Effects and safety of smoking cessation methods in patients with a history of major depressive disorder (p-MDD) or current dysthymia: a systematic review

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Abstract

AIM

To summarize the efficacy and adverse effects of pharmacological and non-pharmacological treatments for smoking cessation in individuals with a history of depressive symptoms (dysthymia) or past major depressive disorder (p-MDD).

METHODS

This systematic review and meta-analysis is linked to a broader systematic review on smoking cessation strategies in patients with severe mental illness, including severe depressive symptoms or recurrent MDD. The current review focuses specifically on individuals with a past diagnosis of MDD or current mild depressive symptoms. We systematically searched PubMed, Embase, CENTRAL, Web of Science, and Scopus for randomized controlled trials (RCT's) evaluating all types of smoking cessation interventions from inception through December 2023. A total of 24 eligible studies were identified. Article screening was independently conducted by two reviewers. Data-extraction was conducted by one reviewer and independently verified by a second. Where appropriate, results were pooled in a meta-analysis. Methodological quality was assessed using the Cochrane Risk of Bias Tool, and the certainty of evidence was evaluated using the GRADE approach. Primary outcomes included short-term (<6 months, STA) and long-term (>6 months, LTA) smoking abstinence. Secondary outcomes were mental health (ME), weight (WE), and serious adverse events (SAEs).

RESULTS

Sixteen randomized controlled trials (2,465 patients) met the inclusion criteria. We found moderate certainty evidence supporting the effectiveness of bupropion for short-term abstinence (OR 4.08, 95% CI 2.30–7.22) and long-term abstinence (OR 4.62, 95% CI 2.09–10.24). Similarly, varenicline showed moderate certainty evidence for short-term (OR 3.40, 95% CI 2.31–5.01) and long-term (OR 2.01, 95% CI 1.39–2.89) abstinence. One small study found evidence supporting clonidine for short-term abstinence (OR 6.97, 95%CI 1.57-30.87), although the certainty of evidence was low. Varenicline was not associated with a significant impact on SAE (OR: 0.96, 95% CI 0.49-1.90), with moderate certainty of evidence. The certainty of evidence for other interventions and secondary outcomes was generally low, primarily due to imprecision and a higher risk of bias.

CONCLUSION

Moderate-certainty evidence supports bupropion and varenicline as effective smoking cessation treatments for both short- and long-term abstinence in individuals with a history of MDD or current dysthymia. Evidence on the effects of smoking cessation methods (SCMs) on mental health, weight, and SAEs was limited, although varenicline did not appear to increase SAE risk. To our knowledge, this is the most comprehensive and up-to-date synthesis of smoking cessation strategies in individuals with p-MDD or current dysthymia conducted in the past decade.

Keywords

Smoking cessation, major depressive disorder, dysthymia, depressive symptoms, bupropion, varenicline, nicotine replacement therapy, clonidine, behavioral interventions.

Abstract (Dutch)

DOELSTELLING
Samenvatten van de effectiviteit en bijwerkingen van farmacologische en niet-farmacologische behandelingen voor rookstop bij personen met milde depressieve symptomen (dysthymie) of een doorgemaakte majeure depressie (p-MDD).

METHODEN
Deze systematische review en meta-analyse maakt deel uit van een bredere systematische review naar strategieën voor stoppen met roken bij patiënten met ernstige psychische aandoeningen, waaronder ernstige depressieve symptomen of MDD. De huidige review richt zich specifiek op personen met een doorgemaakte episode van MDD of huidige milde depressieve symptomen. We hebben systematisch gezocht in PubMed, Embase, CENTRAL, Web of Science en Scopus naar gerandomiseerde gecontroleerde trials (RCT's) over alle vormen van interventies om te stoppen met roken, vanaf het begin tot december 2023. In totaal werden 24 geschikte studies geïdentificeerd. Het screenen van artikelen werd onafhankelijk uitgevoerd door twee onderzoekers. Gegevens werden geëxtraheerd door één onderzoeker en onafhankelijk geverifieerd door een tweede. Waar mogelijk werden de resultaten gepoold in een meta-analyse. De methodologische kwaliteit werd beoordeeld met de Cochrane Risk of Bias Tool, en de bewijskracht werd geëvalueerd met de GRADE-methode. Primaire uitkomstmaten waren kortetermijn (<6 maanden, STA) en langetermijn (>6 maanden, LTA) abstinentie van roken. Secundaire uitkomsten waren mentale gezondheid (ME), gewicht (WE) en ernstige bijwerkingen (SAE's).

RESULTATEN
Zestien RCT's (2.465 patiënten) voldeden aan de inclusiecriteria. We vonden bewijs van matige zekerheid voor de effectiviteit van bupropion bij zowel kortetermijnabstinentie (OR 4.08, 95% CI 2.30–7.22) als langetermijnabstinentie (OR 4.62, 95% CI 2.09–10.24). Ook varenicline toonde matige zekerheid van bewijs voor kortetermijn- (OR 3.40, 95% CI 2.31–5.01) en langetermijnabstinentie (OR 2.01, 95% CI 1.39–2.89). Eén kleine studie vond bewijs ter ondersteuning van clonidine bij kortetermijnabstinentie (OR 6.97, 95% CI 1.57–30.87), hoewel de bewijskracht laag was. Varenicline had geen significant effect op het risico op ernstige bijwerkingen (OR 0.96, 95% CI 0.49–1.90), met matige zekerheid van bewijs. De bewijskracht voor andere interventies en secundaire uitkomsten was over het algemeen laag, voornamelijk door onnauwkeurigheid en een verhoogd risico op bias.

CONCLUSIE
Er is matig zeker bewijs dat bupropion en varenicline effectieve behandelingen zijn om te stoppen met roken op zowel korte als lange termijn bij personen met een voorgeschiedenis van MDD of huidige dysthymie. Er was beperkte evidentie over de effecten van rookstopinterventies (SCMs) op mentale gezondheid, gewicht en ernstige bijwerkingen, hoewel varenicline het risico op ernstige bijwerkingen niet leek te verhogen. Voor zover ons bekend, is dit de meest uitgebreide en recente samenvatting van rookstopstrategieën bij personen met p-MDD of huidige dysthymie in het afgelopen decennium.

Trefwoorden
Rookstop, majeure depressieve stoornis, dysthymie, depressieve symptomen, bupropion, varenicline, nicotinevervangende therapie, clonidine, gedragsinterventies.

Introduction

Major Depressive Disorder (MDD) is one of the most common mental illnesses and has a significant effect on psychosocial functioning and quality of life. Recent statistics estimate that nearly one in five individuals will experience an episode of major depression during their lifetime (lifetime prevalence: 15%-18%) (1). Depression is already an important cause of disability worldwide and its prevalence could continue to rise, becoming the leading cause of global disease burden by 2030 (2). There is a well-documented association between smoking and depression. Research suggests that smokers face a two-fold risk of developing depression (3), while patients with MDD are more likely to smoke than the general population. Likewise, individuals with depressive symptoms (dysthymia) or a history of MDD on average smoke more than those without (4).

The negative impact of smoking on cardiovascular health and mortality is well established and this impact is even more pronounced in individuals with dysthymia or a history of MDD (5,6). The overall relative risk (RR) for developing coronary heart disease in patients with MDD at baseline compared to the general population is 1.64 (7). MDD patients are also at greater risk of mortality due to coronary heart disease (RR 1.8) (8). These statistics highlight the importance of developing adequate as well as tailored smoking cessation methods (SCM) in this population to further reduce modifiable risk factors.

SCM have included pharmacological interventions (such as antidepressants, bupropion, varenicline, nicotine replacement therapy…), psychological interventions (such as cognitive behavioral treatment, mood management interventions, exercise and counselling intervention…) or combinations of both. Despite previous research, developing effective SCM in patients with a history of depression or current dysthymia remains a major challenge that is insufficiently addressed (9,10).

Prior reviews were conducted at least a decade ago and have not been able to draw clear conclusions about the best approach to adequate SCM, including pharmacotherapy and behavioral approaches, due to scarce and heterogenous data. A systematic review published in 2013 highlighted the little available information on the best treatment for smokers with concomitant dysthymia and minor depression (9). A meta-analysis from 2012 found a small positive effect of adding behavioral mood management in patients with a history of depression or current significant depressive symptoms (10). Other behavioral interventions such as digital lifestyle interventions and psychosocial mood management remain under-researched. Trials investigating antidepressants such as fluoxetine and nortriptyline, as well as nicotine replacement therapies (NRT) and bupropion, have shown small positive effects in smokers with a history of depression, although these results are not statistically significant (10,11).

Despite the growing prevalence of smokers with a history of MDD or dysthymia, until now few reviews have summarized SCM specifically in this population and limited progress has been made in tailoring SCM to this subgroup in current clinical practice.

This systematic review aims to provide an updated synthesis of the evidence regarding smoking cessation in individuals with a history of major depression or dysthymia. By addressing this research gap, the review seeks to identify clinically implementable strategies that maximize smoking cessation success while minimizing adverse effects.

Methods

We performed a systematic review and meta-analysis following the guidelines set by Cochrane (12) and the GRADE Working Group (13), and reported the results according to the standards set by the PRISMA 2020 statement (14). The review was designed to assess the effectiveness and safety of smoking cessation interventions in adults with mild depressive symptoms or a history of major depressive disorder.

This review is related to a broader systematic review conducted by Bekkering et al. (2025) (15), which focused on smoking cessation interventions in individuals with psychiatric disorders. While that review included participants with MDD, it was limited to populations with either currently severe depressive symptoms or recurrent MDD. In contrast, the present review targets individuals with a clinical diagnosis of MDD who were not included in the former review.

We were able to build on the search strategy developed for the Bekkering et al. review and contributed actively to that project by participating in the assessment of risk of bias for the included studies.

Eligibility Criteria

We included randomized controlled trials (RCT's) that fulfilled the following PICO criteria:

Population

Adults (≥18 years) with a clinical history of major depressive disorder defined using DSM-5 or ICD-10 classification systems, that may experience current mild depressive symptoms as assessed by validated depression rating scales. Participants had to be active smokers with an expressed intention to reduce or quit smoking. Studies that reported on a mixed population were included only if ≥80% of participants met the above criteria or if results were reported separately.

Intervention

All pharmacological and non-pharmacological interventions aimed at smoking cessation were eligible. Studies involving combination therapies were also eligible. Co-interventions were permitted if applied equally to intervention and control groups.

Comparators

Eligible comparators included placebo, another active intervention, usual care, or no treatment.

Outcomes

Outcomes of interest included short-term abstinence (STA) (≥ 2 weeks), long-term abstinence (LTA) (≥ 6 months), mental health, weight gain, and serious adverse events (SAE). As abstinence may be defined in a variety of ways, we applied a predefined hierarchy of results: biochemically verified outcomes were prioritized over self-reported outcomes; sustained abstinence was preferred over point prevalence; and biochemically validated point prevalence was prioritized over self-reported sustained abstinence. This hierarchy was based on recommendations from a previous Cochrane review on smoking cessation (16).

Search and selection strategy

The literature search was developed for the systematic review of Bekkering et al. (2025), which spanned PubMed, Embase, CENTRAL, Web of Science, and Scopus from inception through December 2023. The full search strategy is available as supplementary material. From the 20783 records identified, 24 full-text articles were identified for potential inclusion in this focused review. Full texts were screened by the two reviewers separately using the predefined inclusion criteria, with disagreements resolved through discussion.

Data Extraction

Data were independently extracted by one reviewer using a data extraction template and verified by a second reviewer. Extracted data included: general information (study ID, trial register number, title), study characteristics (country, publication year, sample size, and funding source), participant characteristics [age, gender, depression severity/history, smoking behavior (cigarettes/day, Fagerström score)], intervention details [type (pharmacological, non-pharmacological, or combination), duration, dosage, comparator], outcomes (short term abstinence, long term abstinence, mental health, serious adverse events, weight change).

Risk of Bias Assessment

The methodological quality of the included studies was assessed using the CLARITY modification of Cochrane Risk of Bias Tool 1.0 (17). Domains included random sequence generation, allocation concealment, blinding (participants, care givers, outcome assessors, and analysts), incomplete outcome data, selective reporting, and other sources of bias. Risk of bias for each criterion was evaluated as “low,” “probably low,” “high,” or “probably high.” For the items on allocation sequence and allocation concealment there is also the option to add ‘No Information’. Assessments were conducted independently by two reviewers, with disagreements resolved by consensus.

Data Analysis and Synthesis

For dichotomous outcomes individual odds ratios with 95% confidence intervals were calculated from the raw extracted data. Similar interventions were grouped and pooled using a random-effects model. We estimated pooled odds ratios with 95% confidence intervals, and I^2 was used to quantify heterogeneity, with a value greater than 50% indicative of substantial heterogeneity (18). These results were visually represented using a forest plot.

For continuous outcomes such as mental health change and weight gain, data were too sparsely and heterogeneously reported to allow for statistical pooling. These outcomes were therefore synthesized narratively following the SWiM reporting guideline (19). Studies were grouped by intervention type and outcome, and available data were summarized using reported means and standard deviations. No standard effect metric was applied due to heterogeneity in measurement instruments and timepoints. For each outcome, results were presented in structured summaries, with attention to consistency and direction of effects. Limitations in data availability and comparability were explicitly considered when drawing conclusions.

All statistical analysis and plots were made using Review Manager 5.

Certainty of Evidence

Certainty of evidence was assessed using the GRADE approach across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias (13). Assessments were performed

separately for each outcome. Given that only randomized controlled trials were included, all outcomes were initially rated as having high certainty. This rating was subsequently downgraded if serious concerns were identified in one or more domains. For instance, methodological limitations within studies led to downgrading for risk of bias, unexplained variability in results to downgrading for inconsistency, and wide confidence intervals or small sample sizes to downgrading for imprecision. The GRADE assessment was carried out by one reviewer and independently checked by a second. Final certainty ratings—categorized as high, moderate, low, or very low—were summarized in a Summary of Findings table.

Results

Search strategy

The review of Bekkering et al. (2025) identified a total of 20783 records through database searching from inception to December 2023. They identified a set of 24 records that didn't meet their inclusion criteria but could potentially be used for our systematic review. The PRISMA flow diagram of their search is available in the supplementary materials.

Twenty-four full text articles were assessed for eligibility. Five studies didn't report separate results for the proportion of participants with mild to moderate, or a history of MDD. Three articles were excluded because they were based on data already included in this review. Sixteen unique RCT's met the inclusion criteria and were included in this review. The last step in this search can be seen in **Figure 1**.

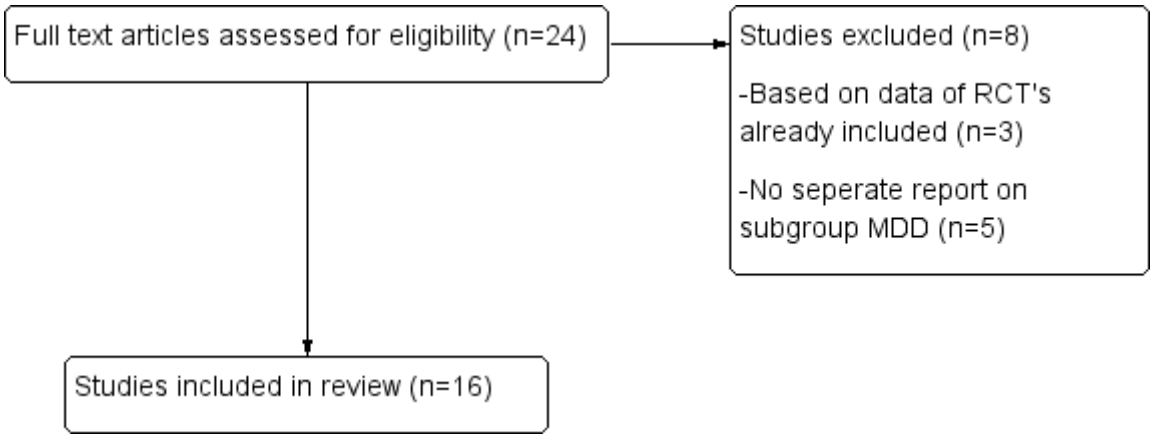


Figure 1: study flow diagram

Included studies

Study characteristics

Most studies (12/16) were conducted in the US. They were published between 1988 and 2023. Sample sizes ranged from 30 to 525, with a median sample size of 113.

The mean age of participant ranged from 39.7 to 53.1 years old. 41.7% of participants were male. At baseline participants smoked on average 23.4 cigarettes a day, and mean score on the Fagerström Test for Nicotine Dependence was 6.5.

Most studies specifically recruited a population of past MDD. Five studies recruited a broader population, either from the general population or individuals with various other mental health conditions. However, they reported separate subgroup analyses for the participants with a history of MDD and were therefore included in this review.

A summary of the main characteristics per study can be found in **Table 1.**

Interventions

Eleven studies compared twelve pharmacological interventions with placebo (20–30) Three of these RCT's examined nicotine replacement therapy (20,24,26), two varenicline (23,30), two bupropion (26,28), two fluoxetine (25,27), one sertraline (21), one nortriptyline (29), and one clonidine (22). Eight studies compared the addition of behavioral interventions with other nonpharmacological

interventions (20,29–35). Four of these RCT's examined the effect of mood management interventions (20,29,31,33), one behavioral activation (30), one contingency management (32), one cognitive behavioral treatment for depression (35), and one exercise (34).
Four RCT's compared 2 interventions at once according to a 2x2 study design (20,26,29,30).
For a summary of study interventions cf. **Table 2.**

Risk of bias

Eight studies (50%) reported an adequately generated randomization sequence; 4 (25%) reported adequately concealed allocation; 11 (69%) of trials blinded patients, 10 (63%) blinded healthcare providers, and 11 (69%) reported blinding outcome assessors. Eleven (69%) reported infrequent loss to follow up, 15 (94%) studies were free of selective outcome reporting. Most trials (15/16, 94%) were at risk for bias for at least one of the domains.
The results of the risk assessment are graphically represented in the risk of bias graph **Figure 2**. The full risk assessment per study can be found in the risk of bias summary in the supplementary materials.

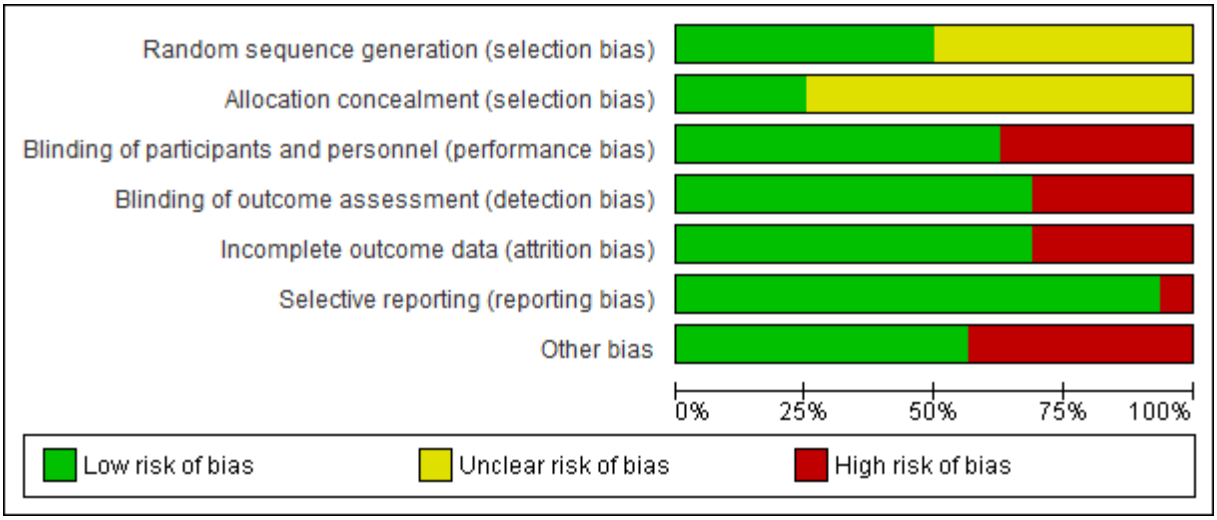


Figure 2: Risk of bias graph review authors' judgements about each risk of bias item presented as percentages across all included studies.

Table 1: Main study characteristics

Study name (NCT record ID)	Country	Sample Size	Mean age	Male (%) total sample	Cigarettes/day	FTND (mean score)	Diagnosis	Mean BDI before treatment	Length of intervention (weeks)	Additional FU (weeks)
Anthenelli et al. (2013) (NCT01078298)	8 countries (US, Spain, Russia, Romania, Hungary, Germany, Croatia, Bosnia and Herzegovina).	525	45.4	0.375	21.1	5.9	p-MDD, c-MDD	NI	12w	40w
Bernard et al. (2015) (NCT01401569)	France	70	48.5	0.4	21.9	6.3	p-MDD	NI	8w	42w
Brown et al. (2001)	US	179	45.1	0.402	27.3	6.8	p-MDD	7.8	6w	46w
Covey et al. (2002)	US	134	45.6	0.365	26.9	6.1	p-MDD	7.4	11.3w	12.7w
Glassman et al. (1988)	US	71	31.85	0.38	31.12		p-MDD	NI	4w	20w
Hall et al. (1994)	US	46(/149)	40.6	0.48	24.9	6.4	p-MDD	6.39	8w	18w
Hall et al. (1996)	US	44(/201)	39.7	0.48	23.8		p-MDD	6.71	8w	44w
Hall et al. (1998)	US	65	41.1	0.354	21.8	5.5	p-MDD	12.1	8w - 12w	52w
Hayford et al. (1998)	US	111/615	43.5	0.34	27.8	7.5	p-MDD	5.8	6w	46w
Hitsman et al. (2023) (NCT02378714)	US	300	50.0	0.45	15.2	5.2	p-MDD, c-MDD	18.7	12w	15w
Saules et al. (2004)	US	30/(150)	39.78	0.455	NA (> or = 15/D)	5.9	p-MDD	4.92	14w	38w
Smith et al. (2003)	US	163/(893)	43.9	0.516	NA (> or = 15/D)	7.4	p-MDD	NI	9w	43w
Spring et al. (2007)	US	109/(247)	44.0	0.65	24.0	6.7	p-MDD	10.9	12w	14w
Thorsteinsson et al. (2001)	US	38	46.2	0.526	28.0	7.1	c-MDD	20.9	2w	1w
Van Der Meer et al. (2010)	The Netherlands	485	43.3	0.235	21.4	5.1	p-MDD	NI	12w	40w
Weidberg et al. (2018) (NCT03163056)	Spain	92	53.07	0.272	20.98	6.04	c-MDD	30.33	8w	0w

p-MDD: participants with a history of Major Depressive Disorder, c-MDD: participants with current Major Depressive Disorder, FTND: Fagerström Test for Nicotine Dependence, BDI: Beck Depression Inventory, FU: Follow-Up, US: United States, NI: No Information

Table 2: Study interventions

2x2 Study Design

Study name	Intervention	Comparison	Co-treatment	Pharmacotherapy dosing
Hall et al. (1996)	2x2 design Group 1: NRT Group 2: Mood management (10× 2h sessions, 8w)	2x2 design Group 1: NA Group 2: Contact-equivalent health education (10× 2h sessions, 8w)	NA	2mg gum at least hourly (12h/day) 3w, ad lib 5w, taper 4w
Hall et al. (1998)	2x2 design Group 1: Nortriptyline Group 2: Mood management (10× 2h sessions, 8w)	2x2 design Group 1: Placebo Group 2: Health education (5× 90min sessions, 8w)	NA	Up to 100mg/d, adjusted via serum levels
Hitsman et al. (2023)	2x2 design Group 1: Varenicline Group 2: Behavioral activation (8× 45min, 12w)	2x2 design Group 1: Placebo Group 2: Standard cessation therapy (12w)	NA	Varenicline titration: 0.5mg 1×/d 3d, 0.5mg 2×/d 4d, 1mg 2×/d 11w
Smith et al. (2003)	2x2 design Group 1: Bupropion Group 2: NRT	2x2 design Group 1: Placebo Group 2: Placebo	NA	Bupropion SR 9w, Nicotine patches 21mg/5w, 14mg/1w, 7mg/1w

Pharmacological Interventions

Study, year	Intervention	Comparison	Co-treatment	Pharmacotherapy dosing
Anthenelli et al. (2013)	Varenicline	Placebo	Weekly cessation counseling	Varenicline 0.5mg 1×/d 3d, 0.5mg 2×/d 4d, 1mg 2×/d 11w
Covey et al. (2002)	Sertraline	Placebo	9 clinical counseling sessions	Titrated to 200mg/d for 6w
Glassman et al. (1988)	Clonidine	Placebo	NA	210-249µg/d titrated over 4w
Hayford et al. (1998)	Bupropion	Placebo	NA	100-300mg/d Bupropion SR 6w
Saules et al. (2004)	Fluoxetine	Placebo	NRT 10w + CBT 6w	Fluoxetine 20mg or 40mg 14w
Spring et al. (2007)	Fluoxetine	Placebo	Group behavioral therapy 9 sessions	Titrated to 60mg/d
Thorsteinsson et al. (2001)	NRT	Placebo	NA	Nicotine patches 21mg/24h 2w + placebo 1w

Behavioral Interventions

Study, year	Intervention	Comparison	Co-treatment	Pharmacotherapy dosing
Bernard et al. (2015)	Exercise + counseling (10× over 8w)	Health education contact	Standard cessation therapy + NRT/Varenicline	NA
Brown et al. (2001)	CBT for depression + condensed cessation (8× 2h sessions, 6w)	Standard treatment (8× 2h sessions, 6w)	NA	NA
Hall et al. (1994)	Mood management (10× 2h group sessions, 8w)	Standard treatment (5× 2h sessions, 8w)	NRT	2mg nicotine gum
Van der Meer et al. (2010)	Mood management (telephone-based CBT)	Proactive telephone counseling	Advice for cessation aids >10 cig/day	NA
Weidberg et al. (2018)	Contingency management	NA	CBT + behavioral activation (8× 90min, 8w) + advice nicotine fading	NA

NRT = nicotine replacement therapy, CBT = cognitive behavioral therapy, SR = sustained release, NA = not applicable.

Main findings

Pharmacological studies

Nicotine replacement therapy

Three studies reported data on short-term abstinence comparing NRT to placebo (20,24,26). The pooled odds ratio (OR) was 1.20 (95% CI 0.44–3.28; I^2 = 63%) in favor of NRT, with very low certainty of evidence (cf. **Figure 3**). Two studies assessed long-term abstinence (20,26), yielding a pooled OR of 0.85 (95% CI 0.44–1.63; I^2 = 0%) in favor of placebo, with low certainty of evidence (cf. **Figure 4**). One study examined mental health outcomes and found no significant differences between groups on BDI, HRSD, or POMS scores (24); certainty was rated very low. No studies reported data on weight gain or serious adverse events.

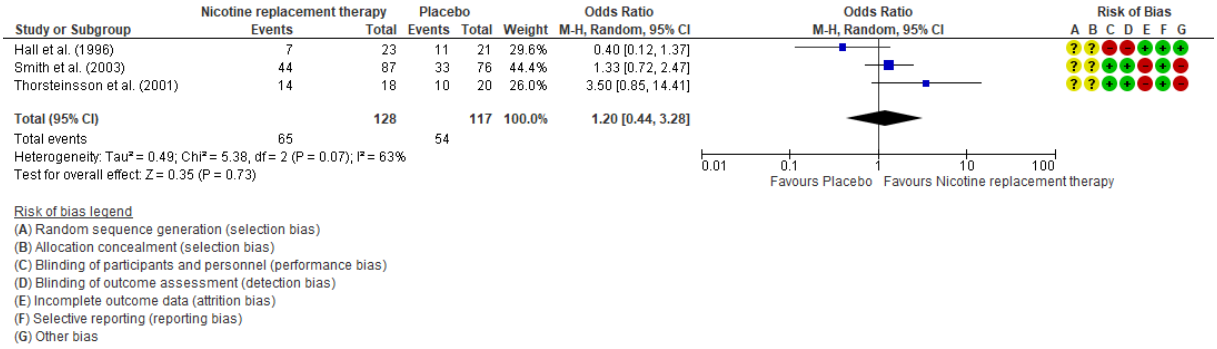


Figure 3: Forrest plot: Short term abstinence, nicotine replacement therapy

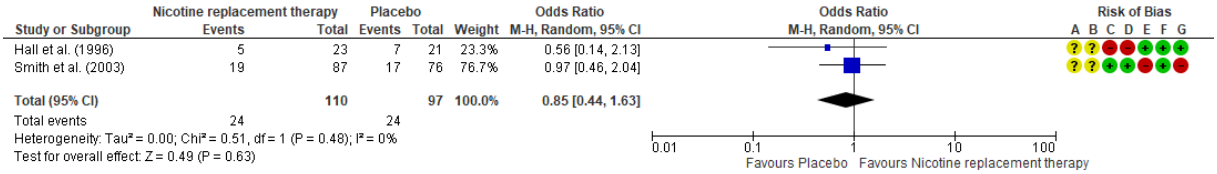


Figure 4: Forrest plot: Long term abstinence, nicotine replacement therapy

Varenicline

Anthenelli et al. (2013) reported short-term abstinence outcomes, with an OR of 3.40 (95% CI 2.31–5.01), and two studies reported long-term abstinence outcomes (23,30), yielding a pooled OR of 2.01 (95% CI 1.39–2.89; I^2 = 0%) in favor of varenicline, with moderate certainty of evidence (cf. **Figure 5**). Two studies reported on serious adverse events (23,30), with a pooled OR of 0.96 (95% CI 0.49–1.90; I^2 = 0%), and moderate certainty of evidence. For mental health, both Anthenelli et al. (2013) and Hitsman et al. (2023) found no statistically significant differences in mood scores between groups; certainty of this evidence was low. No data were available on weight gain.

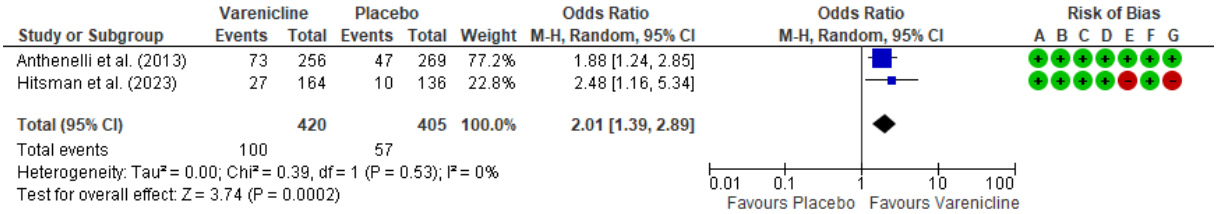


Figure 5: Forrest plot: Long term abstinence, varenicline

Clonidine

Glassman et al. (1988) reported data on short-term abstinence, with an OR of 6.97 (95% CI 1.57–30.87) in favor of clonidine, with low certainty of evidence. No data were available on mental health, weight gain, or serious adverse events.

Bupropion

Two studies assessed short-term abstinence (26,28), resulting in a pooled OR of 4.08 (95% CI 2.30–7.22; $I^2 = 0\%$) in favor of bupropion (cf. **Figure 6**), and two studies reported long-term abstinence (26,28), with a pooled OR of 4.62 (95% CI 2.09–10.24; $I^2 = 0\%$) (cf. **Figure 7**), both with moderate certainty of evidence. No studies reported on mental health, weight gain, or serious adverse events.

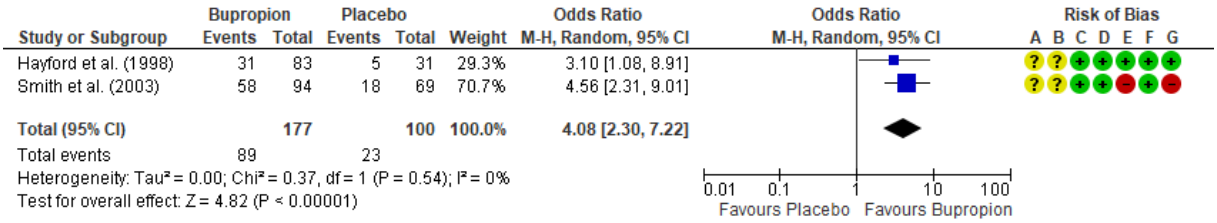


Figure 6: Forrest plot: Short term abstinence, bupropion

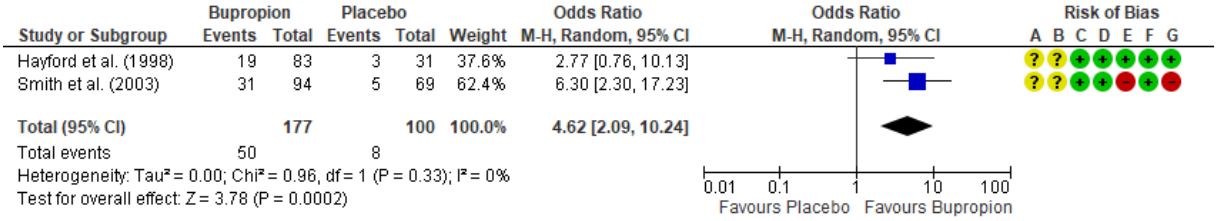


Figure 7: Forrest plot: Long term abstinence, bupropion

Selective serotonin reuptake inhibitors (SSRI's)

Three studies evaluated the effect of SSRI's—specifically sertraline and fluoxetine—on short-term abstinence (21,25,27). The pooled odds ratio (OR) was 1.33 (95% CI: 0.78 to 2.27; $I^2 = 0\%$), showing no statistically significant effect in favor of SSRI's (cf. **Figure 8**). The certainty of evidence for this outcome was moderate. For long-term abstinence, two studies contributed data (21,25), resulting in a pooled OR of 0.80 (95% CI: 0.37 to 1.72; $I^2 = 0\%$), again showing no significant difference between SSRIs and placebo (cf. **Figure 9**). The certainty of evidence for long-term abstinence was low. No data were reported on mental health, weight gain, or serious adverse events.

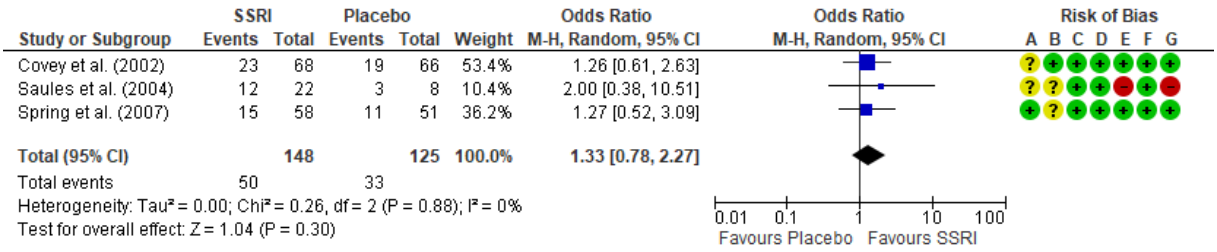


Figure 8: Forrest plot: Short term abstinence, SSRI

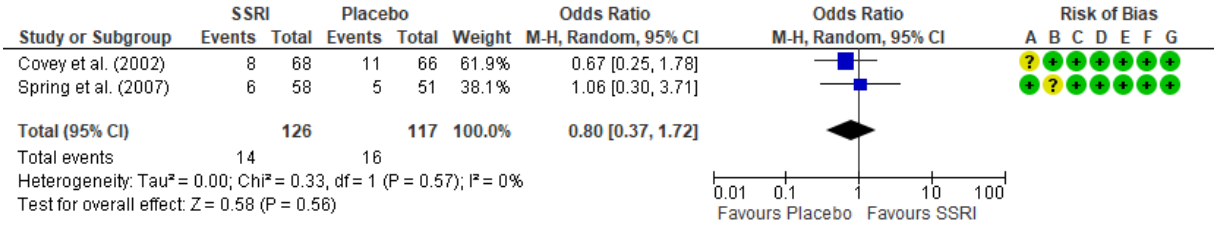


Figure 9: Forrest plot: Long term abstinence, SSRI

Nortriptyline

Hall et al. (1998) assessed short-term abstinence (OR 2.03; 95% CI 0.73–5.61) and long-term abstinence (OR 1.04; 95% CI 0.32–3.39), both with low certainty of evidence (29). No data were reported on mental health, weight gain, or serious adverse events.

Behavioral studies

Behavioral interventions

Six studies assessed short-term abstinence (20,29,31–33,35), with a pooled OR of 1.40 (95% CI 1.07–1.85; I^2 = 0%) in favor of behavioral interventions (cf. **Figure 10**), and five studies reported long-term abstinence (20,29,31,33,35), with a pooled OR of 1.35 (95% CI 0.99–1.85; I^2 = 0%) (cf. **Figure 11**). Certainty of evidence for both outcomes was moderate. Two studies reported on mental health outcomes and found no significant differences between groups (33,35); certainty of evidence was very low. No studies reported on weight gain or serious adverse events.

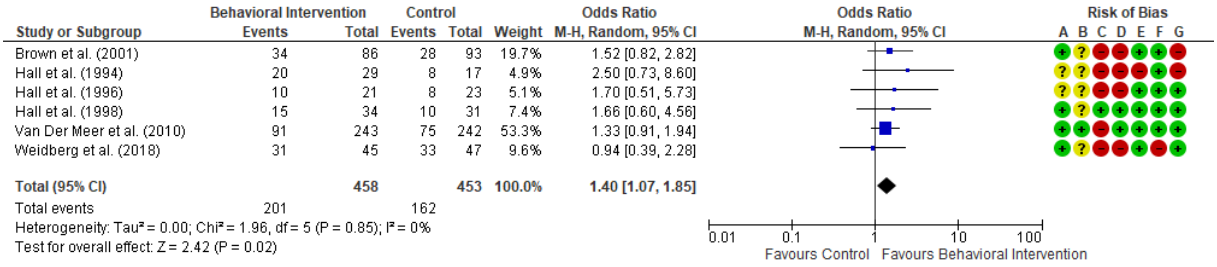


Figure 10: Forrest plot: Short term abstinence, behavioral interventions

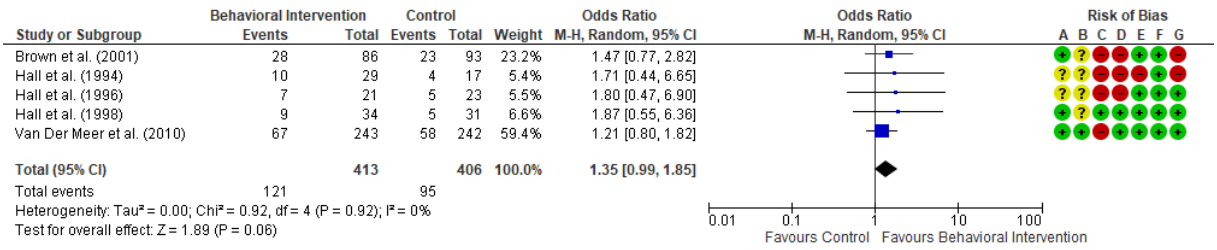


Figure 11: Forrest plot: Long term abstinence, behavioral interventions

Exercise

Bernard et al. (2015) examined the effect of adding exercise to standard cessation therapy. The OR for short-term abstinence was 1.76 (95% CI 0.61–5.05) and for long-term abstinence 1.94 (95% CI 0.51–7.33), with moderate and low certainty of evidence, respectively. Mental health outcomes showed a slightly greater, non-significant, reduction in depressive symptoms in the exercise group, and weight gain was lower at 12 weeks but did not differ significantly by 52 weeks. The certainty of evidence for mental health and weight outcomes was very low. No data were reported on serious adverse events.

Summary Table

Table 3 provides an overview of the effect estimates per intervention, presented as odds ratios with corresponding 95% confidence intervals. The color coding reflects the certainty of evidence, assessed using the GRADE approach. A more detailed table including the corresponding absolute effects is available in the supplementary materials, along with a complete summary of findings and certainty assessment table for each intervention.

Table 3. Summary of results

Outcome / Intervention	NRT	Varenicline	Buproprion	Clonidine	SSRI	TCA (Nortriptyline)	Behavioral interventions	Excercise
STA	N=3 (n=245) OR: 1.20 (95%CI 0.44-3.28)	N=1 (n=525) OR: 3.40 (95%CI 2.31-5.01)	N=2 (n=277) OR: 4.08 (95%CI 2.30-7.22)	N=1 (n=43) OR: 6.97 (95%CI 1.57-30.87)	N=3 (n=273) OR: 1.33 (95%CI 0.78-2.27)	N=1 (n=65) OR: 2.03 (95%CI 0.73 - 5.61)	N=6 (n=911) OR: 1.40 (95%CI 1.07-1.85)	N=1 (n=70) OR: 2.36 (95%CI 0.88-6.34)
LTA	N=2 (n=207) OR: 0.85 (95%CI 0.44-1.63)	N=2 (n=825) OR: 2.01 (95%CI 1.39-2.89)	N=2 (n=277) OR: 4.62 (95%CI 2.09-10.24)	NRS	N=2 (n=243) OR: 0.80 (95%CI 0.37-1.72)	N=1 (n=65) OR: 1.04 (95%CI 0.32-3.39)	N=5 (n=819) OR: 1.35 (95%CI 0.99-1.85)	N=1 (n=70) OR: 1.94 (95%CI 0.51-7.33)
SAE	NRS	N=2 (n=825) OR: 0.96 (95%CI 0.49-1.90)	NRS	NRS	NRS	NRS	NRS	NRS
ME	N=1 (n=38) No significant effect among subjects that remained abstinence during a 3w follow-up period with nicotine patches	N=2 (n=825) No significant differences compared to placebo	NRS	NRS	NRS	NRS	N=2 (n=664) Cognitive-behavioral therapy and a mood management component had no effect on changes of depressive symptoms	N=1 (n=70) No differences compared to control group
WE	NRS	NRS	NRS	NRS	NRS	NRS	NRS	N=1 (n=70) No impact on weight was found

Legende:

High	Moderate	Low	Very Low
We are very confident that the true effect lies close to that of the estimate of the effect	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Outcomes: STA (short term abstinence), LTA (long term abstinence), SAE (serious adverse events), ME (mental health scales), WE (weight).
- Interventions: NRT (Nicotine replacement therapy), SSRI (Selective serotonin reuptake inhibitor), TCA (Tricyclic antidepressive),
- Other abbreviations: NRS (no reporting studies), N (number of studies), n (number of participants), OR (odds ratio), CI (confidence interval)

Discussion

This systematic review and meta-analysis found evidence for bupropion and varenicline as effective SCM for short-term (< 6M) and long-term (> 6M) abstinence in patients with a history of MDD or current dysthymia. Evidence regarding the impact of SCM on mental health outcomes, bodyweight, or severe adverse events was limited, however, varenicline appeared not to be associated with a significant increase in SAEs.

Clonidine

Clonidine showed among all interventions the most profound and statistically significant effect on cessation rates. However, the results were based on a single study involving 43 participants, and the certainty of the evidence was low, indicating that the true effect may differ substantially from the observed estimate. Prior work by Gourlay et al. supports clonidine's efficacy as SCM in the general population, although only 6 RCT's were included, and clinical utility has been limited by side effects (36).

Bupropion

Among all interventions, bupropion demonstrated the second most pronounced and statistically significant effect on both short- and long-term abstinence, for both the relative and absolute effect. These results were rated as moderate certainty evidence, which means, the true effect is likely close to the observed estimate (37).

To date, only one prior review has addressed the use of antidepressants as SCMs in individuals with a history of depression. Gierisch et al. reported modest, non-significant effects across a pooled group of antidepressants (10). In contrast, this meta-analysis treated bupropion separately, as it remains the only antidepressant recommended as a first-line smoking cessation therapy in a general smoking population (38). This analysis revealed that bupropion may be particularly effective in our population, with estimated abstinence rates that may be almost two times higher than those observed in the general smoking population. Wu et al. reported an odds ratio (OR) of 2.13 at 3 months, compared to our findings, which indicate an OR of 4.08 (39). This enhanced effect might reflect an added benefit from bupropion's antidepressant properties in individuals with a history of MDD.

Varenicline

Varenicline showed the third-largest significant and clinically relevant effect for both short- and long-term abstinence. Based on GRADE assessment of moderate certainty, the true effect likely approximates the observed estimate.

To our knowledge, this is the first review to describe varenicline's effectiveness in this specific population. Comparative data in the general smoking population support its efficacy. For instance, Meng et al. demonstrated varenicline's effectiveness in mid- to long-term follow-up periods (16–32 weeks) (40). Similarly, Aryanpur et al. reported high efficacy for both short- and long-term cessation in hospitalized patients (41). The 2018 ACC Expert Consensus recommends varenicline, bupropion, and nicotine replacement therapy (NRT) as first-line pharmacological treatments for smoking cessation (10). Lastly, the more recent 2025 NICE guidelines recommend varenicline and NRT in combination with behavioral interventions (42) . Bupropion was recommended as third option, since it was associated with relatively lower abstinence rates compared to other interventions in the

general smoking population (42).
It is important to note that varenicline is withdrawn from the Belgian market since September 2021 by Pfizer, in consultation with the European Medicines Agency and the Federal Agency for Medicines and Health Products. This discontinuation followed the finding of elevated levels of nitrosamine impurities, a potential carcinogen with prolonged exposure (43).

Behavioral interventions

Individuals with depression who smoke are known to experience higher rates of negative mood, both pre- and post-cessation, which in turn is associated with increased smoking relapse rates (44). Mood management strategies are thought to potentially help mitigate these effects by offering alternative coping mechanisms (45,46). Gierisch et al. found a small but significant benefit when mood management counselling was added to other behavioral interventions, although they did not distinguish between short- vs. long-term abstinence (10).
Our analysis identified a modest, statistically significant effect for behavioral interventions on short-term abstinence, but this effect was not visible at long-term abstinence. The overall certainty of the evidence was low, however, and the true effect may differ substantially from our estimate.

Nicotine replacement therapy (NRT)

We observed a non-significant positive trend for NRT in short-term abstinence and a small negative trend in long-term abstinence, although the certainty of evidence was low. Differentiating between short- and long-term outcomes may have important implications, as prolonged reliance on NRT could indicate greater nicotine dependence and, consequently, an increased vulnerability to smoking relapse.
A previous review that synthesized three trials in previously depressed populations found a modest, although not significant, positive effect of NRT but did not distinguish between short- and long-term abstinence (10). Beis et al. concluded that while NRT may reduce smoking and alleviate withdrawal symptoms among adolescents in the general smoking population, its long-term effectiveness in sustaining long-term smoking cessation is limited (47).
Even though we did not find evidence for NRT as SCM in patients with p-MDD or current dysthymia, based on results in the general smoking population the true potential of NRT might lay in the combination with therapies like varenicline or other behavioral interventions (42,48).

SAE/ME/WE

Overall, the reporting of side effects was limited. Five out of nine studies that considered adverse effects were excluded due to lack of subtractable results. When reported, data were often incomplete and studies investigating broader populations often did not have extractable results for our specific population of p-MDD or current dysthymia patients, introducing a risk of selective reporting bias.
No significant differences in mood evolution (ME) were identified between the intervention and control groups for NRT, varenicline, behavioral interventions, or exercise, suggesting that these interventions likely neither exacerbate nor improve mood relative to placebo. However, the certainty of the evidence was low to very low for most of these comparisons, primarily due to imprecision and, more generally, a higher risk of bias for these safety outcomes. Therefore, the findings should be interpreted with caution given the low certainty of the evidence.
There appear to be no differences between the varenicline intervention and the placebo group regarding serious adverse events (SAEs). The results were rated as having moderate certainty,

indicating that the true effect is likely close to the observed estimate (37). Thomas et al. reported that bupropion increased the odds of serious adverse events compared to placebo (OR 1.27) and that varenicline increased the odds of major adverse neuropsychiatric events compared to bupropion in the general smoking population (OR 1.43) (48). Other evidence from general smoking populations does not support strong associations between cessation pharmacotherapies (including varenicline, bupropion, and NRT) and adverse events. However, improved safety reporting remains essential, as data remain limited (49).

Limitations and strengths

Several limitations should be acknowledged. First, the overall body of evidence on SCMs in individuals with MDD or dysthymia remains limited. Despite evidence that individuals with MDD are motivated to quit smoking (50), clinicians have historically been hesitant to engage this population in cessation treatment due to concerns about exacerbating depressive symptoms (51). Missing or incomplete subgroup data further hinders the possibility of comprehensive analyses, especially for safety outcomes such as weight change, mood evolution, or adverse events.

Second, long-term follow-up was rarely available. Although 60% of studies examined long-term abstinence (>6 months), only one included study followed participants beyond 12 months. This restricts our ability to draw strong conclusions about long-term smoking cessation or downstream health benefits such as cardiovascular risk reduction.

Third, behavioral interventions and NRT were often administered as adjunct “on-demand” therapies in both intervention and control arms in approximately half the studies. While this may reflect real-world clinical practice, it complicates the interpretation of individual treatment effects. Such combinations may produce ceiling effects or mask small effects of an intervention. Furthermore, the frequency, intensity or duration of these co-interventions were often unclear. Cleaner study designs—such as those using a 2x2 factorial format— are better suited to isolating and comparing specific effects. In 3 out of 4 trials with bupropion and varenicline, brief weekly counselling sessions (10–15 minutes) were included during the treatment phase. Other RCT’s often provided intensive psychological support during trials, for instance, involving 8–10 sessions of 1–2 hours, along with the provision of pharmacotherapy at no cost. It is possible that weekly follow-up or intensive behavioral counselling were important contributing factors to the observed effect. Thomas et al. reported that, in the general population, combined pharmacological and behavioral approaches were among the most clinically effective, safe, and cost-effective strategies (48) and abstinence rates were higher among those receiving additional counseling (49).

This review also has several important strengths. To our knowledge, the most recent prior systematic review in this area dates back over a decade (10), positioning our work as the most up-to-date and comprehensive synthesis of SCM effectiveness in individuals with past MDD or current dysthymia.

Second, our review is the first to explicitly distinguish between short- and long-term abstinence outcomes, and to synthesize evidence on adverse effects—including SAEs, mood evolution, and weight effects—in individuals with a history of MDD or current dysthymia.

Third, by grouping studies into broader intervention categories, we maximized analytical power despite small sample sizes and possible study-level heterogeneity. We assessed evidence certainty using GRADE and considered the likely impact of bias and imprecision on effect estimates. Where data permitted, meta-analysis was performed to quantify pooled estimates for clinical guidance.

Finally, this review was derived from a broader project investigating SCMs in individuals with severe

mental illness. As such, our search strategy was intentionally wide, increasing the likelihood of capturing all relevant studies.

Implications for praxis and research

Our findings are most applicable to populations with a history of MDD, as only three studies reported on patients with current dysthymia.

Prior literature suggests that a history of depression adversely affects smoking cessation outcomes in both the short- and long-term (52), highlighting the need for tailored interventions in this subgroup. Our findings indicate that bupropion may be a suitable and personalized option to consider for smoking cessation in patients with p-MDD or current dysthymia. As varenicline is still unavailable on the Belgian market, it is currently not a viable option in general practice. Given that most included studies combined pharmacological treatments with brief psychological counselling or other behavioral interventions, patients may also benefit from regular follow-up to support their cessation efforts.

Evidence on the impact of SCMs on mental health outcomes, weight change, or severe adverse events was sparse. While varenicline did not appear to increase SAEs, these findings warrant cautious interpretation due to limited available data.

Further research is essential to confirm our findings and address existing gaps, particularly concerning the potential adverse effects of SCMs. Future studies should aim to optimize treatment variables such as dosage, duration, sequencing, and the integration of behavioral and pharmacological interventions. To facilitate comparison, trials should ideally employ pure placebo arms or factorial 2x2 designs.

Additionally, studies should consistently report outcomes separately for subgroups such as individuals with a history of MDD or dysthymia. This would enhance the utility of primary data for meta-analyses and improve clinical applicability.

Conclusion

This systematic review and meta-analysis found moderate-certainty evidence supporting the effectiveness of bupropion and varenicline for both short- and long-term abstinence in individuals with a history of MDD or current dysthymia. Pharmacological interventions were often combined with brief psychological counseling weekly.

Evidence on the impact of SCMs on mental health, weight, or SAE was limited, though varenicline appeared not to increase the risk of serious adverse events. Future research may influence our current interpretations for safety outcomes and some of our intervention outcomes (e.g. behavioral interventions, clonidine, NRT).

To our knowledge, this review represents the most comprehensive and up-to-date synthesis of smoking cessation strategies in individuals with p-MDD or current dysthymia conducted in the past decade.

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Supplementary materials

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1. Search strings
2. PRISMA flow diagram
3. Risk of bias summary
4. Summary of results
5. GRADE and SOF tables

1. Search strings

MEDLINE

("Schizophrenia Spectrum and Other Psychotic Disorders"[Mesh] OR "Bipolar and Related Disorders"[Mesh] OR "Mood Disorders"[Mesh] OR "Trauma and Stressor Related Disorders"[Mesh] OR "schizophreni*"[tiab] OR "schizoaffective*"[tiab] OR "schizo-affective*"[tiab] OR "delusional disorder*"[tiab] OR "paranoid disorder*"[tiab] OR "paranoid psychosis"[tiab] OR "schizotypal disorder*"[tiab] OR "psychotic disorder*"[tiab] OR "psychosis"[tiab] OR "catatoni*"[tiab] OR "bipolar*"[tiab] OR "cyclothymi*"[tiab] OR "depressive disorder*"[tiab] OR "depressive disease*"[tiab] OR "depressive illness*"[tiab] OR "depressive episode*"[tiab] OR "depressive state*"[tiab] OR "depressive syndrome*"[tiab] OR "depression*"[tiab] OR "unipolar disorder*"[tiab] OR "manic episode*"[tiab] OR "mania"[tiab] OR "affective disorder*"[tiab] OR "mood disorder*"[tiab] OR "MDD"[tiab] OR "disruptive mood dysregulation disorder*"[tiab] OR "dysthymi*"[tiab] OR "disthymi*"[tiab] OR "dysthimi*"[tiab] OR "premenstrual dysphoric disorder*"[tiab] OR "posttraumatic stress disorder*"[tiab] OR "post-traumatic stress disorder*"[tiab] OR "PTSD"[tiab] OR "acute stress disorder*"[tiab] OR "acute traumatic stress disorder*"[tiab] OR "acute stress reaction"[tiab] OR "reaction to severe stress"[tiab] OR "severe mental illness*"[tiab] OR "serious mental illness*"[tiab] OR "severe mental disorder*"[tiab] OR "serious mental disorder*"[tiab]) AND ("Smoking Cessation"[Mesh] OR "Smoking Reduction"[Mesh] OR "Smoking Prevention"[Mesh] OR "Tobacco Use Cessation"[Mesh] OR "Tobacco Use Cessation Devices"[Mesh] OR "Smoking Cessation Agents"[Mesh] OR "Electronic Nicotine Delivery Systems"[Mesh] OR "Nicotine Chewing Gum"[Mesh] OR "Vaping"[Mesh] OR "stage of change"[tiab] OR "nicotine patch*"[tiab] OR "nicotine transdermal patch*"[tiab] OR "nicotine polacrilex"[tiab] OR "nicotine gum*"[tiab] OR "nicotine chewing gum*"[tiab] OR "Nicorette"[tiab] OR "Nicabate"[tiab] OR "Nicorama"[tiab] OR "Nicotinell"[tiab] OR "Thrive"[tiab] OR "nicotine resinate"[tiab] OR "nicotine inhaler*"[tiab] OR "nicotine inhalant*"[tiab] OR "nicotine delivery device*"[tiab] OR "nicotine delivery system*"[tiab] OR "nicotine nasal spray*"[tiab] OR "nicotine replacement*"[tiab] OR "NRT"[tiab] OR "nicotine lozenge*"[tiab] OR ("Bupropion"[Mesh] OR "bupropion*"[tiab] OR "amfebutamone*"[tiab] OR "Wellbutrin*"[tiab] OR "Wellbatrin*"[tiab] OR "Zyban*"[tiab] OR "Quomen"[tiab] OR "Quomem"[tiab] OR "Aplenzin"[tiab] OR "BVF 033"[tiab] OR "BVF033"[tiab] OR "BW 323*"[tiab] OR "BW323*"[tiab] OR "Budeprion"[tiab] OR "buprion hydrochloride"[tiab] OR "bupropin"[tiab] OR "Buxon"[tiab] OR "Elontril"[tiab] OR "Forfivo*"[tiab] OR "Odranal"[tiab] OR "Zyntabac"[tiab] OR "Varenicline"[Mesh] OR "vareniclin*"[tiab] OR "cdff 0318"[tiab] OR "cdff0318"[tiab] OR "cp 526555*"[tiab] OR "cp526555*"[tiab] OR "oc 01"[tiab] OR "oc01"[tiab] OR "Tyrvaya"[tiab] OR "tartrate"[tiab] OR "yhp 1903"[tiab] OR "yhp1903"[tiab] OR "Chantix"[tiab] OR "Champix"[tiab] OR "Nortriptyline"[Mesh] OR "nortriptylin*"[tiab] OR "nortryptilin*"[tiab] OR

"nortryptylin*"[tiab] OR "nortyline"[tiab] OR "noramitriptyline"[tiab] OR "desitriptyline"[tiab] OR "desmethylamitriptylin"[tiab] OR "Allegron"[tiab] OR "Acetexa"[tiab] OR "Altilev"[tiab] OR "Ateben"[tiab] OR "Atilev"[tiab] OR "Aventyl"[tiab] OR "Avantyl"[tiab] OR "Paxtibi"[tiab] OR "Martimil"[tiab]OR "Nortrilen"[tiab] OR "Pamelor"[tiab] OR "Norfenazin"[tiab] OR "Noritren"[tiab] OR "Norline"[tiab] OR "Norpress"[tiab] OR "Nortrilen"[tiab] OR "Nortrix"[tiab] OR "Norventyl"[tiab] OR "Ortrip"[tiab] OR "Psychotyl"[tiab] OR "Sensaval"[tiab] OR "Sensival"[tiab] OR "Vividyl"[tiab] OR "l 38489"[tiab] OR "cytisine" [Supplementary Concept] OR "cytisine*" [tiab] OR "cytiton" [tiab] OR "citizine" [tiab] OR "cystisin"[tiab] OR "Tabex" [tiab] OR "Tsitizin" [tiab]) AND ("Smoking Cessation"[Mesh] OR "Smoking Reduction"[Mesh] OR "Smoking Prevention"[Mesh] OR "Tobacco Use Cessation"[Mesh] OR ((cessation*[tiab] OR dishabituation[tiab] OR “therapy”[subheading] OR therap*[tiab] OR interv*[tiab] OR “prevention and control”[subheading] OR control*[tiab] OR "stop*"[tiab] OR "quit*"[tiab] OR "abstain*"[tiab] OR "abstin*"[tiab] OR "give*"[tiab] OR "givi*"[tiab] OR "ceas*"[tiab] OR "prevent*"[tiab] OR "reduc*"[tiab] OR "decreas*"[tiab] OR "withdraw*"[tiab]) AND (smok*[tiab] OR “smoking”[Mesh] OR nicotine[tiab] OR “nicotine”[Mesh] OR “Tobacco”[Mesh] OR tobacco[tiab] OR “Tobacco Products”[Mesh] OR “Tobacco use”[Mesh] OR cigarette*[tiab]))) OR "electronic nicotine delivery system*"[tiab] OR "electronic cigarette*"[tiab] OR "E-Cig*"[tiab] OR "vape*"[tiab] OR "vaping"[tiab] OR "vaporiser*"[tiab] OR "vaporizer*"[tiab] OR ((cessation*[tiab] OR dishabituation[tiab] OR “therapy”[subheading] OR therap*[tiab] OR interv*[tiab] OR “prevention and control”[subheading] OR control*[tiab] OR "stop*"[tiab] OR "quit*"[tiab] OR "abstain*"[tiab] OR "abstin*"[tiab] OR "give*"[tiab] OR "givi*"[tiab] OR "ceas*"[tiab] OR "prevent*"[tiab] OR "reduc*"[tiab] OR "decreas*"[tiab] OR "withdraw*"[tiab]) AND (smok*[tiab] OR “smoking”[Mesh] OR nicotine[tiab] OR “nicotine”[Mesh] OR “Tobacco”[Mesh] OR tobacco[tiab] OR “Tobacco Products”[Mesh] OR “Tobacco use”[Mesh] OR cigarette*[tiab]))) AND (("Clinical Trial"[pt] OR placebo[tiab] OR "drug therapy"[sh] OR random*[tiab] OR RCT[tiab] OR "phase 1"[tiab] OR "phase 2"[tiab] OR "phase 3"[tiab] OR "phase 4"[tiab] OR "phase I"[tiab] OR "phase II"[tiab] OR "phase III"[tiab] OR "phase IV"[tiab] OR "clinical study"[tiab] OR "controlled study"[tiab] OR "controlled design"[tiab] OR multicenter[tiab] OR multicentre[tiab] OR "multi center"[tiab] OR "multi centre"[tiab] OR "open label"[tiab] OR "parallel group*"[tiab] OR "double blind*"[tiab] OR "single blind"[tiab])) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])

EMBASE

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'PTSD':ti,ab,kw OR 'trauma and stressor related disorder*':ti,ab,kw OR 'acute stress disorder':ti,ab,kw OR 'acute traumatic stress disorder*':ti,ab,kw OR 'severe mental illness*':ti,ab,kw OR 'serious mental illness*':ti,ab,kw OR 'severe mental disorder*':ti,ab,kw OR 'serious mental disorder*':ti,ab,kw) AND ('smoking cessation'/exp OR 'smoking reduction'/exp OR 'nicotine gum'/exp OR 'smoking cessation agent'/exp OR 'electronic cigarette'/exp OR 'vaping'/exp OR 'smoking cessation program'/exp OR 'smoking prevention'/exp OR 'stage of change':ti,ab,kw OR 'nicotine patch*':ti,ab,kw OR 'nicotine transdermal patch*':ti,ab,kw OR 'nicotine polacrilex':ti,ab,kw OR 'nicotine gum*':ti,ab,kw OR 'nicotine chewing gum*':ti,ab,kw OR 'Nicorette':ti,ab,kw OR 'Nicabate':ti,ab,kw OR 'Nicorama':ti,ab,kw OR 'Nicotinell':ti,ab,kw OR 'Thrive':ti,ab,kw OR 'nicotine resinate':ti,ab,kw OR 'nicotine inhaler*':ti,ab,kw OR 'nicotine inhalant*':ti,ab,kw OR 'nicotine delivery device*':ti,ab,kw OR 'nicotine delivery system*':ti,ab,kw OR 'nicotine nasal spray*':ti,ab,kw OR 'nicotine replacement*':ti,ab,kw OR 'NRT':ti,ab,kw OR 'nicotine lozenge*':ti,ab,kw OR ('amfebutamone'/exp OR 'bupropion*':ti,ab,kw OR 'amfebutamone*':ti,ab,kw OR 'Wellbutrin*':ti,ab,kw OR 'Wellbatrin*':ti,ab,kw OR 'Zyban*':ti,ab,kw OR 'Quomen':ti,ab,kw OR 'Quomem':ti,ab,kw OR 'Aplenzin':ti,ab,kw OR 'BVF 033':ti,ab,kw OR 'BVF033':ti,ab,kw OR 'BW 323*':ti,ab,kw OR 'BW323*':ti,ab,kw OR 'Budeprion':ti,ab,kw OR 'buprion hydrochloride':ti,ab,kw OR 'bupropin':ti,ab,kw OR 'Buxon':ti,ab,kw OR 'Elontril':ti,ab,kw OR 'Forfivo*':ti,ab,kw OR 'Odranal':ti,ab,kw OR 'Zyntabac':ti,ab,kw OR 'varenicline'/exp OR 'vareniclin*':ti,ab,kw OR 'cdff 0318':ti,ab,kw OR 'cdff0318':ti,ab,kw OR 'cp 526555*':ti,ab,kw OR 'cp526555*':ti,ab,kw OR 'oc 01':ti,ab,kw OR 'oc01':ti,ab,kw OR 'Tyrvaya':ti,ab,kw OR 'tartrate':ti,ab,kw OR 'yhp 1903':ti,ab,kw OR 'yhp1903':ti,ab,kw OR 'Champix':ti,ab,kw OR 'Chantix':ti,ab,kw OR 'nortriptyline'/exp OR 'nortriptylin*':ti,ab,kw OR 'nortryptilin*’:ti,ab,kw OR 'nortryptylin*’:ti,ab,kw OR 'nortyline’:ti,ab,kw OR 'noramitriptyline’:ti,ab,kw OR 'desitriptyline’:ti,ab,kw OR 'desmethylamitriptylin’:ti,ab,kw OR 'Allegron’:ti,ab,kw OR 'Acetexa’:ti,ab,kw OR 'Altilev’:ti,ab,kw OR 'Ateben’:ti,ab,kw OR 'Atilev’:ti,ab,kw OR 'Aventyl’:ti,ab,kw OR 'Avantyl’:ti,ab,kw OR 'Paxtibi’:ti,ab,kw OR 'Martimil’:ti,ab,kw OR 'Nortrilen’:ti,ab,kw OR 'Pamelor’:ti,ab,kw OR 'Norfenazin’:ti,ab,kw OR 'Noritren’:ti,ab,kw OR 'Norline’:ti,ab,kw OR 'Norpress’:ti,ab,kw OR 'Nortrilen’:ti,ab,kw OR 'Nortrix’:ti,ab,kw OR 'Norventyl’:ti,ab,kw OR 'Ortrip’:ti,ab,kw OR 'Psychotyl’:ti,ab,kw OR 'Sensaval’:ti,ab,kw OR 'Sensival’:ti,ab,kw OR 'Vividyl’:ti,ab,kw OR 'l 38489’:ti,ab,kw OR 'cytisine'/exp OR 'cytisine*’:ti,ab,kw OR 'cytiton’:ti,ab,kw OR 'citizine’:ti,ab,kw OR 'cystisin’:ti,ab,kw OR 'Tabex’:ti,ab,kw OR 'Tsitizin’:ti,ab,kw AND ('smoking cessation'/exp OR 'smoking reduction'/exp OR 'smoking prevention'/exp OR (('cessation*':ti,ab,kw OR 'dishabituation':ti,ab,kw OR 'therapy'/de OR 'therap*':ti,ab,kw OR 'interv*':ti,ab,kw OR 'prevention and control'/de OR 'control*':ti,ab,kw OR 'stop*':ti,ab,kw OR 'quit*':ti,ab,kw OR 'abstain*':ti,ab,kw OR 'abstin*':ti,ab,kw OR 'give*':ti,ab,kw OR 'givi*':ti,ab,kw OR 'ceas*':ti,ab,kw OR 'prevent*':ti,ab,kw OR 'reduc*':ti,ab,kw OR 'decreas*':ti,ab,kw OR 'withdraw*':ti,ab,kw) AND ('smok*':ti,ab,kw OR 'smoking'/exp OR 'nicotine':ti,ab,kw OR 'nicotine'/exp OR 'tobacco'/exp OR 'tobacco':ti,ab,kw OR 'tobacco use'/exp OR 'cigarette*':ti,ab,kw))) OR 'electronic nicotine delivery system*':ti,ab,kw OR 'electronic cigarette*':ti,ab,kw OR 'E-Cig*':ti,ab,kw OR 'vape*':ti,ab,kw OR 'vaping':ti,ab,kw OR 'vaporiser*':ti,ab,kw OR 'vaporizer*':ti,ab,kw OR (('cessation*':ti,ab,kw OR 'dishabituation':ti,ab,kw OR 'therapy'/de OR 'therap*':ti,ab,kw OR 'interv*':ti,ab,kw OR 'prevention and control'/de OR 'control*':ti,ab,kw OR 'stop*':ti,ab,kw OR 'quit*':ti,ab,kw OR 'abstain*':ti,ab,kw OR 'abstin*':ti,ab,kw OR 'give*':ti,ab,kw OR 'givi*':ti,ab,kw OR 'ceas*':ti,ab,kw OR 'prevent*':ti,ab,kw OR 'reduc*':ti,ab,kw OR 'decreas*':ti,ab,kw OR 'withdraw*':ti,ab,kw) AND ('smok*':ti,ab,kw OR 'smoking'/exp OR 'nicotine':ti,ab,kw OR 'nicotine'/exp OR 'tobacco'/exp OR 'tobacco':ti,ab,kw OR 'tobacco use'/exp OR 'cigarette*':ti,ab,kw)))

AND ('clinical trial'/exp OR placebo:ti,ab,kw OR random*:ti,ab,kw OR 'phase 1':ti,ab,kw OR 'phase 2':ti,ab,kw OR 'phase 3':ti,ab,kw OR 'phase 4':ti,ab,kw OR 'phase I':ti,ab,kw OR 'phase II':ti,ab,kw OR 'phase III':ti,ab,kw OR 'phase IV':ti,ab,kw OR 'clinical study':ti,ab,kw OR 'controlled study':ti,ab,kw OR 'controlled design':ti,ab,kw OR multicenter:ti,ab,kw OR multicentre:ti,ab,kw OR 'multi center':ti,ab,kw OR 'multi centre':ti,ab,kw OR 'open label':ti,ab,kw OR 'parallel group*':ti,ab,kw OR 'double blind*':ti,ab,kw OR 'single blind*':ti,ab,kw) NOT 'conference abstract':it)

WEB OF SCIENCE

TS=("schizophreni*" OR "schizoaffective*" OR "schizo-affective*" OR "delusional disorder*" OR "paranoid disorder*" OR "paranoid psychosis" OR "schizotypal disorder*" OR "psychotic disorder*" OR "psychosis" OR "catatoni*" OR "bipolar*" OR "cyclothymi*" OR "depressive disorder*" OR "depressive disease*" OR "depressive illness*" OR "depressive episode*" OR "depressive state*" OR "depressive syndrome*" OR "depression*" OR "unipolar disorder*" OR "manic episode*" OR "mania" OR "affective disorder*" OR "mood disorder*" OR "depressive disorder*" OR "MDD" OR "disruptive mood dysregulation disorder*" OR "dysthymi*" OR "disthymi*" OR "dysthimi*" OR "premenstrual dysphoric disorder*" OR "trauma and stressor related disorder*" OR "posttraumatic stress disorder*" OR "post-traumatic stress disorder*" OR "PTSD" OR "acute stress disorder*" OR "acute traumatic stress disorder*" OR "acute stress reaction" OR "reaction to severe stress" OR "severe mental illness*" OR "serious mental illness*" OR "severe mental disorder*" OR "serious mental disorder*")

TS=("smoking cessation" OR "smoking reduction" OR "smoking prevention" OR "tobacco use cessation" OR "tobacco use cessation devices" OR "smoking cessation agents" OR "electronic nicotine delivery systems" OR "vaping" OR "stage of change" OR "nicotine patch*" OR "nicotine transdermal patch*" OR "nicotine polacrilex" OR "nicotine gum*" OR "nicotine chewing gum*" OR "Nicorette" OR "Nicabate" OR "Nicorama" OR "Nicotinell" OR "Thrive" OR "nicotine resinate" OR "nicotine inhaler*" OR "nicotine inhalant*" OR "nicotine delivery device*" OR "nicotine delivery system*" OR "nicotine nasal spray*" OR "nicotine replacement*" OR "NRT" OR "nicotine lozenge*" OR ("bupropion*" OR "amfebutamone*" OR "Wellbutrin*" OR "Wellbatrin*" OR "Zyban*" OR "Quomen" OR "Quomem" OR "Aplenzin" OR "BVF 033" OR "BVF033" OR "BW 323*" OR "BW323*" OR "Budeprion" OR "buprion hydrochloride" OR "bupropin" OR "Buxon" OR "Elontril" OR "Forfivo*" OR "Odranal" OR "Zyntabac" OR "vareniclin*" OR "cdff 0318" OR "cdff0318" OR "cp 526555*" OR "cp526555*" OR "oc 01" OR "oc01" OR "Tyrvaya" OR "tartrate" OR "yhp 1903" OR "yhp1903" OR "Chantix" OR "Champix" OR "nortriptylin*" OR "nortryptilin*" OR "nortryptylin*" OR "nortyline" OR "noramitriptyline" OR "desitriptyline" OR "desmethylamitriptylin" OR "Allegron" OR "Acetexa" OR "Altilev" OR "Ateben" OR "Atilev" OR "Aventyl" OR "Avantyl" OR "Paxtibi" OR "Martimil"OR "Nortrilen" OR "Pamelor" OR "Norfenazin" OR "Noritren" OR "Norline" OR "Norpress" OR "Nortrilen" OR "Nortrix" OR "Norventyl" OR "Ortrip" OR "Psychotyl" OR "Sensaval" OR "Sensival" OR "Vividyl" OR "l 38489" OR "cytisine*" OR "cytiton" OR "citizine" OR "cystisin" OR "Tabex" OR "Tsitizin") AND ("smoking cessation" OR "smoking reduction" OR "smoking prevention" OR "tobacco use cessation" OR ((cessation* OR dishabituation OR therap* OR interv* OR “prevention and control” OR control* OR "stop*" OR "quit*" OR "abstain*" OR "abstin*" OR "give*" OR "givi*" OR "ceas*" OR "prevent*" OR "reduc*" OR "decreas*" OR "withdraw*") AND (smok* OR “smoking” OR nicotine OR “nicotine” OR “tobacco” OR “tobacco products” OR “tobacco use” OR cigarette*))) OR "electronic nicotine delivery system*" OR "electronic cigarette*" OR "E-Cig*" OR "vape*" OR "vaping" OR "vaporiser*" OR "vaporizer*" OR ((cessation* OR dishabituation OR therap* OR interv* OR “prevention and control” OR control* OR

"stop*" OR "quit*" OR "abstain*" OR "abstin*" OR "give*" OR "givi*" OR "ceas*" OR "prevent*" OR "reduc*" OR "decreas*" OR "withdraw*") AND (smok* OR “smoking” OR nicotine OR “nicotine” OR “tobacco” OR “tobacco products” OR “tobacco use” OR cigarette*)))

TS=("clinical trial" OR placebo OR "drug therapy" OR random* OR RCT OR "phase 1" OR "phase 2" OR "phase 3" OR "phase 4" OR "phase I" OR "phase II" OR "phase III" OR "phase IV" OR "clinical study" OR "controlled study" OR "controlled design" OR multicenter OR multicentre OR "multi center" OR "multi centre" OR "open label" OR "parallel group*" OR "double blind*" OR "single blind")

SCOPUS

(TITLE-ABS("schizophreni*" OR "schizoaffective*" OR "schizo-affective*" OR "delusional disorder*" OR "paranoid disorder*" OR "paranoid psychosis" OR "schizotypal disorder*" OR "psychotic disorder*" OR "psychosis" OR "catatoni*" OR "bipolar*" OR "cyclothymi*" OR "depressive disorder*" OR "depressive disease*" OR "depressive illness*" OR "depressive episode*" OR "depressive state*" OR "depressive syndrome*" OR "depression*" OR "unipolar disorder*" OR "manic episode*" OR "mania" OR "affective disorder*" OR "mood disorder*" OR "depressive disorder*" OR "MDD" OR "disruptive mood dysregulation disorder*" OR "dysthymi*" OR "disthymi*" OR "dysthimi*" OR "premenstrual dysphoric disorder*" OR "trauma and stressor related disorder*" OR "posttraumatic stress disorder*" OR "post-traumatic stress disorder*" OR PTSD OR "acute stress disorder*" OR "acute traumatic stress disorder*" OR "acute stress reaction" OR "reaction to severe stress" OR "severe mental illness*" OR "serious mental illness*" OR "severe mental disorder*" OR "serious mental disorder*") OR AUTHKEY("schizophreni*" OR "schizoaffective*" OR "schizo-affective*" OR "delusional disorder*" OR "paranoid disorder*" OR "paranoid psychosis" OR "schizotypal disorder*" OR "psychotic disorder*" OR "psychosis" OR "catatoni*" OR "bipolar*" OR "cyclothymi*" OR "depressive disorder*" OR "depressive disease*" OR "depressive illness*" OR "depressive episode*" OR "depressive state*" OR "depressive syndrome*" OR "depression*" OR "unipolar disorder*" OR "manic episode*" OR "mania" OR "affective disorder*" OR "mood disorder*" OR "depressive disorder*" OR "MDD" OR "disruptive mood dysregulation disorder*" OR "dysthymi*" OR "disthymi*" OR "dysthimi*" OR "premenstrual dysphoric disorder*" OR "severe mental illness*" OR "serious mental illness*" OR "severe mental disorder*" OR "serious mental disorder*")) AND (TITLE-ABS("smoking cessation" OR "smoking reduction" OR "smoking prevention" OR "tobacco use cessation" OR "tobacco use cessation devices" OR "smoking cessation agents" OR "electronic nicotine delivery systems" OR "vaping" OR "stage of change" OR "nicotine patch*" OR "nicotine transdermal patch*" OR "nicotine polacrilex" OR "nicotine gum*" OR "nicotine chewing gum*" OR "Nicorette" OR "Nicabate" OR "Nicorama" OR "Nicotinell" OR "Thrive" OR "nicotine resinate" OR "nicotine inhaler*" OR "nicotine inhalant*" OR "nicotine delivery device*" OR "nicotine delivery system*" OR "nicotine nasal spray*" OR "nicotine replacement*" OR "NRT" OR "nicotine lozenge*" OR ("bupropion*" OR "amfebutamone*" OR "Wellbutrin*" OR "Wellbatrin*" OR "Zyban*" OR "Quomen" OR "Quomem" OR "Aplenzin" OR "BVF 033" OR "BVF033" OR "BW 323*" OR "BW323*" OR "Budeprion" OR "buprion hydrochloride" OR "bupropin" OR "Buxon" OR "Elontril" OR "Forfivo*" OR "Odranal" OR "Zyntabac" OR "vareniclin*" OR "cdff 0318" OR "cdff0318" OR "cp 526555*" OR "cp526555*" OR "oc 01" OR "oc01" OR "Tyrvaya" OR "tartrate" OR "yhp 1903" OR "yhp1903" OR "Chantix" OR "Champix" OR "nortriptylin*" OR "nortryptilin*" OR "nortryptylin*" OR "nortyline" OR "noramitriptyline" OR "desitriptyline" OR "desmethylamitriptylin" OR "Allegron" OR "Acetexa" OR "Altilev" OR "Ateben" OR "Atilev" OR "Aventyl" OR "Avantyl" OR "Paxtibi" OR "Martimil"OR "Nortrilen" OR "Pamelor" OR "Norfenazin" OR "Noritren" OR "Norline" OR "Norpress" OR "Nortrilen" OR "Nortrix" OR "Norventyl"

OR "Ortrip" OR "Psychotyl" OR "Sensaval" OR "Sensival" OR "Vividyl" OR "l 38489" OR "cytisine*" OR "cytiton" OR "citizine" OR "cystisin" OR "Tabex" OR "Tsitizin") AND ("smoking cessation" OR "smoking reduction" OR "smoking prevention" OR "tobacco use cessation" OR ((cessation* OR dishabituation OR therap* OR interv* OR “prevention and control” OR control* OR "stop*" OR "quit*" OR "abstain*" OR "abstin*" OR "give*" OR "givi*" OR "ceas*" OR "prevent*" OR "reduc*" OR "decreas*" OR "withdraw*") AND (smok* OR “smoking” OR nicotine OR “nicotine” OR “tobacco” OR “tobacco products” OR “tobacco use” OR cigarette*))) OR "electronic nicotine delivery system*" OR "electronic cigarette*" OR "E-Cig*" OR "vape*" OR "vaping" OR "vaporiser*" OR "vaporizer*" OR ((cessation* OR dishabituation OR therap* OR interv* OR “prevention and control” OR control* OR "stop*" OR "quit*" OR "abstain*" OR "abstin*" OR "give*" OR "givi*" OR "ceas*" OR "prevent*" OR "reduc*" OR "decreas*" OR "withdraw*") AND (smok* OR “smoking” OR nicotine OR “nicotine” OR “tobacco” OR “tobacco products” OR “tobacco use” OR cigarette*))) OR AUTHKEY("smoking cessation" OR "smoking reduction" OR "smoking prevention" OR "tobacco use cessation" OR "tobacco use cessation devices" OR "smoking cessation agents" OR "electronic nicotine delivery systems" OR "vaping" OR "stage of change" OR "nicotine patch*" OR "nicotine transdermal patch*" OR "nicotine polacrilex" OR "nicotine gum*" OR "nicotine chewing gum*" OR "Nicorette" OR "Nicabate" OR "Nicorama" OR "Nicotinell" OR "Thrive" OR "nicotine resinate" OR "nicotine inhaler*" OR "nicotine inhalant*" OR "nicotine delivery device*" OR "nicotine delivery system*" OR "nicotine nasal spray*" OR "nicotine replacement*" OR "NRT" OR "nicotine lozenge*" OR ("bupropion*" OR "amfebutamone*" OR "Wellbutrin*" OR "Wellbatrin*" OR "Zyban*" OR "Quomen" OR "Quomem" OR "Aplenzin" OR "BVF 033" OR "BVF033" OR "BW 323*" OR "BW323*" OR "Budeprion" OR "buprion hydrochloride" OR "bupropin" OR "Buxon" OR "Elontril" OR "Forfivo*" OR "Odranal" OR "Zyntabac" OR "vareniclin*" OR "cdff 0318" OR "cdff0318" OR "cp 526555*" OR "cp526555*" OR "oc 01" OR "oc01" OR "Tyrvaya" OR "tartrate" OR "yhp 1903" OR "yhp1903" OR "Chantix" OR "Champix" OR "nortriptylin*" OR "nortryptilin*" OR "nortryptylin*" OR "nortyline" OR "noramitriptyline" OR "desitriptyline" OR "desmethylamitriptylin" OR "Allegron" OR "Acetexa" OR "Altilev" OR "Ateben" OR "Atilev" OR "Aventyl" OR "Avantyl" OR "Paxtibi" OR "Martimil"OR "Nortrilen" OR "Pamelor" OR "Norfenazin" OR "Noritren" OR "Norline" OR "Norpress" OR "Nortrilen" OR "Nortrix" OR "Norventyl" OR "Ortrip" OR "Psychotyl" OR "Sensaval" OR "Sensival" OR "Vividyl" OR "l 38489" OR "cytisine*" OR "cytiton" OR "citizine" OR "cystisin" OR "Tabex" OR "Tsitizin") AND ("smoking cessation" OR "smoking reduction" OR "smoking prevention" OR "tobacco use cessation" OR ((cessation* OR dishabituation OR therap* OR interv* OR “prevention and control” OR control* OR "stop*" OR "quit*" OR "abstain*" OR "abstin*" OR "give*" OR "givi*" OR "ceas*" OR "prevent*" OR "reduc*" OR "decreas*" OR "withdraw*") AND (smok* OR “smoking” OR nicotine OR “nicotine” OR “tobacco” OR “tobacco products” OR “tobacco use” OR cigarette*))) OR "electronic nicotine delivery system*" OR "electronic cigarette*" OR "E-Cig*" OR "vape*" OR "vaping" OR "vaporiser*" OR "vaporizer*" OR ((cessation* OR dishabituation OR therap* OR interv* OR “prevention and control” OR control* OR "stop*" OR "quit*" OR "abstain*" OR "abstin*" OR "give*" OR "givi*" OR "ceas*" OR "prevent*" OR "reduc*" OR "decreas*" OR "withdraw*") AND (smok* OR “smoking” OR nicotine OR “nicotine” OR “tobacco” OR “tobacco products” OR “tobacco use” OR cigarette*))) AND (TITLE-ABS("clinical trial" OR placebo OR "drug therapy" OR random* OR RCT OR "phase 1" OR "phase 2" OR "phase 3" OR "phase 4" OR "phase I" OR "phase II" OR "phase III" OR "phase IV" OR "clinical study" OR "controlled study" OR "controlled design" OR multicenter OR multicentre OR "multi center" OR "multi centre" OR "open label" OR "parallel group*" OR "double blind*" OR "single blind") OR AUTHKEY("clinical trial" OR placebo OR "drug therapy" OR random* OR RCT OR "phase 1" OR "phase 2" OR "phase 3" OR

"phase 4" OR "phase I" OR "phase II" OR "phase III" OR "phase IV" OR "clinical study" OR "controlled study" OR "controlled design" OR multicenter OR multicentre OR "multi center" OR "multi centre" OR "open label" OR "parallel group*" OR "double blind*" OR "single blind"))

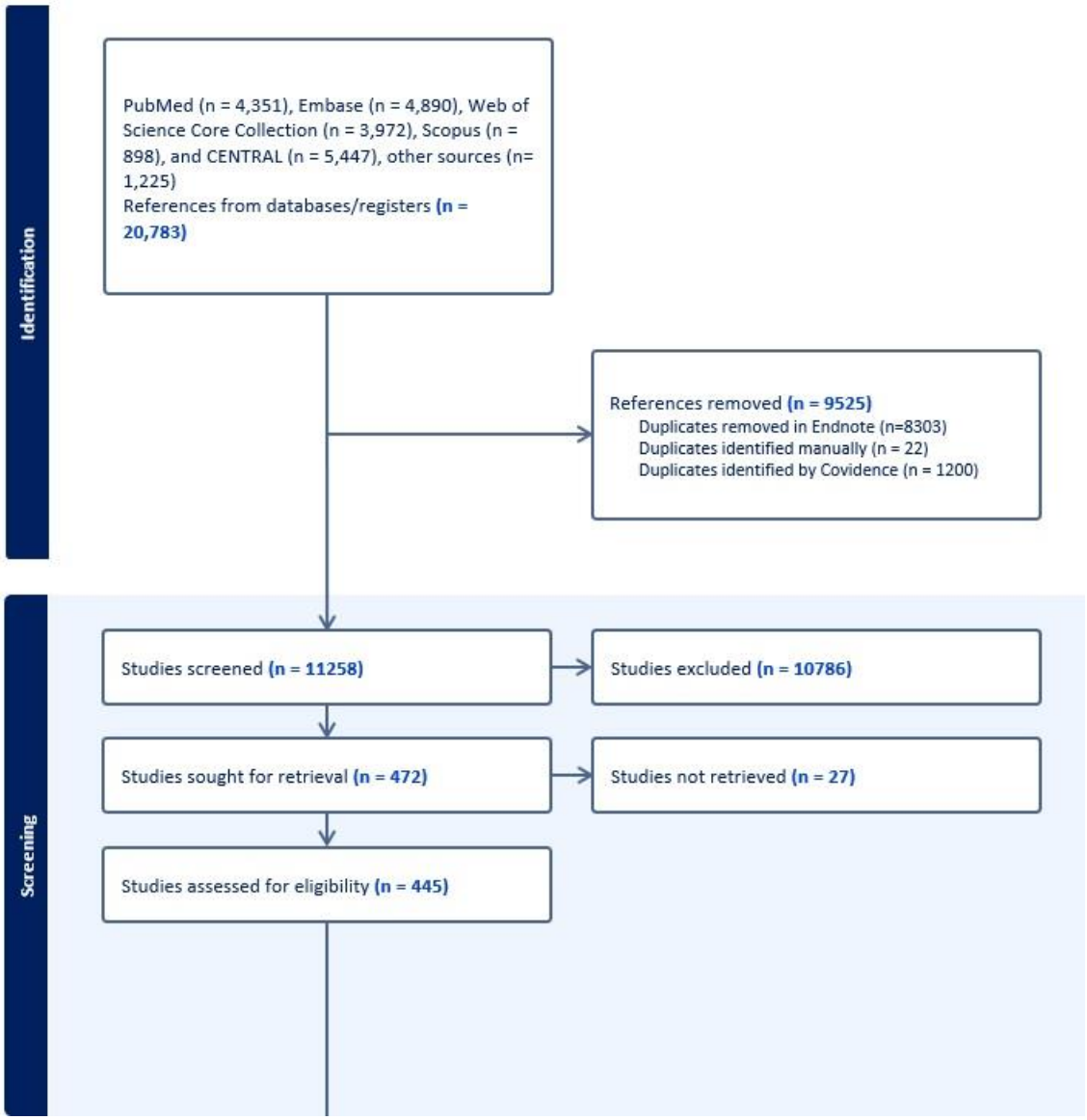
CENTRAL

([mh "Schizophrenia Spectrum and Other Psychotic Disorders"] OR [mh "Bipolar and Related Disorders"] OR [mh "Mood Disorders"] OR [mh "Trauma and Stressor Related Disorders"] OR schizophreni* OR schizoaffective* OR (schizo NEXT affective*) OR ((delusional OR paranoid OR schizotypal OR psychotic) NEXT disorder*) OR psychosis OR catatoni* OR bipolar* OR cyclothymi* OR (depressive NEXT disorder*) OR (depressive NEXT disease*) OR (depressive NEXT illness*) OR (depressive NEXT episode*) OR (depressive NEXT state*) OR (depressive NEXT syndrome*) OR depression* OR (unipolar NEXT disorder*) OR (manic NEXT episode*) OR mania OR (affective NEXT disorder*) OR (mood NEXT disorder*) OR MDD OR (disruptive NEXT mood NEXT dysregulation NEXT disorder*) OR dysthymi* OR disthymi* OR dysthimi* OR (premenstrual NEXT dysphoric NEXT disorder*) OR ("trauma and stressor related" NEXT disorder*) OR ("posttraumatic stress" NEXT disorder*) OR (post NEXT traumatic NEXT stress disorder*) OR "PTSD" OR ("acute stress" NEXT disorder*) OR ("acute traumatic stress" NEXT disorder*) OR "acute stress reaction" OR "reaction to severe stress" OR (severe NEXT mental NEXT illness*) (serious NEXT mental NEXT illness*) OR (severe NEXT mental NEXT disorder*) OR (serious NEXT mental NEXT disorder*):ti,ab,kw)

([mh "Smoking Cessation"] OR [mh "Smoking Reduction"] OR [mh "Smoking Prevention"] OR [mh "Tobacco Use Cessation"] OR [mh "Tobacco Use Cessation Devices"] OR [mh "Smoking Cessation Agents"] OR [mh "Electronic Nicotine Delivery Systems"] OR [mh "Nicotine Chewing Gum"] OR [mh "Vaping"] OR (stage NEXT of NEXT change) OR (nicotine NEXT patch*) OR (nicotine NEXT transdermal NEXT patch*) OR nicotine NEXT (polacrilex OR gum*) OR (nicotine NEXT chewing NEXT gum*) OR Nicorette OR Nicabate OR Nicorama OR Nicotinell OR Thrive OR nicotine NEXT (resinate OR inhaler* OR inhalant*) OR (nicotine NEXT delivery NEXT device*) OR (nicotine NEXT delivery NEXT system*) OR (nicotine NEXT nasal NEXT spray*) OR (nicotine NEXT replacement*) OR NRT OR (nicotine NEXT lozenge*) OR ([mh "Bupropion"] OR bupropion* OR amfebutamone* OR Wellbutrin* OR Wellbatrin* OR Zyban* OR Quomen OR Quomem OR Aplenzin OR (BVF NEXT 033) OR BVF033 OR (BW NEXT 323*) OR BW323* OR Budeprion OR (buprion NEXT hydrochloride) OR bupropin OR Buxon OR Elontril OR Forfivo* OR Odranal OR Zyntabac OR [mh "Varenicline"] OR vareniclin* OR (cdff NEXT 0318) OR cdff0318 OR (cp NEXT 526555*) OR cp526555* OR (oc NEXT 01) OR oc01 OR Tyrvaya OR tartrate OR (yhp NEXT 1903) OR yhp1903 OR Chantix OR Champix OR [mh "Nortriptyline"] OR nortriptylin* OR nortryptilin* OR nortryptylin* OR nortyline OR noramitriptyline OR desitriptyline OR desmethylamitriptylin OR Allegron OR Acetexa OR Altilev OR Ateben OR Atilev OR Aventyl OR Avantyl OR Paxtibi OR Martimil OR Nortrilen OR Pamelor OR Norfenazin OR Noritren OR Norline OR Norpress OR Nortrilen OR Nortrix OR Norventyl OR Ortrip OR Psychotyl OR Sensaval OR Sensival OR Vividyl OR (l NEXT 38489) OR cytisine* OR cytiton OR citizine OR cystisin OR Tabex OR Tsitizin) AND ([mh "Smoking Cessation"] OR [mh "Smoking Reduction"] OR [mh "Smoking Prevention"] OR [mh "Tobacco Use Cessation"] OR ((cessation* OR dishabituation OR therap* OR interv* OR control* OR stop* OR quit* OR abstain* OR abstin* OR give* OR givi* OR ceas* OR prevent* OR reduc* OR decreas* OR withdraw*) AND (smok* OR [mh "Smoking"] OR nicotine OR [mh "Nicotine"] OR [mh "Tobacco"] OR tobacco OR [mh "Tobacco Products"] OR [mh "Tobacco Use"] OR cigarette*))) OR (electronic NEXT nicotine NEXT delivery NEXT system*) OR (electronic NEXT cigarette*) OR E-Cig* OR vape* OR vaping OR vaporiser* OR vaporizer* OR ((cessation* OR dishabituation OR therap* OR interv* OR control*

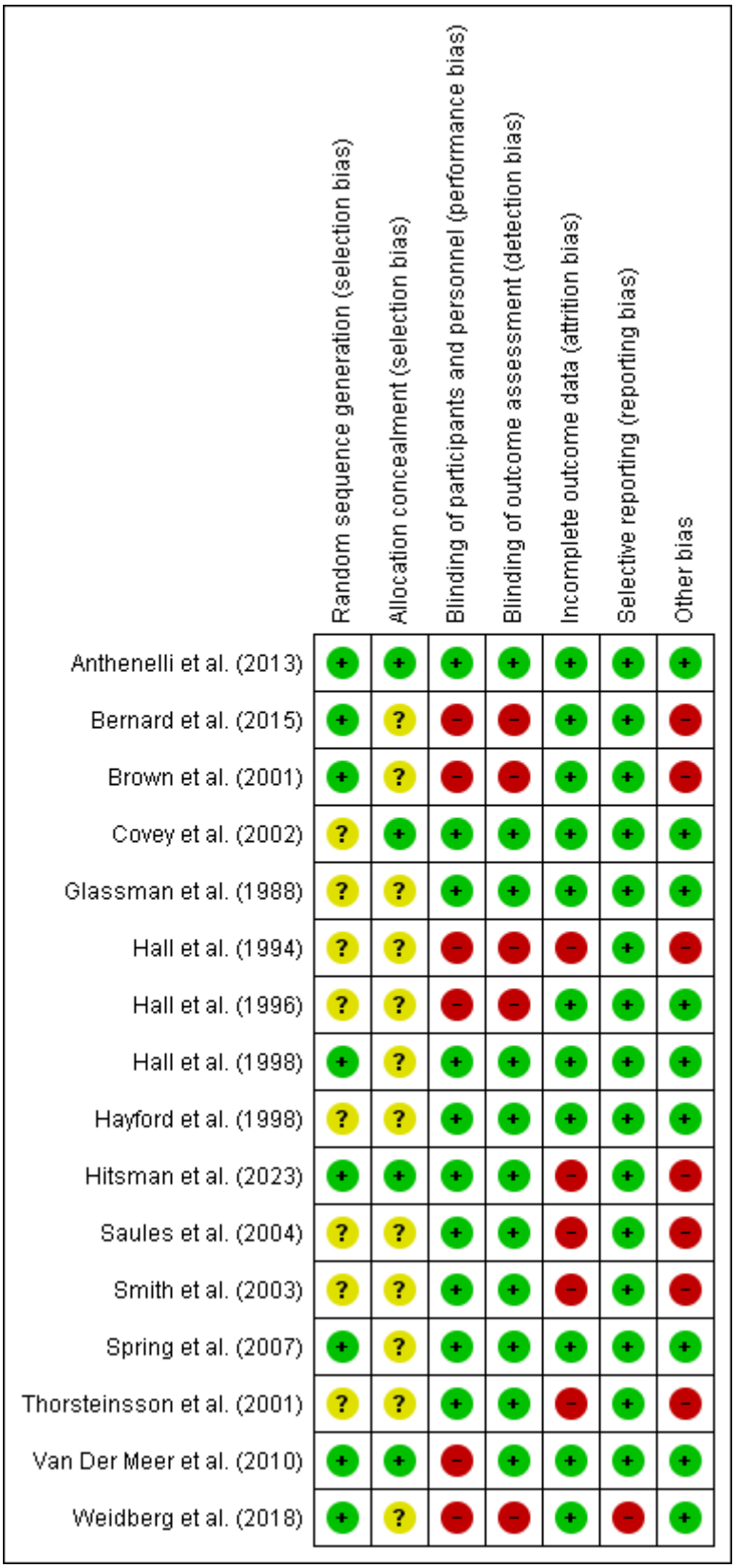
OR stop* OR quit* OR abstain* OR abstin* OR give* OR givi* OR ceas* OR prevent* OR reduc* OR decreas* OR withdraw*) AND (smok* OR [mh "Smoking"] OR nicotine OR [mh "Nicotine"] OR [mh "Tobacco"] OR tobacco OR [mh "Tobacco Products"] OR [mh "Tobacco Use"] OR cigarette*))):ti,ab,kw)

2. PRISMA flow diagram



PRISMA flow diagram *(Adapted with the author's permission from Bekkering et al. (2025)*

3. Risk of bias summary



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

4. Summary of results

Summary of results table, extended version with absolute effect

Outcome / Intervention	NRT	Varenicline	Buproprion	Clonidine	SSRI	TCA (Nortriptyline)	Behavioral interventions	Excercise
STA	N=3 (n=245) Risk with placebo= 50.8% 46 more per 1000 (95%CI 188 fewer to 276 more) OR: 1.20 (95%CI 0.44-3.28)	N=1 (n=525) Risk with placebo= 20.1% 260 more per 1000 (95%CI 166 more to 356 more) OR: 3.40 (95%CI 2.31-5.01)	N=2 (n=277) Risk with placebo=23.0% 319 more per 1000 (95%CI 177 more to 453 more) OR: 4.08 (95%CI 2.30-7.22)	N=1 (n=43) Risk with placebo=13.6% 388 more per 1000 (95%CI 62 more to 693 more) OR: 6.97 (95%CI 1.57-30.87)	N=3 (n=273) Risk with placebo=26.4% 59 more per 1000 (95%CI 45 fewer to 185 more) OR: 1.33 (95%CI 0.78-2.27)	N=1 (n=65) Risk with placebo=30.3% 166 more per 1000 (95%CI 62 fewer to 406 more) OR: 2.03 (95%CI 0.73 -5.61)	N=6 (n=911) Risk with placebo=35.8% 80 more per 1000 (95%CI 16 more to 150 more) OR: 1.40 (95%CI 1.07-1.85)	N=1 (n=70) Risk with placebo=28.6% 200 more per 1000 (95%CI 25 fewer to 431 more) OR: 2.36 (95%CI 0.88-6.34)
LTA	N=2 (n=207) Risk with placebo=24.7% 29 fewer per 1000 (95%CI 121 fewer to 101 more) OR: 0.85 (95%CI 0.44-1.63)	N=2 (n=825) Risk with placebo=14.1% 107 more per 1000 (95%CI 45 more to 181 more) OR: 2.01 (95%CI 1.39-2.89)	N=2 (n=277) Risk with placebo=8.0% 207 more per 1000 (95%CI 74 more to 391 more) OR: 4.62 (95%CI 2.09-10.24)	NRS	N=2 (n=243) Risk with placebo=13.7%) 24 fewer per 1000 (95%CI 81 fewer to 77 more) OR: 0.80 (95%CI 0.37-1.72)	N=1 (n=65) Risk with placebo=21.2% 7 more per 1000 (95%CI 133 fewer to 265 more) OR: 1.04 (95%CI 0.32-3.39)	N=5 (n=819) Risk with placebo=23.4% 58 more per 1000 (95%CI 2 fewer to 127 more) OR: 1.35 (95%CI 0.99-1.85)	N=1 (n=70) Risk with placebo=11.4% 86 more per 1000 (95%CI 53 fewer to 372 more) OR: 1.94 (95%CI 0.51-7.33)
SAE	NRS	N=2 (n=825) Risk with placebo=4.2% 2 fewer per 1000 (95%CI 21 fewer to 35 more) OR: 0.96 (95%CI 0.49-1.90)	NRS	NRS	NRS	NRS	NRS	NRS
ME	N=1 (n=38) No significant effect among subjects that remained abstinence during a 3w follow-up period with nicotine patches	N=2 (n=825) No significant differences compared to placebo	NRS	NRS	NRS	NRS	N=2 (n=664) Cognitive-behavioral therapy and a mood management component had no effect on changes of depressive symptoms	N=1 (n=70) No differences compared to control group
WE	NRS	NRS	NRS	NRS	NRS	NRS	NRS	N=1 (n=70) No impact on weight was found

Legende:

High	Moderate	Low	Very Low
We are very confident that the true effect lies close to that of the estimate of the effect	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- Outcomes: STA (short term abstinence), LTA (long term abstinence), SAE (serious adverse events), ME (mental health scales), WE (weight).
- Interventions: NRT (Nicotine replacement therapy), SSRI (Selective serotonin reuptake inhibitor), TCA (Tricyclic antidepressive),
- Other abbreviations: NRS (no reporting studies), N (number of studies), n (number of participants), OR (odds ratio), CI (confidence interval)

5. GRADE and SOF tables

NRT compared to placebo for Smoking

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With NRT	Relative effect (95% CI)	Risk with placebo	Risk difference with NRT
STA											
245 (3 RCTs)	not serious[a]	serious[b]	not serious	very serious[c]	none	⨁◯◯◯ Very low[a,b,c]	54/117 (46.2%)	65/128 (50.8%)	**OR 1.20** (0.44 to 3.28)	54/117 (46.2%)	**46 more per 1.000** (from 188 fewer to 276 more)
LTA											
207 (2 RCTs)	not serious[a]	not serious	not serious	very serious[c]	none	⨁⨁◯◯ Low[a,c]	24/97 (24.7%)	24/110 (21.8%)	**OR 0.85** (0.44 to 1.63)	24/97 (24.7%)	**29 fewer per 1.000** (from 121 fewer to 101 more)
Mental symptoms											
38 (1 RCT)	serious[d]	not serious	not serious	very serious[e]	none	⨁◯◯◯ Very low[d,e]	No significant effect among subjects that remained abstinence during a 3w follow-up period with nicotine patches				

CI: confidence interval; **OR:** odds ratio

Explanations

a. After carefull consideration, we decided that the risk of bias was not high enough for downgrading the evidence.

b. Due to minor overlap in CI, large I^2, heterogeinity in estimate effect size between studies.

c. CI is very imprecise, sample sizes and number of events are small.

d. No blinding of data-analysts, in combination with subjective outcome measurement.

e. Small sample sizes, small number of events, no quantitative analysis

Varenicline compared to placebo for Smoking

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With Varenicicline	Relative effect (95% CI)	Risk with placebo	Risk difference with Varenicicline
STA											
525 (1 RCT)	not serious	not serious	not serious	serious[a]	none	⨁⨁⨁◯ Moderate[a]	54/269 (20.1%)	118/256 (46.1%)	**OR 3.40** (2.31 to 5.01)	54/269 (20.1%)	**260 more per 1.000** (from 166 more to 356 more)
LTA											
825 (2 RCTs)	not serious	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[b]	57/405 (14.1%)	100/420 (23.8%)	**OR 2.01** (1.39 to 2.89)	57/405 (14.1%)	**107 more per 1.000** (from 45 more to 181 more)
SAE											
825 (2 RCTs)	not serious	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[b]	17/405 (4.2%)	18/420 (4.3%)	**OR 0.96** (0.49 to 1.90)	17/405 (4.2%)	**2 fewer per 1.000** (from 21 fewer to 35 more)
Mental Symptoms											
825 (2 RCTs)	not serious	not serious	not serious	very serious[c]	none	⨁⨁◯◯ Low[c]	No significant differences compared to placebo.				

CI: confidence interval; **OR:** odds ratio

Explanations

a. CI is precise, sample sizes and number of events are small.

b. CI is imprecise, sample sizes and number of events are small.

c. Small sample sizes, small number of events, no quantitative analysis

Bupropion compared to placebo for Smoking

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Bupropion		Risk with placebo	Risk difference with Bupropion
STA											
277 (2 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	23/100 (23.0%)	89/177 (50.3%)	**OR 4.08** (2.30 to 7.22)	23/100 (23.0%)	**319 more per 1.000** (from 177 more to 453 more)
LTA											
277 (2 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	8/100 (8.0%)	50/177 (28.2%)	**OR 4.62** (2.09 to 10.24)	8/100 (8.0%)	**207 more per 1.000** (from 74 more to 391 more)

CI: confidence interval; **OR:** odds ratio

Explanations

a. After carefull consideration, we decided that the risk of bias was not high enough for downgrading the evidence.

b. CI is precise, sample size and number of events are small.

Clonidine compared to placebo for Smoking

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Clonidine		Risk with placebo	Risk difference with Clonidine
STA											
43 (1 RCT)	serious[a]	not serious	not serious	serious[b]	none	⨁⨁◯◯ Low[a,b]	3/22 (13.6%)	11/21 (52.4%)	**OR 6.97** (1.57 to 30.87)	3/22 (13.6%)	**388 more per 1.000** (from 62 more to 693 more)

CI: confidence interval; **OR:** odds ratio

Explanations

a. Data-analysts were not blinded, outcome consisted partly of subjective measurements (self-rapport without verification method).

b. CI is precise, sample sizes and number of events are small.

SSRI compared to placebo for Smoking

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With SSRI		Risk with placebo	Risk difference with SSRI
STA											
273 (3 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	33/125 (26.4%)	50/148 (33.8%)	**OR 1.33** (0.78 to 2.27)	33/125 (26.4%)	**59 more per 1.000** (from 45 fewer to 185 more)
LTA											
243 (2 RCTs)	not serious[a]	not serious	not serious	very serious[c]	none	⨁⨁◯◯ Low[a,c]	16/117 (13.7%)	14/126 (11.1%)	**OR 0.80** (0.37 to 1.72)	16/117 (13.7%)	**24 fewer per 1.000** (from 81 fewer to 77 more)

CI: confidence interval; **OR:** odds ratio

Explanations

a. After carefull consideration, we decided that the risk of bias was not high enough for downgrading the evidence.

b. CI is imprecise, sample sizes and number of events are small.

c. CI is very imprecise, sample sizes and number of events are small.

Nortriptyline compared to placebo for Smoking

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo	With Nortriptyline	Relative effect (95% CI)	Risk with placebo	Risk difference with Nortriptyline
STA											
65 (1 RCT)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low[a]	10/33 (30.3%)	15/32 (46.9%)	**OR 2.03** (0.73 to 5.61)	10/33 (30.3%)	**166 more per 1.000** (from 62 fewer to 406 more)
LTA											
65 (1 RCT)	not serious	not serious	not serious	very serious[a]	none	⨁⨁◯◯ Low[a]	7/33 (21.2%)	7/32 (21.9%)	**OR 1.04** (0.32 to 3.39)	7/33 (21.2%)	**7 more per 1.000** (from 133 fewer to 265 more)

CI: confidence interval; **OR:** odds ratio

Explanations

a. CI is very imprecise, sample sizes and number of events are small.

Behavioral interventions compared to control for Smoking

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With cognitive		Risk with placebo	Risk difference with cognitive
STA											
911 (6 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	162/453 (35.8%)	201/458 (43.9%)	**OR 1.40** (1.07 to 1.85)	162/453 (35.8%)	**80 more per 1.000** (from 16 more to 150 more)
LTA											
819 (5 RCTs)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	95/406 (23.4%)	121/413 (29.3%)	**OR 1.35** (0.99 to 1.85)	95/406 (23.4%)	**58 more per 1.000** (from 2 fewer to 127 more)
Mental health											
664 (2 RCTs)	serious[c]	not serious	not serious	very serious[d]	none	⨁◯◯◯ Very low[c,d]	Cognitive-behavioral therapy and a mood management component had no effect on changes of depressive symptoms				

CI: confidence interval; **OR:** odds ratio

Explanations

a. After carefull consideration, we decided that the risk of bias was not high enough for downgrading the evidence.

b. CI is imprecise, sample sizes and number of events are small.

c. No blinding, in combination with subjective outcome measurement.

d. Small sample sizes, small number of events, no quantitative analysis

Excercise compared to control for Smoking

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With Excercise		Risk with placebo	Risk difference with Excercise
STA											
70 (1 RCT)	not serious[a]	not serious	not serious	serious[b]	none	⨁⨁⨁◯ Moderate[a,b]	10/35 (28.6%)	17/35 (48.6%)	**OR 2.36** (0.88 to 6.34)	10/35 (28.6%)	**200 more per 1.000** (from 25 fewer to 431 more)
LTA											
70 (1 RCT)	not serious[a]	not serious	not serious	very serious[c]	none	⨁⨁◯◯ Low[a,c]	4/35 (11.4%)	7/35 (20.0%)	**OR 1.94** (0.51 to 7.33)	4/35 (11.4%)	**86 more per 1.000** (from 53 fewer to 372 more)
Mental health											
70 (1 RCT)	serious[d]	not serious	not serious	very serious[e]	none	⨁◯◯◯ Very low[d,e]	No significant differences compared to control group				
Weight											
70 (1 RCT)	serious[f]	not serious	not serious	very serious[e]	none	⨁◯◯◯ Very low[e,f]	No impact on weight was found				

CI: confidence interval; **OR:** odds ratio

Explanations

a. After carefull consideration, we decided that the risk of bias was not high enough for downgrading the evidence.

b. CI is imprecise, sample sizes and number of events are small.

c. CI is very imprecise, sample sizes and number of events are small.

d. No blinding, in combination with subjective outcome measurement.

e. Small sample sizes, small number of events, no quantitative analysis

f. No blinding