al. 2016 96 90 126 989 30.1% 0.75 [0.59, 0.97] Cinctripni et al. 2016 96 90 126 989 30.1% 0.75 [0.59, 0.97] Cinctripni et al. 2016 94 343 72 329 17.4% 0.67 [0.48, 0.44] Jorency et al. 2006 44 343 72 329 17.4% 0.67 [0.48, 0.44] Jorency et al. 2006 44 125 67 128 20.4% 0.74 [0.46, 1.20] Oxoralse et al. 2006 44 125 67 128 20.4% 0.77 [0.56], 1.67] Statotal (9% C) 223 23 233 Heterogeneity: Tarue - 0.00; Chi = 2.06, df = 5 (P = 0.44); P = 0% Test for overall effect Z = -1.39 (P - 0.0001) 12.4 MRT vs Placebo Antheneit et al. 2013 0 25 1 27 0.5% 0.36 [0.02, 0.43] Marinet et al. 2016 91 1006 73 999 25.7% 1.24 [0.92, 1.66] Morenti et al. 2013 0 25 1 27 0.5% 0.36 [0.02, 0.43] Heterogeneity: Tarue - 0.00; Chi = 2.06, df = 5 (P = 0.44); P = 0% Test for overall effect Z = -1.39 (P - 0.0001) 12.4 MRT vs Placebo Antheneit et al. 2013 0 25 1 27 0.5% 0.36 [0.02, 0.43] Marinet et al. 1905 13 21 129 2.2% 144 [0.1%; 1.71 [0.21, 2.25] Morenty et al. 1995 132 20 21 106 6.2% 1.59 [0.16]; 1.53] Heterogeneity: Tarue - 0.02; Chi = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect Z = -1.90 (P = 0.00) 12.2 Burpropion vs MRT Antheneit et al. 2006 72 53 9 51 3.5% 289 [15.5 52] Heterogeneity: Tarue - 0.02; Chi = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect Z = 0.40 (P = 0.000) 12.7 Burpropion vs MRT Antheneit et al. 2006 72 53 9 51 3.5% 2.58 [1.17, 11.53] Heterogeneity: Tarue - 0.02; Chi = 1.74 0, (P = 0.17); P = 268 Test for overall effect Z = 0.40 (P = 0.000) 12.7 Burpropion vs MRT Antheneit et al. 2006 72 2.39 44 44 40 9.5% 1.71 [1.21, 2.43] Heterogeneity: Tarue - 0.02; Chi = 1.76 0, (H = 0.99); F = 6% Test for overall effect Z = 0.				71				+ -
Baker et al. 2016 94 4 24 00 662 23.2% 1.83 [1.40, 2.41] Lemman et al. 2015 143 240 135 418 256% 1.50 [0.68, 1.27] Subtotal (95% C) 3090 3316 100.0% 1.35 [0.08, 1.81] Total events 432 381 Heterogenety: Tar*= 0.09; Ch*= 2.0.7; df = 4 (P = 0.0005); F = 0.0% Test for overall effect 2 = 1.34 (P = 0.07) 12.3 Varencificine vs Bupropion Anthenelli et al. 2016 95 990 126 989 30.1% 0.75 [0.59, 0.97] Cincripni et al. 2016 240 349 72 320 17.4% 0.46 [0.46, 0.89] Jonenky et al. 2006 44 349 72 320 17.4% 0.46 [0.46, 0.89] Jonenky et al. 2006 44 343 72 23 240 17.4% 0.46 [0.46, 0.89] Jonenky et al. 2006 44 343 72 2320 17.4% 0.46 [0.46, 0.89] Jonenky et al. 2006 44 343 72 2320 17.4% 0.47 [0.46, 0.84] Heterogenety: Tar*= 0.00; Ch*= 2.06, df = 5 (P = 0.48); P = 0% Test for overall effect Z = 4.39 (P = 0.0001) 12.4 NRT vs Placebo Anthenelli et al. 2016 91 1006 73 999 25.7% 0.124 [0.92, 1.66] Lemma et al. 2016 11 165 125 157 15.9% 1.56 [1.06, 2.58] Jonenky et al. 2006 144 113 5 107 2.7% 0.78 [0.27, 1.24] Lemma et al. 2015 138 418 133 408 35.1% 1.00 [0.82, 1.21] Subtotal (9% C) 1901 1857 100.0% 1.23 [0.02, 1.63] Lemma et al. 2015 128 940 24 444 10.1% 1.42 [1.07, 1.88] Withenell et al. 2016 126 987 399 13.2% 1.42 [1.07, 1.88] Withenell et al. 2016 127 2.32 44 44 41 10.1% 1.77 [1.27, 2.29] Heterogenety: Tar*= 0.02; Ch*= 6.11, df = 5 (P = 0.15); P = 38% Test for overall effect Z = 1.30 (P = 0.05) 12.6 Bupropion vs Placebo Natureal et al. 2006 77 53 9 51 33% 2.88 [1.5, 52] Jonenky et al. 2008 72 53 9 51 33% 2.88 [1.5, 52] Jonenky et al. 2006 77 53 9 51 33% 2.88 [1.5, 52] Jonenky et al. 2006 77 53 9 51 33% 2.89 [1.5, 52] Jonenky et al. 2006 77 53 9 51 33% 2.89 [1.5, 52] Jonenky et al. 2006 77 2.32 44 44 44 10.1% 1.71 [1.71, 2.43] Heterogenethy et al. 2008 72 52 71 27 180 8.3% 3.58 [1.61, 0.3] Withereal effect Z = 3.07 (P = 0.0001) 12.7 Bupropion vs Placebo Nitwes et al. 2006 77 2.22 71 2.48 50% 2.50 [1.44, 1.33, 2.13] Jonenky et al. 2006 77 2.22 71 2.48 50% Contraise et al. 2007 126 57 2.77 80 8.3% 3.	Aveyard et al. 2018							
Subtotal (95% C) 3090 3316 100.0%, 1.33 [0.98, 1.91] Heterogeneity: Tau* 0.00; CN* = 20.07, df + 4 (P = 0.0005); P = 80% Test for overall effect 2 = 1.84 (P = 0.07) Anthenelli et al. 2016 96 990 126 998 30.1% Anthenelli et al. 2016 96 990 126 998 30.1% Oracle set al. 2006 49 349 72 329 17.4% 0.64 (0.46, 0.89] Jonenby et al. 2006 49 343 72 320 17.4% 0.64 (0.46, 0.89] Jonenby et al. 2006 49 343 72 320 17.4% 0.64 (0.46, 0.89] Jonenby et al. 2006 49 343 72 320 17.4% 0.64 (0.46, 0.84] Jonenby et al. 2006 49 343 72 320 17.4% 0.64 (0.46, 0.84] Jonenby et al. 2006 49 343 72 329 72 85 100.0% 0.73 (0.64, 0.84] Jonenby et al. 2006 49 343 72 329 73% 1.24 (0.92, 1.66] Heterogeneity: Tau* 0.00; CN* = 2.06, df = 5 (P = 0.94); P = 0% Test for overall effect Z = 4.39 (P < 1.000) 1.2.4 NRT vs Placebo Anthenelli et al. 2015 136 418 133 408 36.1% 1.00 (0.82, 1.21] Subtotal (95% C) 199 73 324 31 159 20.2% 1.64 (1.06, 2.23] Lerman et al. 2015 136 418 133 408 36.1% 1.00 (0.82, 1.21] Subtotal (95% C) 1991 1857 100.0% 1.23 (0.99, 1.53] 1.24 (10.7, 1.88] Anthenelli et al. 2016 126 099 73 399 12.2% 1.42 (1.07, 1.88] Anthenelli et al. 2016 126 099 73 399 13.2% 1.42 (1.07, 1.88] Anthenelli et al. 2016 126 099 73 399 13.2% 1.42 (1.07, 1.88] Anthenelli et al. 2016 126 099 73 399 13.2% 1.42 (1.07, 1.88] Anthenelli et al. 2016 126 099 73 399 13.2% 1.42 (1.07, 1.88] Anthenelli et al. 2016 126 099 73 399 13.2% 1.42 (1.07, 1.88] Anthenelli et al. 2006 67 72 39 61 3.3% 2.80 (1.5, 5.52] Anthenelli et al. 2006 72 329 44 44 10.1% 1.74 (1.32, 2.29] 4.4% Corstle verts 2 4.1 099 (1.2, 2.4% 48 0.1% 3.58 (1.60, 0.247] 4.4% Corstle verts 2 4.2006 71 22.92 (1.16, 6.2% 1.56 (1.09, 2.56] Anthenelli et al. 2006 72 329 44 44 0.1% 3.58 (1.60, 0.247] 4.4% Corstle verts 2 4.2006 71 22.92 (1.16, 6.2% 1.56 (1.09, 2.56] Anthenelli et al. 2006 72 38 9 44 (1.74, 8.17, 11, 11, 1.71] 4.4% Corstle verts 2 4.2006 71 22.92 (1.16, 6.2% 1.44 (1.11, 1.10, 1.30] 4.4% Corstle verts 2 4.2006 07 12.82 72.83 (1.6, 7.78)		94	424	80	662	23.2%		
Total events 422 381 Heterogeneits 20.07, df = 4 (P = 0.0005); P = 80% Testfor overall effect Z = 1.84 (P = 0.007) 12.3 Varencline vs Bupropion Anhenelli et al 2015 96 900 126 988 30.1% 0.75 (0.59, 0.87) Cincripni et al. 2016 94 313 72 320 17.4% 0.64 (0.46, 0.80) Cincripni et al. 2006 44 313 72 320 17.4% 0.64 (0.46, 0.80) Cincripni et al. 2006 44 313 72 320 17.4% 0.67 (0.56, 1.67) Stabiobal (95% C) 22 392 22 323 Heterogeneits 71 2016 90.6 (df = 5 (P = 0.84); P = 0% Testfor overall effect Z = 4.39 (P < 0.0001) 12.4 NUT vs Placebo Anhenelli et al. 2015 91 1006 73 909 25.7% 0.38 (0.02, 8.43) Heterogeneits 71 2015 91 1006 73 909 25.7% 0.38 (0.02, 8.43) Heterogeneits 71 2015 91 1006 73 909 25.7% 0.38 (0.02, 8.43) Heterogeneits 71 2015 91 1006 73 909 25.7% 0.38 (0.02, 8.43) Heterogeneits 71 2015 91 1006 73 909 25.7% 0.78 (0.52, 12.1) Sache et al. 2003 44 113 5 107 2.7% 0.78 (0.52, 12.1) Sache et al. 2005 44 113 5 107 2.7% 0.78 (0.52, 12.1) Sache et al. 2005 13 64 18 133 408 35.1% 0.00 (0.82, 12.2) Total events 0.45 20 Total events 0.45 20 Total events 0.45 20 Heterogeneits 71 20.0; Ch = 11, df = 5 (P = 0.15); P = 38% Testfor overall effect Z = 1.90 (P = 0.06) 12.8 Rupropion vs Placebo Anhenelli et al. 2015 126 60 62 300 12.7% 1.42 (1.07, 1.88) Anhenelli et al. 2015 126 21 1.46 6.5% 1.55 (1.50, 2.56) Designare et al. 2008 72 329 44 344 10.1% 1.71 (1.2, 2.42) Heterogeneits 71 20.0; Ch = 1.0, df = 1.0; P = 3.9% Testfor overall effect Z = 1.90 (P = 0.00; 1.2% 1.42 (1.07, 1.88) Anhenelli et al. 2005 72 329 44 344 10.1% 1.71 (1.2, 2.42) Heterogeneits 71 2005 86 229 10 0.21 2.32 (1.55, 52) Heterogeneits 71 2005 86 2.32 (1.63, 2.56) Designare et al. 2006 72 329 44 344 10.1% 1.71 (1.2, 2.42) Heterogeneits 71 (0.00; Ch = 1.70; 0.00; 1.48 (1.63, 2.21) Heterogeneits 71 (0.00; Ch = 0.00; 1.22 21 22 21 00.0% 1.86 (1.63, 2.21) Heterogeneits 71 (0.00; Ch = 0.00; 1.22 21 00.0% 1.86 (1.63, 2.21) Heterogeneits 71 (0.00; Ch = 0.00; 1.44 (0.00; 1.44 (1.10; 0.182) Heterogeneits 71, 70, 0.0; Ch = 0.		143		136			1.05 [0.86, 1.27]	†
Heterogeneity: Tau" = 0.02; Ch" = 20.07, df = 4 (P = 0.0005); P = 80% Test for overall effect Z = 1.84 (P = 0.07) Anthenelli et al. 2016 95 900 126 988 30.1% 0.75 (10.50, 0.87) Cincripini et al. 2013 20 86 32 2012 8.3% 0.74 (10.46, 12.01) Cincripini et al. 2006 49 349 72 329 17.4% 0.64 (0.46, 0.89] Jonenhy et al. 2006 44 125 57 125 20.4% 0.79 (10.57, 10.6) Jonenhy et al. 2006 49 343 72 2350 100.0% 0.73 (10.54, 0.84] Total events 222 25 499 24 446 6.4% 0.97 (10.55, 10.7) Total events 222 3250 100.0% 0.73 (0.64, 0.84] Total events 222 333 1155 20.2% 1.24 (0.92, 1.66] Jonenhy et al. 2016 91 1006 73 989 25.7% 1.24 (0.92, 1.66] Law and 2.000 Ch" = 2.06, df = 5 (P = 0.84); P = 0% Test for overall effect Z = 4.33 (P < 0.0001) 1.2.4 NRTV se flassebo Anthenelli et al. 2015 91 1006 73 989 25.7% 1.24 (0.92, 1.66] Jonenhy et al. 2015 91 1006 73 989 25.7% 1.24 (0.92, 1.66] Law and 2.015 136 418 133 408 35.1% 1.00 (10.22, 1.21] Jonenhy et al. 2015 91 1006 73 989 25.7% 1.24 (0.92, 1.66] Jonenhy et al. 2015 91 1005 71 0.05% 1.23 (0.99, 1.53) Total events 345 100 2.2% 1.54 (1.00, 2.23) Law and 2.25 (0.0001) 1.2.6 Rupropion vs Placebo Anthenelli et al. 2015 91 1006 73 999 13.2% 1.74 (1.00, 2.23) Total events 345 100 2.7% 1.23 (0.99, 1.53) Total events 345 100 2.7% 1.23 (0.99, 1.53) Total events 345 100 2.7% 1.23 (0.99, 1.53) Total events 41 1989 41 13 5 107 2.7% 1.24 (1.07, 1.88] Anthenelli et al. 2015 72 39 84 446 1.7% 3.01 (1.11, 8.17) Jonenhy et al. 2006 72 329 44 344 10.1% 1.71 (1.2, 2.43] Matheset at 1.999 103 2.43 31 159 9.5% 1.36 (1.00, 2.33) Jonenhy et al. 2006 77 126 27 123 8.6% 2.00 (1.40, 3.03) Rowina et al. 2006 77 126 27 123 8.6% 2.00 (1.40, 3.03) Total events 036 383 Heterogeneit, Total of 158 100, 0.47 17, 153, 3.08] Jonenhy et al. 2006 77 126 27 123 8.6% 2.00 (1.40, 3.03) Total events 036 383 Heterogeneit, Total of 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect Z = 3.84 (P = 0.0001) 1.27 Bupropion vs NTA Anthenelli etal. 2016 126 998 91 1006 47 3% 1.44 (1.00, 1.82]			3090		3316	100.0%	1.33 [0.98, 1.81]	•
Test for overall effect Z = 1.84 (P = 0.07) 12.3 Varenicline vs Bupropion Antheneli et al. 2015 96 990 126 989 30.1% 0.75 (0.50, 0.97) Oracle et al. 2006 44 343 72 240 17.4% 0.64 (0.46, 0.89) Oracle et al. 2006 44 343 72 240 17.4% 0.67 (0.46, 0.84) Jonenby et al. 2006 44 343 72 240 17.4% 0.67 (0.46, 0.84) Tolal events 222 333 Heterogeneity: Test 0.00; Ch ² = 206 (df = 5 (P = 0.64); P = 0.64); P = 0.64 Tolal events 222 333 Heterogeneity: Tau'e 0.00; Ch ² = 206 (df = 5 (P = 0.64); P = 0.64); P = 0.64); P = 0.64 Tolal events 2016 91 1006 73 999 25.7% 0.36 (100, 2.16) Tolal events 2016 91 1006 73 999 25.7% 0.36 (100, 2.16) Tolal events 2016 91 1006 73 999 25.7% 0.36 (100, 2.16) Tolal events 2016 91 1006 73 999 25.7% 0.36 (100, 2.23) Larman et al. 2015 91 1006 73 999 25.7% 0.76 (102, 2.26) Larman et al. 2016 91 1006 73 999 25.7% 0.76 (102, 2.23) Larman et al. 2016 91 1006 73 999 25.7% 0.76 (102, 2.23) Larman et al. 2016 91 1006 73 999 25.7% 0.76 (102, 2.23) Larman et al. 2016 91 1006 73 999 25.7% 0.76 (102, 2.26) Larman et al. 2016 91 1006 73 999 25.7% 0.76 (102, 2.27) Subtolar (95% Ct) 1991 1857 100.0% 1.23 (109, 1.53) Tolal events 345 268 Heterogeneity: Tau'e 0.02; Ch ² = 0.16); P = 38% Test for overall effect Z = 1.90 (P = 0.06) 12.6 Bupropion vs Placebo Antheoneli et al. 2015 126 989 73 999 13.2% 1.74 (132, 2.29) Tolal events 345 268 Heterogeneity: Tau'e 0.02; Ch ² = 0.17); P = 38% Test for overall effect Z = 1.90 (P = 0.06) 12.6 Bupropion vs Placebo Antheoneli et al. 2007 68 44 64 1.7% 301 (111, 81, 71) Jonenby et al. 2006 72 328 44 344 10.1% 1.71 (12, 2.43) Hot et al. 2006 72 340 42 340 98% 1.71 (12, 2.43) Hot et al. 2006 72 126 21 34 34% 2.29 (111, 11, 81, 71) Jonenby et al. 2006 77 126 27 128 86% 2.06 (1, 40, 30.3) Rown at et al. 2006 77 126 27 128 86% 2.06 (1, 40, 30.3) Tonnes et al. 2006 77 126 13 4.73% 1.44 (10.9, 1.82) Hot et al. 2006 77 126 999 91 1006 47.3% 1.44 (10.9, 1.82) Heterogeneity: Tau'e 1.00; Ch' = 1.00; Ch' = 1.00; M' = 1.99; F = 28\% Test for overall								
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				'= 4 (P =	0.0005); I² = 80%	б	
Anthenelli et al. 2016 96 900 126 968 30.1% 0.75 (0.50, 0.97) Cincripini et al. 2016 49 343 72 320 17.4% 0.64 (0.46, 0.80) Jorenby et al. 2006 49 343 72 320 17.4% 0.64 (0.46, 0.80) Jorenby et al. 2006 44 125 57 128 20.4% 0.78 (0.57, 1.06) Zhang et al. 2006 44 125 57 128 20.4% 0.78 (0.57, 1.06) Zhang et al. 2002 25 499 24 464 6.4% 0.97 (0.55, 1.67) Total events 222 3230 100.0% Total events 222 3230 100.0% Total events 223 25 127 0.5% 0.36 (0.52, 61) Heterogeneity, Tau" = 0.00; Chi" = 2.06, df = 5 (P = 0.44); P = 0% Test for overall effect. Z = 4.39 (P < 0.0001) 12.4 NRT vs Placebo Anthenelli et al. 2016 3 1 1006 73 999 25.7% 1.24 (0.92, 1.66) Lamma et al. 2016 13 0 25 17 15.5% 0.36 (0.62, 2.68) Jorenby et al. 1994 41 156 25 157 15.5% 1.05 (1.06, 2.58) Jorenby et al. 1994 34 113 5 107 2.7% 0.76 (0.21, 2.75) Total events 345 268 Heterogeneity, Tau" = 0.02; Chi" = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect. Z = 1.00 P = 0.00 12.6 Burpopion vs Placebo Anthwelli et al. 2016 128 300 62 300 12.7% 1.74 (1.32, 2.29) Chichigni et al. 2007 69 400 12 193 4.4% 2.77 (1.54, 500) Chick et al. 2008 77 53 9 51 3.8% 2.88 (1.57); 5.52) Total events 345 268 Heterogeneity, Tau" = 0.02; Chi" = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect. Z = 1.90 (P = 0.00) 12.6 Burpopion vs Placebo Anthwelli et al. 2006 77 53 9 51 3.8% 2.88 (1.57); 5.52) Chichigni et al. 2006 77 53 9 51 3.8% 2.88 (1.57); 5.52) Heterogeneity, Tau" = 0.02; Chi" = 1.78, df = 31 (2 + 1.18) MCattry et al. 1998 103 243 31 159 9.95% 2.171; 1.53, 3.08) Jorenby et al. 12006 77 230 44 46 1.7% 300 (1.10, 1.7) Jorenby et al. 2006 77 229 10 234 3.56% 3.55 (1.81; 7.06) Nides et al. 2006 77 240 42 340 9.8% 1.75 (1.00, 3.03) Mides et al. 2006 77 240 42 340 9.8% 2.206 (1.40, 3.03) Total events 43 200 45 71 28 27 128 8.0% 1.55 (1.00, 2.33) Total events 43 200 45 71 28 27 128 8.0% 1.55 (1.00, 2.33) Total events 41.2007 45 989 91 1006 47.3% 1.44 (1.10, 1.82) Jorenby et al. 1999 103 243 73 243 52.7% 1.44 (1.10, 3.03) Total	Test for overall effect: Z =	1.84 (P =	0.07)					
Anthenelli et al. 2016 96 900 126 968 30.1% 0.75 (0.50, 0.97) Cincripini et al. 2013 20 86 322 102 8.3% 0.74 (0.46, 1.20) Orazles et al. 2006 49 343 72 340 17.4% 0.64 (0.46, 0.80) Thises et al. 2006 44 125 57 158 20.4% 0.78 (0.57, 1.06) Thises et al. 2006 44 125 57 158 20.4% 0.78 (0.57, 1.06) Thises et al. 2006 42 329 22 330 Total events 22 329 22 3230 100.4% Total events 22 329 22 3230 100.4% Total events 22 32 380 Heterogeneity, Tau" = 0.00; Ch ^{-T} = 2.06, dr 5 6 (° = 0.44), (° = 0.% Total events 21 2016 31 1006 73 999 25.7% 1.24 (0.92, 1.66) Total events 21 2016 20 25 17 15.5% Dorenty et al. 1994 41 156 25 157 15.5% Subbala (95K-Ch) 12.26, dr 5 6 (° = 0.44), (° = 0.% Total events 345 208 Heterogeneity, Tau" = 0.02; Ch ^{-T} = 8.11, dr = 5 (° = 0.15), (° = 38% Total events 345 268 Heterogeneity, Tau" = 0.02; Ch ^{-T} = 8.11, dr = 5 (° = 0.15), (° = 38% Total events 345 268 Heterogeneity, Tau" = 0.02; Ch ^{-T} = 8.11, dr = 5 (° = 0.15), (° = 38% Total events 345 268 Heterogeneity, Tau" = 0.02; Ch ^{-T} = 8.11, dr = 5 (° = 0.15), (° = 38% Total events 345 268 Heterogeneity, Tau" = 0.02; Ch ^{-T} = 2.04, 44 10.1% 1.24 (1.02, 1.28) Anthwelli et al. 2007 69 400 12 193 4.4% 2.77 (1.54, 500) 1.2.6 Bupropion vs Placebo Anthwelli et al. 2006 77 53 9 51 3.3% 2.89 (1.57, 1.53) Dorenty et al. 1999 103 243 31 159 9.9% 2.217 (1.54, 500) Hadrogeneity, Tau" = 0.02; Ch ^{-T} = 1.76, dr = 1.3 (° = -1.71), (° = 26% Total events 335 229 10 234 3.55% 3.56 (1.16, 1.53) Heterogeneity, Tau" = 0.02; Ch ^{-T} = 1.76, dr = 1.3 (° = -1.71), (° = 26% Total events 22 9 164 Heterogeneity, Tau" = 0.02; Ch ^{-T} = 1.76, dr = 1.3 (° = -1.71), (° = 26% Total events 22 9 164 Heterogeneity, Tau" = 0.02; Ch ^{-T} = 1.78, dr = 1.3 (° = -1.71), (° = 26% Total events 22 9 164 Heterogeneity, Tau" = 0.00; Ch ^{-T} = 0.00; (° = 0.09), (° = 0.0% Total events 0.22 9 164 Heterogeneity, Tau" = 0.00; Ch ^{-T} = 0.00; (° = 0.09), (° = 0.0% Total events 0.22 9 164 Heterogeneity, Tau" = 0.00; Ch ^{-T} = 0.00; (° = 0.17), (° = 0.99), (° = 0.6%	1 2 3 Varenicline vs Run	ropion						
Chardpini et al. 2013 20 88 32 102 8.2% 0.74 (0.46, 1.20) Jonenby et al. 2006 44 343 72 329 17.4% 0.67 (0.46, 0.89) Hindse et al. 2006 44 125 57 126 20.4% 0.78 (0.57, 1.06) Zhang et al. 2002 25 499 24 464 6.4% 0.97 (0.57, 1.06) Total events 282 333 Total events 282 335 100.0% 0.73 (0.64, 0.84) Heterogeneity, Tau" = 0.00; Ch" = 2.06, df = 5 (P = 0.84); P = 0% Test for versal effect Z = 4.39 (P - 0.0001) 1.2.4 NRT vs Placebo Antheneit et al. 2015 91 1006 73 998 25.7% 1.24 (0.92, 1.66) Lerman et al. 2013 0 25 1 27 0.5% 0.36 (0.02, 6.43) Heterogeneity, Tau" = 0.02; Ch" = 8.11, df = 5 (P = 0.84); P = 0% Test for versal effect Z = 4.39 (P - 0.0001) 1.2.4 NRT vs Placebo Antheneit et al. 2015 91 1066 73 998 25.7% 1.24 (0.92, 1.66) Lerman et al. 2015 91 1066 73 918 25.7% 1.66 (1.06, 2.58) Lerman et al. 2015 92 44 11 15 92 27 0.5% 0.36 (0.02, 6.43) Lerman et al. 2015 136 418 133 408 35.1% 1.00 (0.82, 1.21) Lerman et al. 2015 136 418 133 408 35.1% 1.00 (0.82, 1.21) Lerman et al. 2015 136 418 133 408 35.1% 1.00 (0.82, 1.21) Lerman et al. 2016 126 928 73 999 13.2% 1.74 (1.32, 2.29) Total events 345 268 Heterogeneity, Tau" = 0.02; Ch" = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect Z = 1.30 (P = 0.06) Total events 345 2768 Heterogeneity, Tau" = 0.02; Ch" = 7.3 999 13.2% 1.74 (1.92, 1.85) Jonenby et al. 2006 72 320 44 344 10.1% 1.71 (1.21, 2.49) Hot et al. 2006 72 320 44 344 10.1% 1.71 (1.21, 2.41) Hot et al. 2006 72 320 44 341 158 9.3% 2.277 (1.54, 500) Jonenby et al. 2006 72 320 44 324 0.98% 1.571 (1.00, 2.47) Fossibi et al. 2006 72 320 44 32 40 9.8% 1.571 (1.00, 2.47) Heterogeneity, Tau" = 0.02; Ch" = 1.60; df = 0.17); P = 26% Total events 93 36 383 Heterogeneity, Tau" = 0.02; Ch" = 0.00; H = 0.09; P = 0.0% Total events 93 36 383 Heterogeneity Tau" = 0.00; Ch" = 0.00; H = 0.09; P = 0.0% Test for overall effect Z = 9.84 (P = 0.0001) Heterogeneity Tau" = 0.00; Ch" = 0.00; H = 0.00; H = 0.09; P = 0.0% Test for overall effect Z = 0.84 (P = 0.0001)			gan	126	990	30.1%	0.75 (0.69, 0.97)	
Gonzales et al. 2006 49 349 72 329 17.4% 0.64 (0.46) (0.89) Nides et al. 2006 44 125 57 126 0.75 (0.57, 106) Nides et al. 2006 44 125 57 126 0.75 (0.57, 106) Stubiotal (95% CI) 2392 2350 100.0% 0.75 (0.56, 167) Total events 282 383 Helerogeneity, Tau" = 0.00; Ch" = 2.06, df = 5 (P = 0.44); P = 0.% Test for overall effect Z = 4.39 (P < 0.0001)								
Jonenby et al. 2006 Helerogeneity: Tau" = 0.00; Ch" = 2.06, df = 5 (P = 0.84); P = 0% Total events Total events Total events Helerogeneity: Tau" = 0.00; Ch" = 2.06, df = 5 (P = 0.84); P = 0% Test for overall effect; Z = 4.39 (P < 0.0001) 1.2.4 NRT vs Placebo Anthenelli et al. 2016 Anthenelli et al. 2016 Helerogeneity: Tau" = 0.00; Ch" = 2.08, df = 5 (P = 0.84); P = 0% Test for overall effect; Z = 4.39 (P < 0.0001) 1.2.4 NRT vs Placebo Anthenelli et al. 2016 Helerogeneity: Tau" = 0.02; Ch" = 3.11, df = 5 (P = 0.84); P = 0% Test for overall effect; Z = 4.39 (P < 0.0001) 1.2.4 NRT vs Placebo Anthenelli et al. 2015 Helerogeneity: Tau" = 0.02; Ch" = 5.11, df = 5 (P = 0.15); P = 38% Test for overall effect; Z = 1.90 (P = 0.05) 1.2.6 Burpoin vs Placebo Anthenelli et al. 2016 Helerogeneity: Tau" = 0.02; Ch" = 5.11, df = 5 (P = 0.15); P = 38% Test for overall effect; Z = 1.90 (P = 0.05) 1.2.6 Burpoin vs Placebo Anthenelli et al. 2016 Helerogeneity: Tau" = 0.02; Ch" = 5.11, df = 5 (P = 0.15); P = 38% Test for overall effect; Z = 1.90 (P = 0.05) 1.2.6 Burpoin vs Placebo Anthenelli et al. 2006 Dalsgan et al. 2007 Helerogeneity: Tau" = 0.02; Ch" = 5.11, df = 5 (P = 0.15); P = 38% Test for overall effect; Z = 1.90 (P = 0.05) 1.2.6 Burpoin vs Placebo Anthenelli et al. 2006 Dalsgan et al. 2006 Dalsgan et al. 2007 Helerogeneity: Tau" = 0.02; Ch" = 5.17; P = 25% Test for overall effect; Z = 9.07 (P < 0.00001) 1.2.7 Burpoin vs NRT Anthenelli et al. 2006 Tatal events Dals 229 Helerogeneity: Tau" = 0.02; Ch" = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect; Z = 3.84 (P = 0.0001) Helerogeneity: Tau" = 0.00; Ch = 0.00; H = 0								
Nides et al 2006 44 125 57 126 20.4% 078 [0.57, 106] Total events 282 383 Heterogeneity: Tau" = 0.00, Ch ⁻⁹ = 0.84); P = 0% Total events 282 383 Heterogeneity: Tau" = 0.00, Ch ⁻⁹ = 0.84); P = 0% Test for overall effect Z = 4.39 (P < 0.0001) 1.2.4 NRT vs Placebo Anthenelli et al. 2016 91 1006 73 989 25.7% 1.24 [0.82, 1.66] Exoler te al. 2013 0 25 1 27 0.5% 0.36 [0.02, 8.43] Lerman et al. 2015 136 418 133 408 35.1% 1.00 [0.82, 1.21] Subtotal (95% CI) 1991 1857 100.0% 1.23 [0.98, 1.53] Lerman et al. 2015 136 418 133 408 35.1% 1.00 [0.82, 1.21] Subtotal (95% CI) 1991 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneity: Tau" = 0.02; Ch ⁻⁰ = 0.1, dr = 5 (P = 0.15); P = 38% Test for overall effect Z = 1.90 (P = 0.06) 1.2.6 Burporton vs Placebo Anthenelli et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenelli et al. 2016 72 329 44 344 10.1% 1.77 [1.21, 2.41] Hagestrain et al. 2006 77 2329 44 344 10.1% 2.77 [1.53, 3.08] Jorenby et al. 1999 103 243 31 159 95% 2.27 [1.53, 3.08] Jorenby et al. 2006 77 126 2.77 128 8.78 2.80 [1.61, 5.15, 5.2] Hoit et al. 2006 77 126 2.77 128 8.8% 2.20 [1.61, 5.15, 5.2] Hoit et al. 2006 77 126 2.77 128 8.8% 2.20 [1.61, 0.3, 3.3] Heterogeneity: Tau" = 0.02; Ch ⁻⁰ = 1.760, dr = 1.3 (P = 0.17); P = 26% Test for overall effect Z = 9.07 (P < 0.0001) 1.2.7 Iburporton vs NTX Anthenelli et al. 2006 17 126 2.77 128 8.8% 1.58 [1.63, 2.13] Total events 93 36 13.8% Heterogeneity: Tau" = 0.00; Ch ⁻¹ = 1.760, dr = 1.3 (P = 0.17); P = 26% Test for overall effect Z = 9.00 (P = 1.000) 1.2.7 Burporton vs NTX Anthenelli et al. 2006 126 989 91 1006 47.3% 1.41 [1.19, 1.80] Anthenelli et al. 2006 122 99 164 Heterogeneity: Tau" = 0.00; Ch ⁻¹ = 1.760, dr = 1.3 (P = 0.9); P = 0% Test for overall effect Z = 3.84 (P = 0.0001)								
Zhang et al. 2022 25 499 24 484 6.4% 0.97 [0.56, 1.67] Total events 232 383 Helerogeneity, Tau" = 0.00; Chi" = 2.06, df = 5 (P = 0.84); P = 0% Test for verall effect. Z = 4.39 (P < 0.0001) 1.2.4 NRT vs Placebo Anthenelli et al. 2016 91 1006 73 999 25.7% 0.36 [0.02, 8.43] Harris et al. 1094 41 156 25 157 15.9% 1.36 [1.06, 2.23] Harris et al. 1994 41 156 25 157 15.9% 1.06 [0.23, 1.56] Lorenshy et al. 1999 73 243 31 159 20.2% 1.54 [1.06, 2.23] Lerman et al. 2015 136 418 133 408 35.1% 1.00 [0.82, 1.21] Subtotal (95% C) 1991 1857 100.0% 1.23 [0.98, 1.53] Total events 345 268 Helerogeneity, Tau" = 0.02; Chi" = 8.11, df = 5 (P = 0.15); P = 38% Test for voreall effect. Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Anthenelli et al. 2006 72 329 44 344 10.1% 1.74 [1.32, 2.29] Chicriphi et al. 2016 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 3.01 [1.11, 8.17] Jorenshy et al. 1999 103 243 31 159 9.3% 2.89 [1.51, 54.500] Gonzale et al. 2006 72 329 44 344 10.1% 3.01 [1.11, 8.17] Jorenshy et al. 2006 72 329 44 344 10.1% 3.05 [1.17, 15.4, 500] Gonzale et al. 2006 72 72 40 42 420 9.8% 1.27 [1.52, 52] Haggsträm et al. 2006 72 72 40 42 420 9.8% 1.71 [1.21, 2.43] Haggsträm et al. 2006 45 128 13 366 5.5% 9.59 [1.37, 67.29] Tonkes et al. 2006 45 128 13 368 2.58 [1.81, 7.05] Nuclear tel 2.006 72 129 103 243 31 159 9.9% 2.17 [1.53, 3.08] Jorenshy et al. 2006 45 128 13 368 2.58 [1.81, 7.05] Nuclear tel 2.006 72 129 103 243 355 [1.81, 7.05] Helerogeneity, Tau" = 0.02; Chi" = 17.50, df = 13 (P = 0.17); P = 26% Test for overall effect. Z = 3.84 (P = 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2006 122 129 164 Helerogeneity, Tau" = 0.00; Chi" = 17.60, df = 13 (P = 0.9); P = 0% Test for overall effect. Z = 3.84 (P = 0.0001)		44						
Total events 282 383 Heterogeneity: Tau ² = 0.00; Chi ² = 2.06; df = 5 (P = 0.84); P = 0% Test for verall effect $Z = 4.39$ ($P < 0.0001$) 1.2.4 NRT vs Placebo Anthenelli et al. 2016 91 1006 73 999 25.7% 1.24 (0.92, 1.66) Ebbert et al. 2013 0 25 1 27 0.5% 0.36 (0.02, 8.43) Harris et al. 1994 41 156 25 157 15.9% 1.65 (1.06, 2.50) Jorenby et al. 1999 73 243 31 159 20.2% 1.54 (1.06, 2.23) Lerman et al. 2015 136 418 133 408 35.1% 1.00 (0.82, 1.21) Sache et al. 1983 4 113 5 107 2.7% 0.76 (0.21, 2.75) Subtotal (95% CI) 1961 1857 100.0% 1.23 (0.99, 1.53) Total events 345 268 Heterogeneity: Tau ² = 0.02 (Ch ² = 8.11, df = 5 ($P = 0.15$); $P = 38\%$. Test for overall effect $Z = 1.90$ ($P = 0.06$) 1.2.6 Bupropion vs Placebo Antuwall et al. 2002 88 300 62 300 12.7% 1.42 (1.07, 1.88) Antheneill et al. 2016 126 989 73 999 13.2% 1.74 (1.32, 2.29) Chichipini et al. 2016 32 102 21 106 6.2% 1.58 (0.98, 2.56) Chichipini et al. 2016 27 53 9 51 3.8% 2.89 (1.51, 5.52) Haggsträm et al. 2006 27 53 9 51 3.8% 2.89 (1.51, 5.52) Holt et al. 2006 72 324 4 344 10.1% 1.77 (1.53, 3.08) Jorenby et al. 2006 72 340 42 340 9.8% 1.71 (1.21, 2.43) Mides et al. 2006 72 126 27 123 8.8% 2.06 (1.40, 3.03) Tornes et al. 2003 126 527 27 180 8.9% 2.06 (1.40, 3.03) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.37, 6.7.29) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.30, 2.33) Jorenby et al. 2006 57 126 27 123 8.6% 9.206 (1.40, 3.03) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.30, 2.33) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.30, 2.33) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.37, 6.7.29) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.30, 2.33) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.30, 2.33) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.09, 2.33) Tornes et al. 2003 126 527 27 180 8.9% 1.59 (1.09, 2.33) Tornes et al. 2003 126 527 127 (1.22, 2.7% 1.41 (1.10, 1.82) Jorenby et al. 1999 103 243 73 243 52.7% 1.41 (1.10, 1.82) Tornes et al. 2006 6.77 126 27 123 2.7% 1.41 (1.10, 1.82) Jo	Zhang et al. 2022	25	499	24	464	6.4%		
Heterogeneity: Tau ² = 0.00; Ch ² = 2.06; df = 5 (P = 0.84); P = 0% Test for overall effect Z = 4.39 (P < 0.0001) 1.2.4 NRT vs Placebo Antheneili et al. 2015 91 1006 73 999 25.7% 1.24 [0.92, 1.66] Ebbert et al. 2013 0 25 1 27 0.5% 0.36 [0.02, 8.43] Harris et al. 1994 41 156 25 157 159% 1.65 [10, 62, 56] Jorenby et al. 1999 73 243 31 159 20.2% 1.54 [1.06, 2.23] Jerman et al. 2015 136 418 133 408 35.1% 1.00 [0.24, 1.21] Subtotal (95% CI) 19861 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneity: Tau ² = 0.02; Ch ² = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Antheneili et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Chichrighini et al. 2013 21 002 1146 8.3% 1.57 [1.00, 2.47] Fossal et al. 2007 69 400 12 193 4.4% 2.77 [1.54, 5.00] Ognzales et al. 2006 72 329 44 344 101% 1.71 [1.21, 2.41] Haggstram et al. 2006 77 329 44 344 101% 1.71 [1.21, 2.41] Haggstram et al. 2006 77 126 27 123 8.6% 2.98[1.51, 5.52] Uncerthy et al. 1999 103 243 31 159 9.9% 2.17 [1.54, 5.00] Gonzales et al. 2006 77 126 27 123 8.6% 1.59 [1.39, 5.52] Tonnesen et al. 2006 77 126 27 123 8.6% 3.00 [1.40, 3.03] McCarthy et al. 1999 103 243 31 159 9.9% 2.17 [1.54, 5.00] Morena et al. 2006 77 126 27 123 8.6% 3.00 [1.40, 3.03] Heterogeneity: Tau ² = 0.07; Ch ² = 17, 60, df = 13 (P = 0.7); P = 26% Test for overall effect Z = 0.07; CP = 0.000(1) 1.2.7 Bupropion vs NRT Antheneili et al. 2006 17 229 10 244 3.5% 3.58 [1.61, 7.05] Nide et al. 2006 77 126 27 123 8.6% 1.59 [1.09, 1.32] Total events 936 383 Heterogeneity: Tau ² = 0.07; CP = 0.000(1) 1.2.7 Bupropion vs NRT Antheneili et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 527.5% 1.441 [1.09, 1.82] Total events 229 164 Heterogeneity: Tau ² = 0.07; CP = 0.000; 11 4.11 (1.18, 1.68] Muthotal (95% CI) 1232 1249 100.0% 1.441 [1.10, 1.82] Jorenby et al. 1999 103 243 77 243 52.7% 1.441 [1.09, 1.82] Meterogeneity: Tau ² = 0.00; CFi = 0.00; df = 16 0.00;	Subtotal (95% CI)		2392		2350	100.0%	0.73 [0.64, 0.84]	◆
Testfor overall effect Z = 4.39 ($P < 0.0001$) 1.2.4 NRT vs Placebo Anthenelli et al. 2015 91 1006 73 999 25.7% 1.24 [0.92, 1.66] Harris et al. 1994 41 156 25 157 15.9% 0.36 [0.02, 8.43] Harris et al. 1994 41 156 25 157 15.9% 1.65 [1.06, 2.58] Jornehy et al. 1993 44 113 5 107 2.7% 0.76 [0.21, 2.70] Subtotal (95% CI) 1961 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneity: Tau ² = 0.02 ($P = 0.15$); $P = 39$ % Testfor overall effect Z = 1.90 ($P = 0.06$) 1.2.6 Burpropion vs Placebo Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Chicripini et al. 2001 68 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Chicripini et al. 2001 69 400 12 193 4.4% 2.77 [1.54, 5.00] Gonzales et al. 2006 77 53 9 51 3.8% 2.89 [1.51, 5.52] Holt et al. 2006 77 53 9 51 3.8% 2.89 [1.51, 5.52] Holt et al. 2006 77 126 27 123 8.6% 2.06 [1.40, 3.03] Jorenby et al. 2006 77 126 27 123 8.6% 1.59 [1.37, 6.7.29] Tonnesen et al. 2006 77 126 27 123 8.6% 1.59 [1.37, 6.7.29] Tonnesen et al. 2006 77 126 27 123 8.6% 1.59 [1.37, 6.7.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.39, 2.33] Mides et al. 2006 77 126 27 123 8.6% 2.06 [1.40, 3.03] Total events 936 383 Heterogeneiky: Tau ² = 0.07, CP = 0.0001) 1.2.7 Burpropion vs NRT Anthenelli effect Z = 9.07, CP = 0.0001) 1.2.7 Burpropion vs NRT Anthenelli effect Z = 0.07, CP = 0.000, 11 006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 2006 126 126 989 11 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Total events 229 10.44 Heterogeneiky: Tau ² = 0.02, CPr = 17.60, df = 13 (P = 0.9); P = 0% Testfor overall effect Z = 3.84 (P = 0.0001)								
1.24 NRT vs Placebo Anthenelli et al. 2016 91 1006 73 999 25.7% 1.24 [0.92, 1.66] Ebbert et al. 2013 0 25 1 27 0.5% 0.36 [100, 2, 8.43] Jorenby et al. 1994 41 156 25 157 159% 1.56 [1.06, 2.23] Lerman et al. 2015 136 418 133 408 51:% 1.00 [0.82, 1.27] Sachs et al. 1993 4 113 5 107 2.7% 0.76 [0.21, 2.75] Subtotal (95% CI) 1961 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneibt, Tau"=0.02, Chi"= 8.11, dir=5 (P = 0.15); P = 38% 1.85 [0.98, 2.56] Test for overall effect: Z = 1.90 (P = 0.06) 1.24 [1.07, 1.88] Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Chichipini et al. 2006 72 329 44 10.1% 1.77 [1.54, 500] 9 9 1.77 [1.54, 500] 9 9 1.71 [1.21, 2.41] 44 45 1.71 [1.21, 2.41] 44 1.71% 1.71 [1.21, 2.41]				: 5 (P = 0	l.84); I²÷	= 0%		
Anthenelli et al. 2016 91 1006 73 999 25.7%, 1.24 (0.32, 1.66) Ebbert et al. 2013 0 25 1 27 0.5% 0.36 (0.02, 8.43) Harris et al. 1994 41 156 25 157 15.9%, 1.55 (1.06, 2.58) Jorenby et al. 1993 73 243 31 159 20.2%, 1.54 (1.06, 2.23) Lemma et al. 2015 136 418 133 408 35.1%, 1.00 (0.82, 1.21) Sachs et al. 1993 4 113 5 107 2.7%, 0.76 (0.21, 2.75) Subtotal (95% CI) 1961 1857 100.0%, 1.23 (0.99, 1.53) Total events 345 268 Heterogeneiby, Tau"= 0.02, Chi"= 8.11, dfr = 5 (P = 0.15), P = 38% Test for overall effect. Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Anthenelli et al. 2012 88 300 62 300 12.7%, 1.42 (1.07, 1.88) Anthenelli et al. 2013 32 102 21 106 6.2%, 1.58 (0.98, 2.56) Dategaro et al. 2004 61 221 20 114 6.8%, 1.57 (1.00, 2.47) Forsati et al. 2006 72 329 44 344 10.1%, 1.71 (1.21, 2.41) Haggstram et al. 2006 72 329 44 344 10.1%, 1.71 (1.21, 2.41) Haggstram et al. 2006 72 329 44 344 10.1%, 1.71 (1.21, 2.41) Haggstram et al. 2006 72 329 44 344 10.1%, 1.71 (1.21, 2.41) Haggstram et al. 2006 72 340 42 340 9.8%, 1.79 (1.53, 3.08) Jorenby et al. 1999 103 243 31 159 9.9%, 2.17 (1.53, 3.08) Heterogeneiby, Tau" = 0.02, Chi" = 1.76, 0.47 3%, 2.66 (1.40, 303) Rovina et al. 2006 57 126 27 123 8.65%, 2.66 (1.40, 303) Rovina et al. 2006 57 126 27 123 8.65%, 2.66 (1.40, 303) Rovina et al. 2006 57 126 27 123 8.65%, 2.66 (1.40, 303) Rovina et al. 2006 57 126 27 123 8.65%, 2.66 (1.40, 303) Rovina et al. 2006 57 126 27 123 8.65%, 2.66 (1.40, 303) Rovina et al. 2007 (P = 1.760, df = 1.3 (P = 0.17); P = 26% Test for overall effect: Z = 3.84 (P = 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3%, 1.41 [1.19, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 8.16] Heterogeneiby, Tau" = 0.00, Chi = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 0.01 0.1 1 10	Test for overall effect: Z =	4.39 (P <	0.0001)					
Anthenelli et al. 2016 91 1006 73 999 25.7% 1.24 (0.32, 1.66) Exbert et al. 2013 0 25 1 27 0.5% 0.36 (0.02, 8.43) Harris et al. 1994 41 156 25 157 15.9% 1.55 (1.06, 2.58) Joren by et al. 1999 73 243 31 159 20.2% 1.54 (1.06, 2.23) Lemma et al. 2015 136 418 133 408 35.1% 10.00 (0.82, 1.21) Sachs et al. 1983 4 113 5 107 2.7% 0.76 (0.21, 2.75) Subtotal (95% CI) 1961 1857 100.0% 1.23 (0.99, 1.53) Total events 345 268 Heterogeneiby: Tau" = 0.02; Chi" = 5.11, dfr = 5 (P = 0.15); P = 38% Test for overall effect. Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Anthenelli et al. 2012 88 300 62 300 12.7% 1.42 (1.07, 1.88) Anthenelli et al. 2013 21 106 6.2% 1.58 (0.99, 2.56) Dategaro et al. 2004 61 221 20 114 6.8% 1.57 (1.00, 2.47) Forsant et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 329 44 344 10.1% 1.71 (1.21, 2.41) Haggistram et al. 2006 72 340 42 340 9.8% 1.71 (1.21, 2.43) McCarthy et al. 1999 103 243 31 159 9.9% 2.171 (1.53, 3.08) Hot et al. 2006 57 126 27 123 8.6% 2.06 (1.40, 303) Rovina et al. 2006 57 126 27 123 8.6% 2.06 (1.40, 303) Rovina et al. 2006 57 126 27 123 8.6% 2.06 (1.40, 303) Total events 936 383 Heterogeneibly: Tau" = 0.02; Chi" = 17.60, df = 13 (P = 0.17); I" = 26% Test for overall effect: Z = 3.84 (P = 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.19, 1.82] Joren by et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 8.16] Heterogeneibly: Tau" = 0.02; Chi" = 17.60, df = 13 (P = 0.17); I" = 26% Test for overall effect: Z = 3.84 (P = 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.19, 1.82] Joren by et al. 1999 1	124 NRT vs Placebo							
Ebbertetal 2013 0 25 1 27 0.5% 0.36 [002, 8.43] Harris et al. 1994 41 156 25 157 15.9% 1.65 [1.06, 2.58] Jorrehy et al. 1993 44 1135 107 2.7% 0.76 [0.21, 2.75] Subtotal (95% CI) 1961 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneity. Tau ² = 0.02, Chi ² = 8.1, 41 = 5 (P = 0.15), P = 38% Test for overall effect Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Ahluwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenell et al. 2013 32 102 21 106 6.2% 1.59 [0.98, 2.56] Chichiphi et al. 2003 61 22 20 114 6.8% 1.57 [1.00, 2.47] Fossati et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 3.01 [1.11, 8.17] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.368 [1.81, 7.05] Jorenby et al. 2008 35 229 10 234 3.5% 3.60 [1.81, 7.05] Mides et al. 2008 35 7 126 27 7 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.596 [1.37, 67.29] Total events 936 383 Bubtotal (95% CI) 4116 3225 100.0% 1.43 [1.11, 8.17] Jorenby et al. 2009 45 169 1 36 0.5% 9.596 [1.37, 67.29] Total events 936 383 Bubtotal (95% CI) 4116 3225 100.0% 1.43 [1.10, 9.13] Total events 936 383 Bubtotal (95% CI) 126 527 27 180 8.8% 1.41 [1.10, 1.30] 1.2.7 Bupropion vs NRT Anthenell et al. 2016 126 989 91 1006 47.3% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity. Tau ² = 0.00; Chi ² = 1.0; 0, f1 3 (P = 0.9); P = 0% Test for overall effect Z = 3.84 (P = 0.0001)		01	1006	72	000	26 7%	1 24 10 02 1 661	
Harris et al. 1994 41 156 25 157 15.9% 1.56 1.06, 2.58 Jorenhy et al. 1999 73 243 31 159 20.2% 1.54 11.06, 2.23 Lerrman et al. 2015 136 418 133 408 35.1% 1.00 [0.82, 1.21] Sachs et al. 1993 4 113 5 107 2.7% 0.76 [0.21, 2.75 Subtotal (95% CI) 1961 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneity. Tau ² = 0.02, Chi ² = 8.11, df = 5 (P = 0.15), P = 38% Test for overall effect Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Anturvalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenell et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Cheriphiel et al. 2013 32 102 21 106 6.2% 1.57 [1.00, 2.47] Forsati et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Forsati et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 53 9 5f 1.3.8% 2.89 [1.51, 5.52] Holt et al. 2006 72 3340 42 340 9.8% 1.71 [1.54, 5.00] Operative at al. 2006 72 340 42 340 9.8% 2.171 [1.53, 3.08] Jorenhy et al. 2006 72 129 10 234 3.5% 3.58 [1.51, 7.05] Nides et al. 2006 72 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2008 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonal events 936 383 Heterogeneity. Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect Z = 9.07 (P < 0.00001) 1.27 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.18, 1.68] Heterogeneity. Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.001)								
Jorenby et al. 1999 73 243 31 159 20.2% 1.44 [1.06, 2.23] Lerman et al. 2015 136 418 133 408 35.1% 1.00 [0.82, 1.21] Subtotal (95% CI) 1961 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneity. Tau ² = 0.02; Ch ² = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect: Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Cincripini et al. 2013 32 102 21 106 6.2% 1.58 [0.98, 2.56] Dalsgare et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 339 61 3.8% 2.89 [1.51, 5.52] Holt et al. 2006 72 340 42 340 9.8% 1.71 [1.54, 5.00] Orenzels et al. 2006 72 71 126 5.77 10.2, 2.47] Forsati et al. 2006 72 71 25 72 123 8.6% 2.06 [1.40, 3.03] Revina et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.06] Nicke set al. 2006 77 126 72 71 23 8.6% 2.06 [1.40, 3.03] Revina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2006 57 126 72 71 23 8.6% 2.06 [1.40, 3.03] Revina et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Tonesen et al. 2009 45 169 1 38 0.5% 9.59 [1.37, 67.29] Total events 9.29 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
Lerman et al. 2015 136 418 133 408 35.1% 1.00 [0.82, 1.21] Sachs et al. 1993 4 113 5 107 2.7% 0.76 [0.21, 2.75] Total events 345 268 Heterogeneity. Tau ² = 0.02; Chi ² = 8.11, drf = 5 (P = 0.15); P = 38% Test for overrall effect Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Ahluwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenell et al. 2016 126 989 73 999 13.2% 1.56 [0.96, 2.56] Dalsgaro et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossati et al. 2006 72 329 44 344 10.1% 1.77 [1.51, 5.50] Jorenby et al. 2006 72 329 44 344 10.1% 1.77 [1.51, 5.52] Holt et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 334 1159 9.9% 2.17 [1.55, 3.08] Jorenby et al. 2006 72 128 10 224 3.5% 3.58 [1.37, 1.55] Nides et al. 2006 77 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2008 55 229 10 224 3.5% 3.58 [1.37, 1.06] Nides et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% Cl) 4116 3225 100.0% 1.48 [1.63, 2.13] Total events 238 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% Cl) 1232 124 9 100.6 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1208 126 989 91 1066 47.3% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect Z = 3.84 (P = 0.0001)								
Sachs et al. 1993 4 113 5 107 2.7% 0.76 [0.21, 2.75] Subtotal (95% CI) 1961 1857 100.0% 1.23 [0.99, 1.53] Total events 345 268 Heterogeneity: Tau ² = 0.02; Chi ² = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Ahluwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenell et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Cincipipini et al. 2013 32 102 21 106 6.2% 1.58 [0.98, 2.56] Dalegapt et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossati et al. 2006 72 329 44 344 10.1% 1.77 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 1.77 [1.21, 2.43] McCarthy et al. 1999 103 243 31 159 9.9% 2.17 [1.53, 3.08] Jorenby et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2006 57 126 27 123 8.6% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.68 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.00; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect Z = 9.07 (P < 0.0001) 1.2.7 Bupropion vs NRT Anthenell et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect Z = 9.07 (P < 0.0001) 1.2.7 Bupropion vs NRT Anthenell et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect Z = 3.84 (P = 0.0001)								+
Total events 345 268 Heterogeneity: Tau ² = 0.02; Chi ² = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Anthenelli et al. 2016 126 999 73 999 13.2% 1.74 [1.32, 2.29] Cincipini et al. 2016 126 999 73 999 13.2% 1.74 [1.32, 2.29] Cincipini et al. 2016 12 20 114 6.8% 1.57 [1.00, 2.47] Fossali et al. 2007 69 400 12 193 4.4% 2.77 [1.54, 5.00] Gonzales et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Holt et al. 2006 72 340 42 340 9.8% 1.77 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.06] Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% Ci) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); I ² = 26% Test for overall effect: Z = 9.00, chi ² = 0.00, df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 0.01 0.1 1 00						2.7%		
Heterogeneity: Tau [*] = 0.02; Chi [*] = 8.11, df = 5 (P = 0.15); P = 38% Test for overall effect: Z = 1.90 (P = 0.06) 1.2.6 Bupropion vs Placebo Antuwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Cinciripini et al. 2013 32 102 21 106 6.2% 1.56 [0.98, 2.56] Dalsgare et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossati et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 340 42 340 9.8% 1.77 [1.53, 3.08] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.56 [1.81, 7.05] Nides et al. 2008 35 229 10 234 3.5% 3.56 [1.81, 7.05] Nides et al. 2008 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 126 527 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2003 126 527 27 180 8.8% 1.56 [1.09, 2.33] Subtotal (95% Cl) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau [*] = 0.02; Chi [*] = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.00 (Chi [*] = 0.00, 0f = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau [*] = 0.00; Chi [*] = 0.00, 0f = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)	Subtotal (95% CI)							◆
Test for overall effect: $Z = 1.90$ (P = 0.06) 1.2.6 Bupropion vs Placebo Ahluwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Chicripini et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Dalsgare et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossali et al. 2007 69 400 12 193 4.4% 2.77 [1.54, 500] Gonzales et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 01.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 340 42 340 9.8% 1.71 [1.53, 308] Jorenby et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2008 57 126 27 123 8.6% 2.06 [1.40, 303] Rovina et al. 2008 57 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1222 1249 100.0% 1.41 [1.11, 1.80] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)	Total events	345		268				
1.2.6 Bupropion vs Placebo Ahluwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Cinciripini et al. 2013 32 102 21 106 6.2% 1.56 [0.98, 2.56] Dalegare et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossati et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggeträm et al. 2006 72 329 44 344 1.7% 3.01 [1.11, 8.17] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2006 72 340 42 340 9.8% 1.76 [1.41, 7.05] Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2003 126 527 27 180 8.8% 1.58 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.41 [1.09, 1.82]	Heterogeneity: Tau² = 0.0)2; Chi² = 8	3.11, df=	= 5 (P = 0	.15); I⁼:	= 38%		
Ahluwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 229] Cinciripini et al. 2013 32 102 21 106 6.2% 1.56 [0.98, 2.56] Dalsgare et al. 2007 69 400 12 193 4.4% 2.77 [1.54, 500] Gonzales et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 88 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 303] Rovina et al. 2006 57 126 27 123 8.6% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1222 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)	Test for overall effect: Z =	1.90 (P =	0.06)					
Ahluwalia et al. 2002 88 300 62 300 12.7% 1.42 [1.07, 1.88] Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 229] Cinciripini et al. 2013 32 102 21 106 6.2% 1.56 [0.98, 2.56] Dalsgare et al. 2007 69 400 12 193 4.4% 2.77 [1.54, 500] Gonzales et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 88 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 303] Rovina et al. 2006 57 126 27 123 8.6% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1222 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)	1 2 6 Dupropion vo Di-	obo						
Anthenelli et al. 2016 126 989 73 999 13.2% 1.74 [1.32, 2.29] Cinciripini et al. 2013 32 102 21 106 6.2% 1.56 [0.98, 2.56] Dalegare et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossati et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggstäm et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggstäm et al. 2006 72 38 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.58 [1.91, 7.05] Nides et al. 2003 126 527 27 180 8.8% 1.58 [1.92, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Ch ² = 17.60, df = 1 3 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1222 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)			200		202	40.70	1 10 11 00 1 00	
Choiripini et al. 2013 32 102 21 106 6.2% 1.56 [0.98, 2.56] Dalsgare et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossati et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 38 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 1999 103 243 31 159 9.9% 2.17 [1.53, 3.08] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 45 169 1 325 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 1 26 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								<u> </u>
Dalsgaro et al. 2004 61 221 20 114 6.8% 1.57 [1.00, 2.47] Fossali et al. 2007 69 400 12 193 4.4% 2.77 [1.54, 5.00] Gonzales et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 27 53 9 51 3.8% 2.89 [1.51, 5.52] Holt et al. 2005 23 88 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 1999 103 243 31 159 9.9% 2.17 [1.53, 3.08] Jorenby et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2006 57 126 27 123 8.6% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); I ² = 26% Test for overall effect: Z = 9.07 (P < 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1222 1224 100.0% 1.41 [1.11, 1.80] Subtotal (95% CI) 1222 1249 100.0% 1.41 [1.11, 1.80] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
For stati et al. 2007 69 400 12 193 4.4% 2.77 [1.54, 5.00] Gonzales et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 72 340 42 31 159 9.9% 2.17 [1.53, 3.08] Jorenby et al. 2006 72 340 42 340 9.8% 1.77 [1.51, 3.08] McCarthy et al. 2008 36 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Heterogeneity: Tau ² = 0.02; Ch ² = 17.60, df = 13 (P = 0.17); I ² = 26% Test for overall effect: Z = 9.07 (P < 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1222 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00, df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
Gonzales et al. 2006 72 329 44 344 10.1% 1.71 [1.21, 2.41] Haggsträm et al. 2006 77 53 9 51 3.8% 2.89 [1.51, 552] Holt et al. 2005 23 88 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 1999 103 243 31 159 9.9% 2.17 [1.53, 3.08] McCarhy et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarhy et al. 2008 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.56 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); I ² = 26% Test for overall effect: Z = 3.84 (P = 0.0001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.19, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 29 164 Heterogeneity: Tau ² = 0.00; Chi ² = 1.00, df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
Haggsträm et al. 2006 27 53 9 51 3.8% 2.89 [1.51, 5.52] Holt et al. 2005 23 88 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 1999 103 243 31 159 9.9% 2.17 [1.53, 3.08] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Total events 936 383 Jorenby et al. 1999 103 243 73 243								_ _ _
Holt et al. 2005 23 88 4 46 1.7% 3.01 [1.11, 8.17] Jorenby et al. 1999 103 243 31 159 9.9% 2.17 [1.53, 3.08] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2008 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
Jorenby et al. 1999 103 243 31 159 9.9% 2.17 [1.53, 3.08] Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 243] McCathy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2008 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67, 29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 29 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
Jorenby et al. 2006 72 340 42 340 9.8% 1.71 [1.21, 2.43] McCarthy et al. 2008 35 229 10 234 3.5% 3.58 [1.81, 7.05] Nides et al. 2008 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00 (df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
$ \begin{array}{c} \text{McCattry et al. 2008} & 35 & 229 & 10 & 234 & 3.5\% & 3.58 [1.81, 7.05] \\ \text{Nides et al. 2006} & 57 & 126 & 27 & 123 & 8.6\% & 2.06 [1.40, 3.03] \\ \text{Rovina et al. 2009} & 45 & 169 & 1 & 36 & 0.5\% & 9.59 [1.37, 67.29] \\ \text{Tonnesen et al. 2003} & 126 & 527 & 27 & 180 & 8.8\% & 1.59 [1.09, 2.33] \\ \text{Subtotal (95\% CI)} & 4116 & 3225 100.0\% & 1.86 [1.63, 2.13] \\ \text{Heterogeneity: Tau2 = 0.02; Chi2 = 17.60, df = 13 (P = 0.17); I2 = 26\% \\ \text{Test for overall effect: } Z = 9.07 (P < 0.00001) \\ 1.2.7 \ \text{Bupropion vs NRT} \\ \text{Anthenelli et al. 2016} & 126 & 989 & 91 & 1006 & 47.3\% & 1.41 [1.09, 1.82] \\ \text{Jorenby et al. 1999} & 103 & 243 & 73 & 243 & 52.7\% & 1.41 [1.11, 1.80] \\ \text{Subtotal (95\% CI)} & 1232 & 1249 & 100.0\% & 1.41 [1.11, 1.80] \\ \text{Total events} & 229 & 164 \\ \text{Heterogeneity: Tau2 = 0.00; Chi2 = 0.00, df = 1 (P = 0.99); I2 = 0\% \\ \text{Test for overall effect: } Z = 3.84 (P = 0.0001) \\ \end{array}$								
Nides et al. 2006 57 126 27 123 8.6% 2.06 [1.40, 3.03] Rovina et al. 2009 45 169 1 36 0.5% 9.59 [1.37, 67.29] Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; ChF ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; ChF ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)		35			234			
Tonnesen et al. 2003 126 527 27 180 8.8% 1.59 [1.09, 2.33] Subtotal (95% CI) 4116 3225 100.0% 1.86 [1.63, 2.13] Total events 936 383 Heterogeneity: Tau ² = 0.02; Ch ² = 17.60, df = 13 (P = 0.17); P = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.11, 1.80] Total events 229 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00 df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 0.01 0.1 1 10	Nides et al. 2006	57	126	27	123	8.6%		
Subtotal (95% CI) 4116 3225 100.0% 1.86 $(1.63, 2.13)$ Total events 936 383 Heterogeneity: Tau ² = 0.02; Ch ² = 17.60, df = 13 (P = 0.17); I ² = 26% Test for overall effect: Z = 9.07 (P < 0.00001)								
Total events 936 383 Heterogeneity: Tau ² = 0.02; Chl ² = 17.60, df = 13 (P = 0.17); I ² = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% Cl) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chl ² = 0.00, df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)		126		27				
Heterogeneity: Tau ² = 0.02; Chi ² = 17.60, df = 13 (P = 0.17); I ² = 26% Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% Cl) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)			4116		3225	100.0%	1.86 [1.63, 2.13]	•
Test for overall effect: Z = 9.07 (P < 0.00001) 1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001)								
1.2.7 Bupropion vs NRT Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% Cl) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau² = 0.00; Ch² = 0.000 df = 1 (P = 0.99); P² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)					= 0.17);	l*= 26%		
Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 0.01 0.1 1 10	rest for overall effect: Z =	9.07 (P <	v.v0001)				
Anthenelli et al. 2016 126 989 91 1006 47.3% 1.41 [1.09, 1.82] Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00, df = 1 (P = 0.99); P = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 0.01 0.1 1 10	1.2.7 Bupropion vs NPT							
Jorenby et al. 1999 103 243 73 243 52.7% 1.41 [1.11, 1.80] Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18, 1.68] Total events 229 164 Heterogeneity: Tau ^z = 0.00; Chi ^z = 0.00, df = 1 (P = 0.99); I ^z = 0% Test for overall effect: Z = 3.84 (P = 0.0001)		100	000	04	1006	47 204	1 41 [1 00 4 02]	-
Subtotal (95% CI) 1232 1249 100.0% 1.41 [1.18; 1.68] Total events 229 164 Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); i ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 0.01 0.1 1 10								_
Total events 229 164 Heterogeneity: Tau ² = 0.00; Ch ² = 0.00, df = 1 (P = 0.99); I ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001) 0.01 0.1 1 10		103		13				
Heterogeneity: Tau ² = 0.00; Chi ² = 0.00, df = 1 (P = 0.99); i ² = 0% Test for overall effect: Z = 3.84 (P = 0.0001)		229		164			[
Test for overall effect: Z = 3.84 (P = 0.0001)).00, df=		.99); I ^z :	= 0%		
0.01 0.1 1 10								
		-	,					
								. store metterial i divere control

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

	Experime	ental	Contr	ol		Risk Ratio	Risk Ratio
Study or Subgroup	Events				Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.1.1 Varenicline vs Pla							
Anthenelli et al. 2016	83	990	39	999	8.3%	2.15 [1.48, 3.11]	
Bolliger et al. 2011	16	390	2	198	3.3%	4.06 [0.94, 17.49]	
Cinciripini et al. 2013	13	86	11	106	6.2%	1.46 [0.69, 3.09]	
Ebbert et al. 2015	86	751	43	742	8.4%	1.98 [1.39, 2.81]	
Fagerström et al. 2010	17	213	3	218	4.1%	5.80 [1.72, 19.50]	· · · · · · · · · · · · · · · · · · ·
Gonzales et al. 2006	36	349	19	344	7.5%	1.87 [1.09, 3.19]	
Gonzales et al. 2000 Gonzales et al. 2014	36	249	8	245	6.3%	4.43 [2.10, 9.33]	
Jorenby et al. 2006	45						
		343	12	340	7.0%	3.72 [2.00, 6.90]	
Lerman et al. 2015	186	420	182	418	9.1%	1.02 [0.87, 1.19]	
Nides et al. 2006	19	125	10	123	6.4%	1.87 [0.91, 3.86]	
Oncken et al. 2006	15	129	6	121	5.4%	2.34 [0.94, 5.85]	
Rennard et al. 2012	61	486	5	165	5.5%	4.14 [1.69, 10.13]	
Rigotti et al. 2010	28	355	6	359	5.6%	4.72 [1.98, 11.26]	
Tonnesen et al. 2013	35	70	26	69	8.3%	1.33 (0.90, 1.95)	
Tsai et al. 2007	7	126	1	124	2.0%	6.89 [0.86, 55.17]	
William et al. 2007	57	251	9	126	6.7%	3.18 [1.63, 6.21]	
Subtotal (95% CI)		5333		4697	100.0%	2.42 [1.75, 3.36]	•
Total events	740		382				
Heterogeneity: Tau ² = 0.1	30; Chi ² = 8	3.53, df	= 15 (P ·	< 0.000	01); I ² = 8	2%	
Fest for overall effect: Z =	= 5.30 (P < 0	0.00001)				
		<u> </u>					
1.1.2 Varenicline vs NR	r						
Anthenelli et al. 2016	83	990	111	1006	25.4%	0.76 [0.58, 1.00]	
Aubin et al. 2008	44	376	31	370	19.5%	1.40 [0.90, 2.16]	+
Baker et al. 2016	98	424	95	662	26.0%	1.61 [1.25, 2.08]	-
Lerman et al. 2015	186	420	182	418	29.2%	1.02 [0.87, 1.19]	↓ 1
Subtotal (95% CI)	100	2210	102		100.0%	1.13 [0.83, 1.55]	▲
Total events	411	2210	419	2100	1001077	into [olooj hoo]	
Heterogeneity: Tau ² = 0.1		7 00 46		0 0005	12 - 020	,	
-			= 3 (P =	0.0005); 17 = 83%	0	
Test for overall effect: Z =	= 0.78 (P = 0	J.44)					
4.4.2 Maranialina un Duu	renien						
1.1.3 Varenicline vs Bug							100-000
Anthenelli et al. 2016	83	990	47	989	22.1%	1.76 [1.25, 2.50]	-
Cinciripini et al. 2013	13	86	6	102	10.3%	2.57 [1.02, 6.47]	
Gonzales et al. 2006	36	349	18	329	17.3%	1.89 [1.09, 3.25]	
Jorenby et al. 2006	45	343	20	340	18.3%	2.23 [1.35, 3.70]	
Nides et al. 2006	19	125	15	126	15.5%	1.28 [0.68, 2.40]	
Zhang et al. 2022	18	499	27	464	16.5%	0.62 [0.35, 1.11]	
Subtotal (95% CI)		2392		2350	100.0%	1.55 [1.06, 2.26]	◆
Total events	214		133				
Heterogeneity: Tau ² = 0.1	14: Chi ² = 1	3.98. df	= 5 (P =	0.02); P	² = 64%		
Test for overall effect: Z =							
1.1.4 NRT Vs Placebo							
Anthenelli et al. 2016	111	1006	39	999	25.3%	2.83 [1.98, 4.03]	
Aveyard et al. 2018	9	880	1	860	8.5%	8.80 [1.12, 69.27]	
Harris et al. 1994	47	156	9	157	21.8%	5.26 [2.67, 10.35]	
Jorenby et al. 1999	47		4	159	17.8%		
		243				7.20 [2.64, 19.64]	_
Lerman et al. 2015	182	418 2703	132	408	26.5% 100.0%	1.35 [1.13, 1.61]	
Subtotal (95% CI)		2105	405	2000	100.0%	3.46 [1.67, 7.15]	
Total events	393		185			~	
Heterogeneity: Tau ² = 0.1	•		= 4 (P <	0.0000	1); l² = 90	%	
Test for overall effect: Z =	= 3.34 (P = 0	0.0008)					
A C Dunnelson							
1.1.5 Bupropion vs plac				t gantesi	a chaine anns an		L
Anthenelli et al. 2016	47	989	39	999	44.3%	1.22 [0.80, 1.84]	
	18	329	19	344	19.5%	0.99 [0.53, 1.85]	-+-
Gonzales et al. 2006		243	4	159	6.0%	1.80 [0.58, 5.55]	
	11	240	12	340	15.6%	1.67 [0.83, 3.36]	+
Jorenby et al. 1999	11 20	340		234	1.3%	2.04 [0.19, 22.38]	
Gonzales et al. 2006 Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008		229	1				
Jorenby et al. 1999 Jorenby et al. 2006	20		1 10	123	13.2%	1.46 [0.68, 3.13]	
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008	20 2	229		123	13.2% 100.0%	1.46 [0.68, 3.13] 1.30 [0.98, 1.71]	•
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI)	20 2 15	229 126	10	123			•
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Total events	20 2 15 113	229 126 22 56	10 85	123 2199	100.0%		•
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1	20 2 15 113 00; Chi ² = 1	229 126 22 56 .86, df =	10 85	123 2199	100.0%		•
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI)	20 2 15 113 00; Chi ² = 1	229 126 22 56 .86, df =	10 85	123 2199	100.0%		•
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0. Test for overall effect: Z =	20 2 15 113 00; Chi ² = 1 = 1.85 (P = 0	229 126 22 56 .86, df =	10 85	123 2199	100.0%		•
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ^e = 0.1 Fest for overall effect: Z = 1.1.6 Bupropion vs NRT	20 2 15 113 00; Chi ^z = 1 = 1.85 (P = 0	229 126 2256 .86, df=).06)	10 85 5 (P = 0	123 2199 .87); I ^z :	100.0% = 0%	1.30 (0.98, 1.71)	_
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = 1.1.6 Bupropion vs NRT Anthenelli et al. 2016	20 2 15 113 00; Chi ² = 1 = 1.85 (P = 0 47	229 126 22 56 .86, df = 0.06) 989	10 85 5 (P = 0 111	123 2199 .87); I ² 1006	100.0% = 0% 63.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60)	•
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = 1.1.6 Bupropion vs NRT Anthenelli et al. 2016 Jorenby et al. 1999	20 2 15 113 00; Chi ^z = 1 = 1.85 (P = 0	229 126 2256 .86, df= 0.06) 989 243	10 85 5 (P = 0	123 2199 .87); I ² 1006 243	100.0% = 0% 63.0% 37.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60) 0.25 (0.13, 0.47)	
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = 1.1.6 Bupropion vs NRT Anthenelli et al. 2016 Jorenby et al. 1999 Subtotal (95% CI)	20 2 15 00; Chi ² = 1 = 1.85 (P = 0 47 11	229 126 22 56 .86, df = 0.06) 989	10 85 5 (P = 0 111 44	123 2199 .87); I ² 1006 243	100.0% = 0% 63.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60)	- -
Jorenby et al. 2006 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = 1.1.6 Bupropion vs NRT Anthenelli et al. 2016 Jorenby et al. 1999 Subtotal (95% CI) Total events	20 2 15 00; Chi ² = 1 = 1.85 (P = 0 47 11 58	229 126 2256 .86, df = 0.06) 989 243 1232	10 85 5 (P = 0 111 44 155	123 2199 .87); I ² 1006 243 1249	100.0% = 0% 63.0% 37.0% 100.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60) 0.25 (0.13, 0.47)	→
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = 1.1.6 Bupropion vs NRT Anthenelli et al. 2016 Jorenby et al. 1999 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1	20 2 15 00; Chi ² = 1 = 1.85 (P = 0 47 11 58 08; Chi ² = 2	229 126 2256 .86, df = 0.06) 989 243 1232 .22, df =	10 85 5 (P = 0 111 44 155	123 2199 .87); I ² 1006 243 1249	100.0% = 0% 63.0% 37.0% 100.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60) 0.25 (0.13, 0.47)	- -
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2006 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.1 Fest for overall effect: Z = 1.1.6 Bupropion vs NRT Anthenelli et al. 2016 Jorenby et al. 1999 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.1	20 2 15 00; Chi ² = 1 = 1.85 (P = 0 47 11 58 08; Chi ² = 2	229 126 2256 .86, df = 0.06) 989 243 1232 .22, df =	10 85 5 (P = 0 111 44 155	123 2199 .87); I ² 1006 243 1249	100.0% = 0% 63.0% 37.0% 100.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60) 0.25 (0.13, 0.47)	→
lorenby et al. 1999 lorenby et al. 2006 AcCarthy et al. 2008 McCarthy et al. 2008 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.1 Fest for overall effect: Z = I.1.6 Bupropion vs NRT Anthenelli et al. 2016 Jorenby et al. 1999 Subtotal (95% CI) Fotal events Heterogeneity: Tau ² = 0.1	20 2 15 00; Chi ² = 1 = 1.85 (P = 0 47 11 58 08; Chi ² = 2	229 126 2256 .86, df = 0.06) 989 243 1232 .22, df =	10 85 5 (P = 0 111 44 155	123 2199 .87); I ² 1006 243 1249	100.0% = 0% 63.0% 37.0% 100.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60) 0.25 (0.13, 0.47)	→
Jorenby et al. 1999 Jorenby et al. 2006 McCarthy et al. 2008 Nides et al. 2008 Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.1 Test for overall effect: Z = 1.1.6 Bupropion vs NRT Anthenelli et al. 2016 Jorenby et al. 1999 Subtotal (95% CI) Total events	20 2 15 00; Chi ² = 1 = 1.85 (P = 0 47 11 58 08; Chi ² = 2	229 126 2256 .86, df = 0.06) 989 243 1232 .22, df =	10 85 5 (P = 0 111 44 155	123 2199 .87); I ² 1006 243 1249	100.0% = 0% 63.0% 37.0% 100.0%	1.30 (0.98, 1.71) 0.43 (0.31, 0.60) 0.25 (0.13, 0.47)	

0.01 0.1 1 10 Favours intervention Favours control

Figure 3. Continued

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

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

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 alpha4beta2 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 industrysponsored 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 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 metaanalysis—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.I., N.J., P.D., P.C., P.V.; Writing – review & editing: C.P., C.I., N.J., P.D., P.C., P.V.; Supervision: C.I., N.J.; Validation: C.I., P.C.; Visualization: C.I.; 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

- Tobacco. World Health Organization. [Internet]. https://www.who.int/fr/ news-room/fact-sheets/detail/tobacco.
- 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/.
- 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.
- Perriot J, Underner M, Peiffer G. Smoking cessation in "difficult smokers". *Revue des maladies respiratoires*. 2012;29(4):448–461.
- 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.
- 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.

- 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.
- Cahill K, Stevens S, Lancaster T. Pharmacological treatments for smoking cessation. JAMA. 2014;311(2):193–194. doi:10.1001/jama.2013.283787.
- 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.
- 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.
- Marlatt GA, Donovan DM, eds. Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. 2nd ed. New York: Guilford Press; 2005.
- 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.
- 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.
- 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.
- Hartmann-Boyce J, McRobbie H, Butler AR, et al. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2021;4(4):CD010216.
- Benowitz NL. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. *Annu Rev Pharmacol Toxicol*. 2009;49: 57–71.
- 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.
- Zhang L, Samet J, Caffo B, Punjabi NM. Cigarette smoking and nocturnal sleep architecture. Am J Epidemiol. 2006;164(6):529–537.
- 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.
- Liao Y, Xie L, Chen X, et al. Sleep quality in cigarette smokers and nonsmokers: findings from the general population in central China. BMC Public Health. 2019;19(1):808
- 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.
- 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.
- 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.
- 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.
- Jaehne A, Loessl B, Bárkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. *Sleep Med Rev.* 2009;13(5):363–377.
- 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.
- 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.
- 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.
- Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest.* 2014;146(5):1387–1394. doi:10.1378/ chest.14-0970.

- Salanti G, Higgins JPT, Ades AE, Ioannidis JPA. Evaluation of networks of randomized trials. *Stat Methods Med Res.* 2008;17(3):279–301.
- Riley RD, Jackson D, Salanti G, et al. Multivariate and network metaanalysis 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.
- 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&con ceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FMED DRA%2F10040991. Accessed October 25, 2022.
- Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia [Internet]. www.covidence.org.
- Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:14898.
- 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.
- Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration, 2020.
- Ahluwalia JS, Harris KJ, Catley D, Okuyemi KS, Mayo MS. Sustainedrelease 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.
- 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.
- Aveyard P, Lindson N, Tearne S, et al. Nicotine preloading for smoking cessation: the preloading RCT. *Health Technol Assess*. 2018;22(41):1–84.
- 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.
- Bolliger CT, Issa JS, Posadas-Valay R, et al. Effects of varenicline in adult smokers: a multinational, 24-week, randomized, double-blind, placebocontrolled 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, Søes-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.
- 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.
- 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.
- 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.
- 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.
- 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.

- 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 $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006; **296**(1):47–55.
- Haggsträm 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.
- 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.
- 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 alphabeta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006;**296**(1):56–63.
- Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustainedrelease bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999;340(9):685–691.
- 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 placebocontrolled trial. *Lancet Respir Med.* 2015;3(2):131–138. doi:10.1016/S2213-2600(14)70294-2.
- 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.
- 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 $\alpha 4\beta 2$ 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.
- 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.
- Rennard S, Hughes J, Cinciripini PM, et al. A randomized placebocontrolled trial of varenicline for smoking cessation allowing flexible quit dates. *Nicotine Tob Res.* 2012;14(3):343–350.
- 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.
- 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.
- 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.
- 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.
- Tonnesen P, Mikkelsen K. Varenicline to stop long-term nicotine replacement ment use: a double-blind, randomized, placebo-controlled trial. *Nicotine Tob Res.* 2013;15(2):419–427.
- Tonnesen P, Tonstad S, Hjalmarson 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 $\alpha 4\beta 2$ nicotinic acetylcholine receptor partial

agonist, as a new therapy for smoking cessation in Asian smokers. *Clin Ther.* 2007;**29**(6):1027–1039.

- 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.
- 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, doubleblind, 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.
- Gourlay SG, Forbes A, Marriner T, McNeil JJ. Predictors and timing of adverse experiences during trandsdermal 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.
- 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.
- 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.
- Page F, Coleman G, Conduit R. The effect of transdermal nicotine patches on sleep and dreams. *Physiol Behav.* 2006;88(4-5):425–432.
- 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.

- Pataka A, Frantzidis C, Nday C, et al. Polysomnographic changes after varenicline administration for smoking cessation. *ERJ Open Res.* 2019; 5(3):156.
- 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.
- 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.
- 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.
- Lewis DA. Sleep in patients with asthma and chronic obstructive pulmonary disease. Curr Opin Pulm Med. 2001;7(2):105–112.
- 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.
- Hughes JR, Hatsukami D. Signs and symptoms of tobacco withdrawal. Arch Gen Psychiatry. 1986;43(3):289–294. doi:10.1001/archpsyc.1986.01800030107013.
- Morin CM. Insomnia: Psychological assessment and management. Vol. xvii. New York, NY: Guilford Press; 1993:238.
- 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.
- 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.
- Dorner 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.
- 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.
- 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.