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Inequity in smoking cessation clinical trials testing pharmacotherapies: exclusion of smokers with mental health disorders

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ABSTRACT

Objectives People suffering from mental health disorder (MHDs) are often under-represented in clinical research though the reasons for their exclusion are rarely recorded. As they have higher rates of smoking and nicotine dependence, it is crucial that they are adequately represented in clinical trials of established pharmacotherapy interventions for smoking cessation. This review aims to examine the practice of excluding smokers with MHDs and reasons for such exclusion in clinical trials evaluating pharmacotherapy treatments for smoking cessation.

Data source The Cochrane database of systematic reviews was searched until September 2020 for reviews on smoking cessation using pharmacotherapies.

Study selection Randomised controlled trials (RCTs) within the selected Cochrane reviews were included.

Data extraction Conducted by one author and independently verified by three authors.

Data synthesis We included 279 RCTs from 13 Cochrane reviews. Of all studies, 51 (18.3%) explicitly excluded participants with any MHDs, 152 (54.5%) conditionally excluded based on certain MHD criteria and 76 (27.2%) provided insufficient information to ascertain either inclusion or exclusion. Studies of antidepressant medications used for smoking cessation were found to be 3.33 times more likely (95% CI 1.38 to 8.01, p=0.007) to conditionally exclude smokers with MHDs than explicitly exclude compared with studies of nicotine replacement therapy.

Conclusion Smokers with MHDs are not sufficiently represented in RCTs examining the safety and effectiveness of smoking cessation medications. Greater access to clinical trial participation needs to be facilitated for this group to better address access to appropriate pharmacotherapeutic interventions in this vulnerable population.

INTRODUCTION

Tobacco smoking is up to three times more prevalent among people with mental health disorders (MHDs), and rates are highest in people with severe mental illness (SMI).[1–4] Physical illness caused by smoking is attributed to 81% of the 13–30 years' reduced life expectancy among people with SMI.[5]

Numerous barriers to supporting people with mental illnesses to quit smoking exist.[6 7] Despite contrary evidence, myths about smokers with MHDs being uninterested to quit have perpetuated, contributing to a culture of permitting smoking.[8] Concerningly, smokers with MHDs are less likely to receive cessation advice in healthcare services and in psychiatric settings have reduced access to cessation support compared with other smokers.[7] Systematic review evidence shows, however, that smokers with MHDs are as willing to quit as other smokers and that their psychological quality of life improves significantly after quitting.[9]

Several pharmacological interventions are recommended as potential treatments for smoking cessation. These include nicotine replacement therapies (NRTs), bupropion (an atypical antidepressant), varenicline or cytisine (nicotinic acetylcholine receptor (nAChR) partial agonist) and electronic cigarettes (e-cigarettes). Although data show that these treatments are both safe and effective in people with MHDs,[10 11] this group of smokers is under-represented in smoking cessation research and in medical research more generally.[12 13] Potential reasons why people with MHDs might be excluded from clinical trials include high rates of attrition, medication contraindications, low medication compliance and ethical and safety concerns.[13–15]

The results of disseminated well-designed RCTs can affect the adoption—or not—of new treatments into clinical practice.[15] There is often a lack of evidence, especially from pivotal studies, to support clinicians in making informed decisions about prescribing treatments in specific subpopulations, for example, smokers with MHDs. A 2019 systematic review and meta-analysis of RCTs comparing the effectiveness and safety of pharmacological and behavioural programmes for smoking cessation in people with SMI found only 28 studies involving only 1947 participants relevant to this population and recommended that further RCTs were needed.[16] Not having enough data about specific patient populations has serious clinical implications as clinicians may be cautious to prescribe treatments for smoking cessation proven safe and effective only in more general populations.[15] To address this important issue of equitable access to smoking cessation therapies in RCTs, this review aimed to examine the practice of exclusion of people with MHDs from RCTs that tested pharmacotherapeutic interventions for smoking cessation and the factors associated with such exclusion.

METHODOLOGY

Search strategy

The Cochrane Database of Systematic Reviews in *The Cochrane Library* was searched for all reviews with the following terms in the title, abstract or

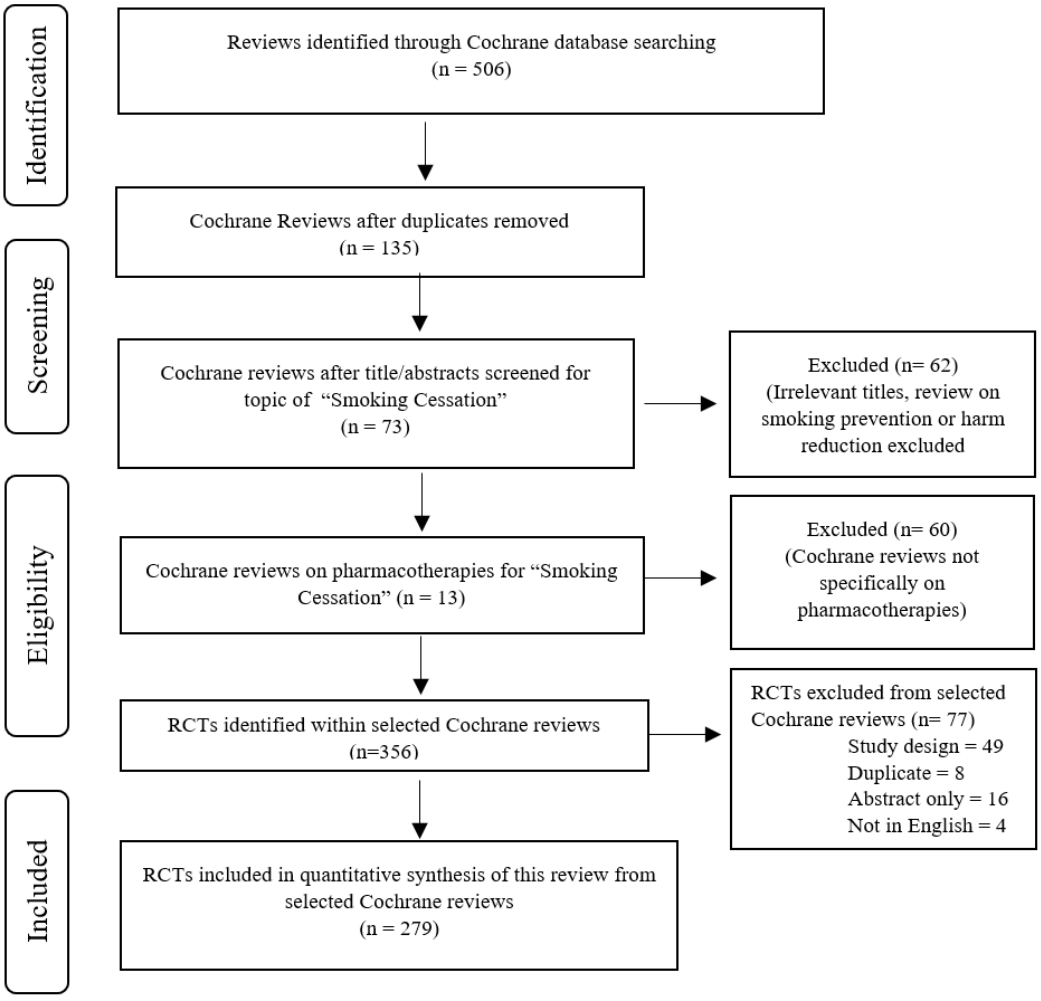

Figure 1 The PRISMA flow chart of the process of identification and eligibility of studies. Online supplemental table provides details of the 279 included RCTs. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials.

keyword fields: quit smoking, smoking cessation, smoking cessation treatment, smoking abstinence, cigarette smoking and tobacco use cessation. The initial search was conducted on 1 October 2019 (updated on 1 October 2020) and contained results until 30 September 2020, and the latest Cochrane reviews published prior to this date was included. Although this is not a systematic review with meta-analysis, a systematic search strategy following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses was followed to identify relevant studies (summarised in figure 1).

Inclusion and exclusion criteria

Included studies were required to be RCTs that had been included in the identified Cochrane reviews and tested the effectiveness and/or safety of pharmacological treatments for smoking cessation. Only pharmacological treatments were focused on this review in order to address the important issue discussed earlier that many prescribers may be reluctant to prescribe smoking cessation agents due to concerns around medication contraindications, low medication adherence, and ethical and safety concerns of prescribing first-line smoking cessation medications to people with MHDs. There was no limit as to the population group studied, and studies were required to examine tobacco smoking abstinence or reduction to quit. Only trials in which individuals were randomly allocated to receive a specific pharmacological therapeutic regimen or placebo or non-placebo control regimen were included. Studies were excluded if they assessed smokeless tobacco; the study design was not an RCT; the intervention was not pharmacological but rather psychosocial (eg, behavioural therapy or hypnotherapy only); the intervention targeted smoking prevention or uptake; the abstinence outcome measurement was less than 6 months; results were published only in abstract form; or if the manuscript was not written in English. For studies with multiple papers resulting from the same dataset, only the main outcomes paper was included in the analyses.

Definition of MHDs and SMIs

MHDs were defined as a range of mental disorders that includes, but is not limited to, depression, anxiety, personality disorder, anorexia bulimia or eating disorder and psychotic disorders, and alcohol and other drug use disorders. SMIs were defined as a subset of MHDs; psychosis spectrum disorders (including schizophrenia); and the major affective disorders including bipolar disorder and severe depression.

Data extraction

The titles and abstracts of all identified Cochrane reviews and RCTs within these reviews were assessed for relevance by one reviewer (SRT), and all relevant studies were assessed in full against the inclusion and exclusion criteria by the same reviewer. Data extraction was conducted by one of the review authors (SRT) and was independently verified by two other review authors (JML and RJC) and checked by a third reviewer (HM) to reach a consensus. A data extraction form was developed based on discussion among review authors and included: the year of publication, country of origin, sample size, study design, type of intervention, type of comparison treatment, participant recruitment method, study setting, participant selection criteria, study funding source and outcome measurement length and type of biochemical verification of outcomes adopted. Each trial was characterised according to its eligibility criteria to identify the inclusion or exclusion of participants with MHDs. Specifically, the selection/eligibility criteria of studies were screened for the mention of MHDs to establish inclusion or exclusion, and only the methods section and the Consolidated Standards of Reporting Trials (CONSORT) diagram of published journal articles were followed for this information.

Measures of MHD participant inclusion/exclusion

Studies were coded as reporting participants with MHDs if they mentioned MHDs in general (eg, antipsychotic medications use) or more specifically mentioned psychiatric disorder, or other specific diagnostic terms (eg, depression, schizophrenia, manic disorder, etc), or any MHD symptoms (suicidal ideation, psychiatric instability) in their participant selection/eligibility criteria. A decision tree explaining various categories of inclusion/exclusion of participants with MHDs was followed (see supplementary figure 1). Based on details provided in the participant selection criteria of each study, studies were categorised into explicitly excluded (ie, specifically indicated exclusion and listed types of MHDs/diagnosis that were excluded); conditionally excluded (ie, listed exact MHD conditions that had been excluded and from the description, an inference was able to be made that other types of MHDs not mentioned had therefore been included); included (ie, clearly stated no MHD condition had been excluded); unclear (provided insufficient information to draw any conclusion or made generalised comments, such as '[individuals with] any physical or mental health conditions that would prevent participants from completing the study were excluded'). All identified MHD exclusion criteria were classified under the following groups: exclusion based on (1) SMIs, (2) drug and alcohol dependence, (3) psychoactive medication use, (4) mild to moderate MHDs, (5) unstable symptoms and (6) medication contraindication.

Measures of other variables

Pharmacological interventions for smoking cessation were classified according to generic group and type of smoking cessation aid. Generic groups were based on the literature: NRT (patch, gum, lozenges, tablets, oral strips, inhaler, and nasal and mouth spray), antidepressants (bupropion, fluoxetine, venlafaxine, paroxetine, selegiline, moclobemide, nortriptyline, sertraline, St. John's wort and S-Adenosyl-L-methionine), nicotine receptor partial agonists (varenicline, cytisine and dianicline) and other (including anxiolytics, selective type 1 cannabinoid receptor antagonists (rimonabant), electronic cigarettes, clonidine, lobeline, mecamylamine, Nicobrevin, opioid antagonists, nicotine vaccines and silver acetate).[17] If studies tested another medication against NRT (eg, nAChR vs NRT, bupropion vs NRT), they were counted once and classified under the non-NRT group. As the terms efficacy and effectiveness were used variously in the trials included in this review, the term used in the referenced study was replicated when referring to that study. Otherwise, the term effectiveness is used.

Data were extracted to identify if participants received additional support with the primary pharmacotherapy treatment to aid smoking cessation. Studies that provided additional supports were categorised by type of support (behavioural vs self-help material). For behavioural support, further data extraction was conducted for type (eg, counselling or cognitive–behavioural therapy), delivery method (eg, in person and via phone) and delivery mode (eg, individual vs group). The funding source of RCTs was categorised as 'industry', 'non-industry' or 'unspecified' depending on the information provided in the paper. RCTs that received funding or free medication from multiple sources were categorised as 'industry' if at least one of the sources was from pharmaceutical industries. Participant recruitment source for RCTs was categorised into community volunteers (through mass media or social media advertisement), healthcare setting, smoking cessation clinic or unspecified (no information provided). Studies that recruited participants from multiple sources (eg, general practice clinics, community volunteers and hospitals) were classified only once under 'healthcare setting' if at least one of the sources was from healthcare setting.

Data analysis

Differences between studies that excluded participants with MHDs and those that did not were evaluated using χ^2 tests of statistical significance for all categorical variables. ORs and 95% CIs were estimated, and p values <0.05 were considered statistically significant. Statistical tests were performed only on the subset of studies that indicated whether participants with MHDs were included or excluded. Logistic regression analysis was used to examine the independence of associations between selected variables and the exclusion of patients with MHDs. As this review did not identify any study that unconditionally included any/all types of MHDs, further analyses were conducted comparing the frequencies of explicitly excluding all classes of MHDs versus conditionally excluding others, after removing studies where methods were unclear. A binary logistic regression was constructed with conditional versus explicit exclusion as the outcome variable and with publication year and class of medication as predictor variables.

RESULTS

A total of 13 Cochrane systematic reviews were identified that assessed the effectiveness of different pharmacotherapies for smoking cessation.[18–30] From all studies included within these reviews, 279 RCTs met the inclusion criteria for the current review after screening for study design, duplicates, language and other specific criteria (figure 1). The included trials represented a variety of treatment, funding sources and other characteristics (table 1). The most common pharmacotherapy of focus was NRT (43.4%) followed by antidepressant medications (32.6%), nAChR partial agonist (13.6%) and others (10.4%).

Of all included studies, inclusion/exclusion criteria relating to MHDs were reported in 72.8% of the RCTs, while the remainder did not provide enough information to determine these (table 2). No studies were identified that included all smokers with MHDs without any conditions (eg, stable vs unstable). The majority (54.5%) of RCTs conditionally excluded people based

Table 1 Characteristics of RCTs

Characteristics	N (%) of trials
Country of origin	
USA	158 (56.6)
UK	20 (7.2)
Multinational	22 (7.9)
Other	79 (28.3)
Year of publication	
1971–1983	10 (3.6)
1984–1995	61 (21.8)
1996–2007	111 (39.8)
2008–2019	97 (34.8)
Trial size (participants)	
>500	197 (70.6)
<500	82 (29.4)
Class of pharmacotherapy intervention	
Antidepressants	91 (32.6)
nAChR partial agonists	38 (13.6)
NRTs	121 (43.4)
Others	29 (10.4)
Trial funding source	
Pharmaceutical industry	156 (55.9)
Non-industry	87 (31.2)
Unspecified	36 (12.9)
Additional behavioural support	
Yes	229 (82.1)
No	24 (8.6)
Unknown	26 (9.3)
Participant recruitment	
Community volunteers	155 (55.6)
Healthcare setting	78 (28.0)
Smoking cessation clinic	25 (9.00)
Unspecified	21 (7.40)

nAChR, nicotinic acetylcholine receptor; NRTs, nicotine replacement therapies; RCTs, randomised controlled trials.

on certain MHD criteria and 18.3% explicitly excluded smokers with any diagnosis of MHDs. Some exclusion criteria are likely to be related to contraindications for medication use (see online supplemental table 1 for a summary), but study authors were rarely explicit about this. Although 40% of RCTs had a CONSORT diagram, very few (9.8%) that mentioned MHDs in their selection criteria presented data on MHD-based exclusion in their CONSORT diagram.

The conditional or explicit exclusion of smokers with MHDs differed by class of pharmacotherapy treatment (table 3). RCTs of antidepressants and nAChR partial agonists had a higher proportion of conditionally exclude 81.3% and 68.4% versus explicitly exclude 14.3% and 26.3%, respectively. For half of all trials including the trials of NRTs as treatment, 50% were unclear in their methodologies as to whether smokers with MHDs were excluded or included. Among studies where exclusion of people with MHDs could be identified, the proportion of studies explicitly excluding versus conditionally excluding classes of MHDs differed by pharmacotherapy type (table 3).

Table 2 Exclusion/inclusion of participants with MHDs in 279 included RCTs

	n (%)
Mention MHD population in selection criteria	
Yes	203 (72.8)
No	76 (27.2)
Exclusion or inclusion	
Explicitly exclude	51 (18.3)
Conditionally exclude	152 (54.5)
Unclear (not enough information)	76 (27.2)

MHDs, mental health disorders; RCTs, randomised controlled trials.

Table 3 Exclusion of people with MHDs by class of pharmacotherapies

Characteristics	Explicitly exclude n=51	Conditionally exclude n=152	Unclear n=76
Class of pharmacotherapy			
Antidepressants	13 (14.3)	74 (81.3)	4 (4.4)
nAChR partial agonists	10 (25.6)	27 (69.2)	2 (5.1)
NRT	18 (15.0)	42 (35.0)	60 (50.0)
Other	10 (34.5)	9 (31.0)	10 (34.5)

X^2 test between explicit versus conditional exclusion by the class of medication p value 0.004.
MHDs, mental health disorders; nAChR, nicotinic acetylcholine receptor; NRT, nicotine replacement therapy.

Time trends of exclusion or inclusion of MHD participants

In studies conducted in the earlier years, between 1971 and 1994, most examined NRT (n=54), with only one study of a nAChR partial agonist and eight studies of other medications. Most of these early RCTs did not specify (unclear) whether the MHD population was included or excluded. This changed over time with the proportion of studies with unclear MHD selection criteria decreasing and the proportion of studies explicitly or conditionally excluding increasing (figure 2). These trends aligned with the commencement of trials of antidepressants in 1995 and the nAChR partial agonist in 2006 (except for one early trial).[31]

During 1984–1995, an increasing proportion of conditional exclusion trials was noticeable, although there was a slight decrease in later years (2008–2019). Over time, the proportion of studies that explicitly excluded participants with any MHDs also increased, while for some studies, MHD selection criteria remained unclear (figure 2).

In a binary logistic regression analysis, publication year (OR=0.95, 95% CI 0.89 to 1.00, p=0.051) did not reach significance as a predictor of conditional exclusion in the adjusted model, nor was there a significant interaction between publication year and class of medication (table 4). Adjusting for publication year, studies of antidepressant medications were found to be 3.33 times more likely (95% CI 1.38 to 8.01, p=0.007) to conditionally exclude smokers with MHDs than explicitly exclude compared with studies of NRT.

MHD exclusion criteria

Data were further examined to identify the MHD criteria for exclusion used to conditionally exclude across different classes of medication (figure 3). Each class of MHD was excluded from more than half of studies of antidepressants that conditionally included some MHDs suggesting that most of these studies excluded multiple classes of MHDs.

Participants with drug and alcohol use disorder and SMI were excluded somewhat more frequently than the other classes of

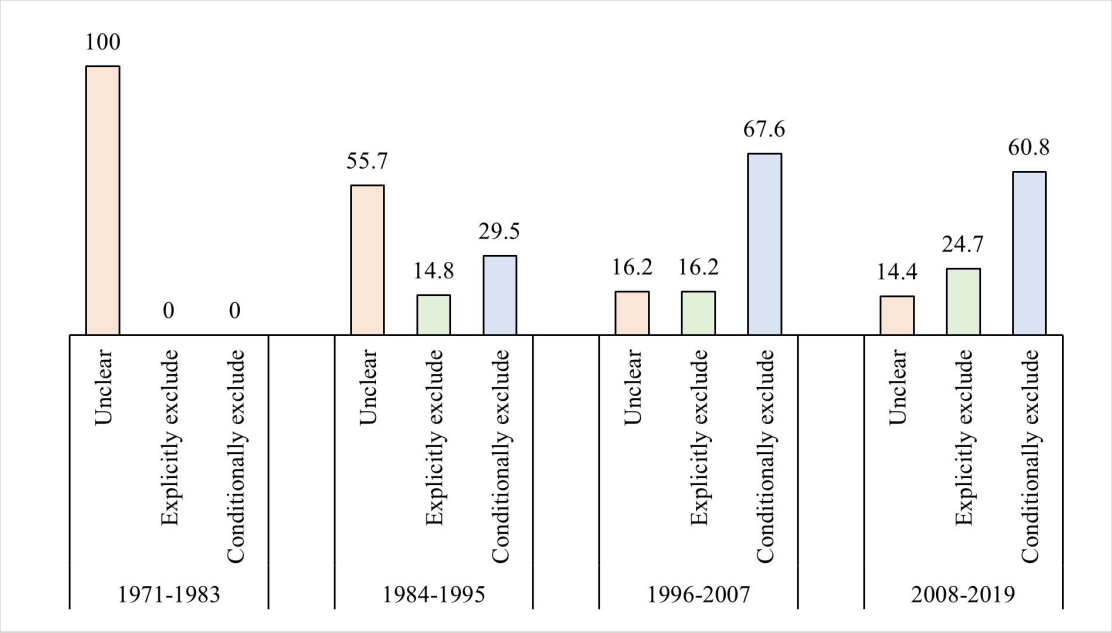

Figure 2 Proportions of selected studies with unclear exclusion criteria, criteria explicitly excluding all classes of MHDs and criteria conditionally excluding some classes of MHDs categorised by years of publication. Proportions add up to 100% within each year category. MHDs, mental health disorders.

MHD across all pharmacotherapy treatments. Among studies that conditionally excluded some classes of MHDs and included others, trials of nAChR partial agonists were the most likely to include participants with drug and alcohol dependence but the least likely to include people with SMI. In contrast, trials of NRTs had the highest rate of exclusion based on drug and alcohol dependence, while none were excluded due to medication contraindication or mild to moderate MHDs.

DISCUSSION

Summary of findings

The present review included smoking cessation treatment trials conducted over the past five decades to explore the inclusion/exclusion of people with MHDs and found that most studies utilised exclusion criteria that explicitly and/or conditionally prevented the enrolment of this high-priority smoking population.

Over one-quarter (27.2%) of all included trials provided inadequate information regarding participant selection criteria to allow the determination of whether MHD populations were included or excluded. This aligns with evidence that inclusion/exclusion criteria have been under-reported in published trials,[32 33] which limits knowledge as to what extent findings relate to specific populations.

More than half of all trials (54.5%) conditionally excluded specific MHD categories and 18.3% explicitly excluded participants with any diagnosis of MHDs. This finding highlights significant inequity in access to smoking cessation intervention research in this highly vulnerable group. Although this review did not specifically explore conditional/explicit exclusion based on MHD diagnosis, the findings align with those of a 2011 meta-analysis of 54 RCTs assessing the effectiveness of pharmacotherapies for smoking cessation that found similarly high rates of exclusion across studies for MHD groups: 40.7% current depression, 35.2% current psychosis, 33.3% current bipolar disorder and 31.5% current panic disorder.[34] While such exclusions could be driven by the researchers and by the regulatory and/or ethics committee approving the trials, the lack of explicit evidence from research to guide effective treatment in this group due to under-representation in RCTs indicates inequity in health outcome research and delivery.[35] The pragmatic application of RCT findings is compromised and often contributes very little to clinical practice when the population for whom the intervention is most applicable are excluded from study participation.[15 36] As

Table 4 Likelihood of conditional exclusion of people with MHDs by the class of medication unadjusted and adjusted for publication year of smoking cessation RCTs

	Unadjusted		Adjusted	
Trial characteristics	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Publication year	0.95 (0.92 to 0.99)	0.008	0.95 (0.89 to 1.00)	0.051
Class of medication				
NRT	1.00	–	1.00	–
Antidepressants	2.38 (1.06 to 5.33)	0.035	3.33 (1.38 to 8.01)	0.007
nAChR partial agonists	1.09 (0.44 to 2.71)	0.856	1.87 (0.65 to 5.38)	0.245
Others	0.38 (0.13 to 1.08)	0.070	0.39 (0.13 to 1.16)	0.092

Base compared to NRTs. Logistic regression.
MHDs, mental health disorders; nAChR, nicotinic acetylcholine receptor; NRT, nicotine replacement therapy; RCTs, randomised controlled trials.

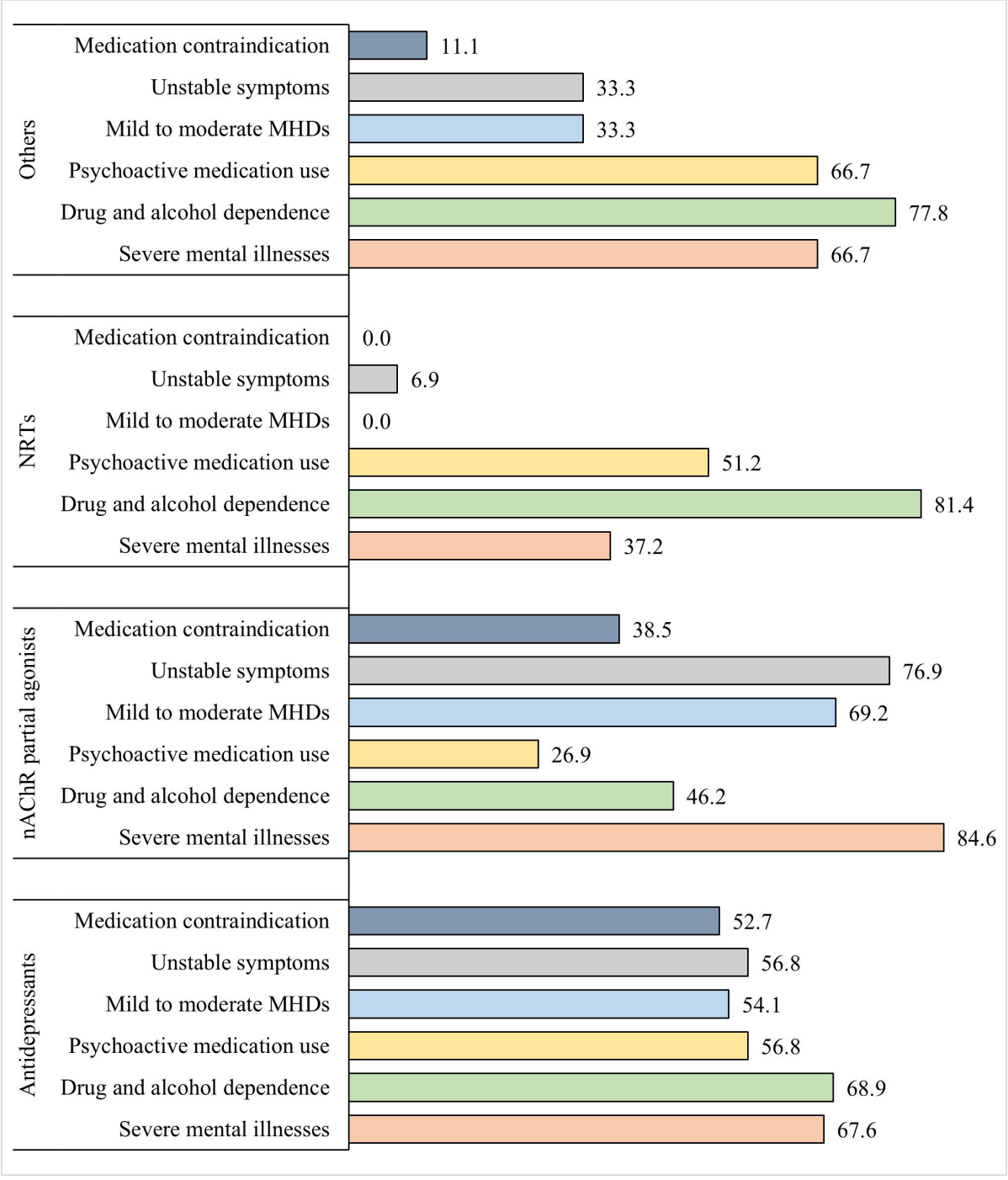

Figure 3 Exclusion criteria used in studies that conditionally excluded smokers with MHDs. Proportion of studies that conditionally excluded MHDs, % does not add up to 100 as categories are not mutually exclusive. MHDs, mental health disorders; nAChR, nicotinic acetylcholine receptor; NRTs, nicotine replacement therapies.

treatments and interventions are developed and tested, equitable opportunities to participate in RCTs are important to improve the health of this vulnerable population group and to address disparities such as the large mortality gap.

Although the exclusion of people with MHDs from clinical trials has been longstanding, data from this review suggest that over time there has been a change in exclusion/inclusion, with more trials conditionally or explicitly excluding and fewer trials providing a lack of clear reporting on this important information. The publication and dissemination of the CONSORT statement between 1996 and 1998 may have influenced the trend observed that more details about participant eligibility were provided in more recent trials.[15] The finding that the majority of the NRTs trials conducted between 1971 and 1995 did not clarify inclusion/exclusion of MHD may be explained by lack of attention to detailing MHD as a vulnerable group or might, optimistically, indicate that people with MHDs were not excluded given that there are few contraindications to NRT and no known drug interactions.[37] A slow increase in the number of studies explicitly excluding participants with any diagnosis of MHDs in the later years is plausibly explained by recognition of potential neuropsychiatric serious/adverse events such as suicidality

and aggression related to some treatments that have received significant interest related to perceived safety such as bupropion and varenicline.[38] With accumulating evidence of the safety and effectiveness of these medications, in 2016 the US Food and Drug Administration removed the black box warning about neuropsychiatric reactions that had been assigned to frontline treatments antidepressant bupropion and the nAChR partial agonist varenicline.[39] Thereafter, an increase in the number of studies that conditionally included participants with certain MHD diagnoses while excluding others is noticeable. After adjusting for RCT publication year the results indicate that, compared with the trials of NRT, antidepressant trials were more likely to conditionally exclude some MHD categories rather than explicitly excluding all MHDs in general. However, some caution needs to be applied to this finding as antidepressant and nAChR partial agonist trials for smoking cessation started much later than NRT trials, and thus there are more limited data on antidepressant and nAChR partial agonist trials. Furthermore, studies whose exclusion criteria were unclear were excluded from this analysis, and the proportion of such studies was greatest among the NRT group.

SMI and drug and alcohol abuse were used as the reason for exclusion more frequently than other MHD categories. A 2007 review of 149 (n=5399) trials of smoking cessation identified that 42% of NRT trials and 68.2% of antidepressant trials had used drug and alcohol-related exclusion,[40] compared with 81.4% and 68.9% found in the current review. Bupropion is contraindicated in patients undergoing abrupt withdrawal from alcohol,[41] which may be a legitimate reason for excluding some people in this group, but it is not clear why the proportion of those excluded is highest among the NRT studies. Existing literature on exclusion criteria indicated that a large proportion (50%–100%) of individuals with drug and alcohol use disorder would be excluded from treatment research.[42] This could be explained by the unique barrier that smokers with drug and alcohol use disorder face, in addition to commonly perceived barriers to smokers in the general population (eg, anxiety and weight gain), such as the belief that it will be harder to tolerate alcohol or drug craving without smoking.[43] Another study investigating the reasons for exclusion from a smoking cessation RCT identified that self-reported diagnosis of SMIs was the primary reason for excluding 28% of the 1206 treatment-seeking smokers who expressed interest in participating in the trial.[13] While people suffering from SMI continue to smoke at higher rates than the general population, care providers often do not address nicotine addiction in this population because of the common misbelief that treatment could worsen the patient's mental illness or that the patient lacks the motivation to quit.[44] There are, however, no good quality data to support this standpoint.[45] In order to increase recruitment of participants with MHDs into smoking cessation trials, it is important to clarify such misapprehensions among healthcare providers and researchers. Trials must be designed to ensure access to additional support to cater for participants' mental health needs, for example, by appointing designated mental health professionals in their research teams. Other proven strategies such as financial incentives, abridged questionnaires and prenotification can be adopted to improve recruitment and retention of participants with MHDs in research studies.[46]

Strengths and limitations

The present review only included RCTs included in Cochrane reviews, which comprise the most reliable studies meeting stringent quality criteria. Using such a strategy, this review is unlikely to have missed relevant RCTs. However, although the latest published Cochrane reviews have been followed, only RCTs published before the search being conducted for each of the Cochrane reviews are included in this current review. Since several of the included Cochrane reviews have not been updated, it is possible that some RCTs conducted recently that would otherwise meet the inclusion criteria of this review would not have been included. One criterion often expected to be met in smoking cessation trials included in Cochrane reviews is a minimum 6-month follow-up. However, often studies that include people with MHDs have a much shorter follow-up period and thus one limitation of exclusively focusing on Cochrane reviews is that this may have led to an overestimation of exclusion of people with MHDs. Included RCTs were not classified based on their trial phase in this review, which may have impacted on participant eligibility. Although many countries may not commonly use antidepressant treatments for smoking cessation, this review includes trials of antidepressants as it is important to comprehensively report on the inclusion/exclusion of people with MHDs from all types of smoking cessation trials and countries, so that the findings from the study can then be applied as relevant in a range of settings around the world.

Only the methods sections and CONSORT diagram of published articles were examined for participant selection criteria and not the study protocol, which might have provided additional details. However, this review identified that reporting and/or operationalisation of MHD exclusion criteria in journal publications varies across studies, which may make it challenging for any reader to clearly understand how individual cases of MHDs were treated. For example, one study might exclude on the basis of 'history of psychiatric illnesses', while another may specify 'current major depression', and yet another will exclude 'psychotic disorders'. Given the variety of conditions and lack of detailed information on methods of exclusion, studies were categorised here based on the face value of the criteria detailed. It was not always possible to conclude how specific scenarios (eg, clinically resolved and time limits) were treated in each RCT, and this ambiguity is likely to also have faced any researchers or study clinicians making decisions about whom to enrol in a given RCT.

Conclusion

In conclusion, this review identified evidence of smoking cessation RCTs excluding people with MHDs and a gap in practice of proper reporting of the exclusion/inclusion criteria. Research suggests that the disparity in smoking rates among persons with MHDs relative to the general population will worsen over time if their needs remain unaddressed.[2] Concerns may exist among researchers about recruitment of participants with MHDs and about retention given possible higher rates of withdrawal and loss to follow-up.[42] However, as smokers with MHDs are at particular risk for negative health outcomes attributed to cigarette smoking,[2 47 48] evidence to guide clinicians to prescribe smoking cessation treatment to this population is much needed. Future steps to address the current inequity in research practice include that researchers should make transparent the proportion of people with MHDs included and those who were excluded and for what reason.

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Contributors SRT, JML, VB, HM and RJC conceived and designed the study. The search, selection and data extraction were conducted by SRT and evaluation of the quality of data extraction was performed by JML, HM and RJC. Analysis of data was

conducted by SRT, and all authors contributed to the interpretation and development of the manuscript. The final version of the manuscript is approved for submission by all authors.

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REFERENCES

1 Lawrence D, Mitrou F, Zubrick SR. Smoking and mental illness: results from population surveys in Australia and the United States. *BMC Public Health* 2009;9:285–85.
2 Williams JM, Steinberg ML, Griffiths KG, *et al*. Smokers with behavioral health comorbidity should be designated a tobacco use disparity group. *Am J Public Health* 2013;103:1549–55.
3 Glasheen C, Hedden SL, Forman-Hoffman VL, *et al*. Cigarette smoking behaviors among adults with serious mental illness in a nationally representative sample. *Ann Epidemiol* 2014;24:776–80.
4 Schroeder SA. Smoking cessation should be an integral part of serious mental illness treatment. *World Psychiatry* 2016;15:175–6.
5 Peckham E, Bradshaw TJ, Brabyn S, *et al*. Exploring why people with SMI smoke and why they may want to quit: baseline data from the SCIMITAR RCT. *J Psychiatr Ment Health Nurs* 2016;23:282–9.
6 Twyman L, Bonevski B, Paul C, *et al*. Perceived barriers to smoking cessation in selected vulnerable groups: a systematic review of the qualitative and quantitative literature. *BMJ Open* 2014;4:e006414.
7 Prochaska JJ, Das S, Young-Wolff KC. Smoking, mental illness, and public health. *Annu Rev Public Health* 2017;38:165–85.
8 Lawn S, Campion J. Achieving smoke-free mental health services: lessons from the past decade of implementation research. *Int J Environ Res Public Health* 2013;10:4224–44.
9 Taylor G, McNeill A, Girling A, *et al*. Change in mental health after smoking cessation: systematic review and meta-analysis. *BMJ* 2014;348:g1151.
10 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;387:2507–20.
11 Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? *Addiction* 2010;105:1176–89.
12 Humphreys K, Blodgett JC, Roberts LW. The exclusion of people with psychiatric disorders from medical research. *J Psychiatr Res* 2015;70:28–32.
13 Webb Hooper M, Asfar T, Unrod M, *et al*. Reasons for exclusion from a smoking cessation trial: an analysis by Race/Ethnicity. *Ethn Dis* 2019;29:23–30.
14 Lembke A, Humphreys K. A call to include people with mental illness and substance use disorders alongside 'regular' smokers in smoking cessation research. *Tob Control* 2016;25:261.
15 Van Spall HGC, Toren A, Kiss A, *et al*. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA* 2007;297:1233–40.
16 Pearsall R, Smith DJ, Geddes JR. Pharmacological and behavioural interventions to promote smoking cessation in adults with schizophrenia and bipolar disorders: a systematic review and meta-analysis of randomised trials. *BMJ Open* 2019;9:e027389.
17 Cahill K, Stevens S, Perera R, *et al*. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database Syst Rev* 2013;2015.
18 Hartmann-Boyce J, McRobbie H, Bullen C, *et al*. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev* 2016;11.
19 Hughes JR, Stead LF, Hartmann-Boyce J, *et al*. Antidepressants for smoking cessation. *Cochrane Database Syst Rev* 2014;288.
20 Hughes JR, Stead LF, Lancaster T, *et al*. Anxiolytics for smoking cessation. *Cochrane Database Syst Rev* 2000;2011.
21 Gourlay SG, Stead LF, Benowitz N, *et al*. Clonidine for smoking cessation. *Cochrane Database Syst Rev* 2004;259.
22 Stead LF, Hughes JR, Cochrane Tobacco Addiction Group. Lobeline for smoking cessation. *Cochrane Database Syst Rev* 2012;30.
23 Lancaster T, Stead LF, Cochrane Tobacco Addiction Group. Mecamylamine (a nicotine antagonist) for smoking cessation. *Cochrane Database Syst Rev* 1998;56.
24 Stead LF, Lancaster T. Nicobrevin for smoking cessation. *Cochrane Database Syst Rev* 2006;2:CD005990.
25 Cahill K, Lindson-Hawley N, Thomas KH, *et al*. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2016;5:CD006103.
26 Hartmann-Boyce J, Cahill K, Hatsukami D, *et al*. Nicotine vaccines for smoking cessation. *Cochrane Database Syst Rev* 2012;23.
27 Hartmann-Boyce J, Chepkin SC, Ye W, *et al*. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database Syst Rev* 2018;2019.
28 David SP, Lancaster T, Stead LF, *et al*. Opioid antagonists for smoking cessation. *Cochrane Database Syst Rev* 2013;7.
29 Cahill K, Ussher MH. Cannabinoid type 1 receptor antagonists for smoking cessation. *Cochrane Database Syst Rev* 2011;3.
30 Lancaster T, Stead LF, Cochrane Tobacco Addiction Group. Silver acetate for smoking cessation. *Cochrane Database Syst Rev* 2012;25.
31 Scharfenberg G, Benndorf S, Kempe G. [Cytisine (Tabex) as a pharmaceutical aid in stopping smoking]. *Dtsch Gesundheitsw* 1971;26:463–5.
32 Gross CP, Mallory R, Heiat A, *et al*. Reporting the recruitment process in clinical trials: who are these patients and how did they get there? *Ann Intern Med* 2002;137:10–16.
33 Gandhi M, Ameli N, Bacchetti P, *et al*. Eligibility criteria for HIV clinical trials and generalizability of results: the gap between published reports and study protocols. *AIDS* 2005;19:1885–96.
34 Le Strat Y, Rehm J, Le Foll B. How generalisable to community samples are clinical trial results for treatment of nicotine dependence: a comparison of common eligibility criteria with respondents of a large representative general population survey. *Tob Control* 2011;20:338.
35 Stapleton JA. Commentary on Banham & Gilbody (2010): The scandal of smoking and mental illness. *Addiction* 2010;105:1190–1.
36 Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. are the results of the study valid? Evidence-based medicine Working group. *JAMA* 1993;270:2598–601.
37 Moore D, Aveyard P, Connock M, *et al*. Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* 2009;338:b1024.
38 Moore T. *ISMP quarter Watch: monitoring FDA MedWatch reports*. Philadelphia PA: ISMP Quarter Watch, 2014.
39 US Food and Drug Administration. FDA drug safety communication: FDA revises description of mental health side effects of the stop-smoking medicines chantix (varenicline) and Zyban (bupropion) to reflect clinical trial findings. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-description-mental-health-side-effects-stop-smoking [Accessed 3 Mar 2021].
40 Leeman RF, Huffman CJ, O'Malley SS. Alcohol history and smoking cessation in nicotine replacement therapy, bupropion sustained release and varenicline trials: a review. *Alcohol Alcohol* 2007;42:196–206.
41 Hays JT, Ebbert JO. Bupropion sustained release for treatment of tobacco dependence. *Mayo Clin Proc* 2003;78:1020–4.
42 Moberg CA, Humphreys K. Exclusion criteria in treatment research on alcohol, tobacco and illicit drug use disorders: a review and critical analysis. *Drug Alcohol Rev* 2017;36:378–88.
43 McHugh RK, Votaw VR, Fulciniti F, *et al*. Perceived barriers to smoking cessation among adults with substance use disorders. *J Subst Abuse Treat* 2017;74:48–53.
44 Weiner E, Ahmed S. Smoking cessation in schizophrenia. *Curr Psychiat Rev* 2013;9:164–72.
45 Ahmed S, Virani S, Kotapati VP, *et al*. Efficacy and safety of varenicline for smoking cessation in schizophrenia: a meta-analysis. *Front Psychiatry* 2018;9:428.
46 Liu Y, Pencheon E, Hunter RM, *et al*. Recruitment and retention strategies in mental health trials - A systematic review. *PLoS One* 2018;13:e0203127.
47 Miller BJ, Paschall CB, Svendsen DP. Mortality and medical comorbidity among patients with serious mental illness. *Psychiatr Serv* 2006;57:1482–7.
48 Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis* 2006;3:A42.

Inequity in Smoking Cessation Clinical Trials Testing Pharmacotherapies: Exclusion of Smokers with Mental Health Disorders

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Supplementary material

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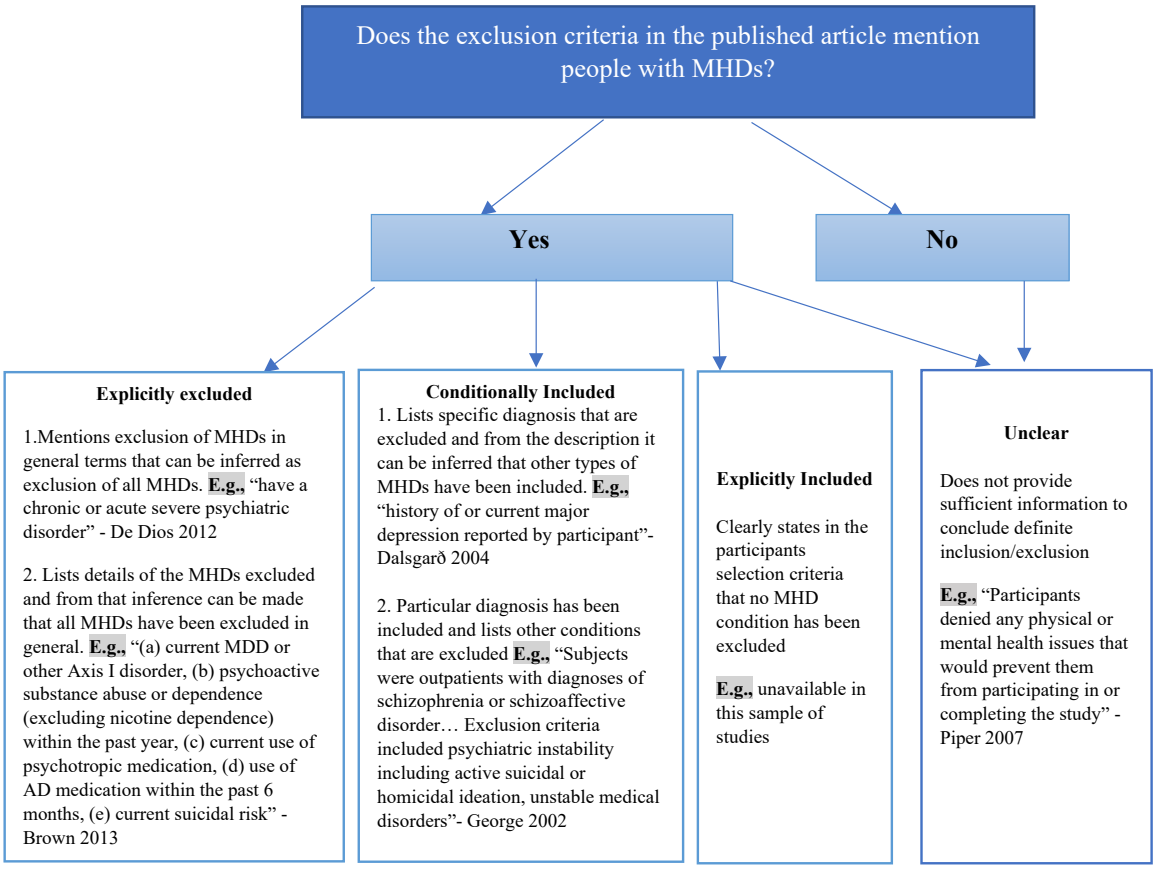

Figure 1: Decision tree to guide MHD population exclusion/inclusion data extraction

Search strategy

- Identifying all Cochrane reviews on smoking cessation: following search terms were used to identify reviews only on the Cochrane Database of Systematic Reviews without any time limits or filters
  - "quit smoking", "smoking cessation", "smoking cessation treatment", "smoking abstinence", "smoking abstinence", "cigarette smoking", "tobacco use cessation"
- This search identified 506 reviews, 371 duplicated were removed, and further 62 were excluded as "smoking cessation" was not the focus of review. Based on literature pharmacotherapies used for smoking cessation were identified (table 2 in this document), and 60 reviews were excluded as they were not specifically on any of the identified pharmacotherapies for smoking cessation.
- RCTs included within the remaining 13 Cochrane Reviews were checked against the inclusion/exclusion criteria of this review and out of 356 RCTs 279 were included. The PRISMA flow diagram (Figure 1 in main document) provides further details.

Table 1**:** Smoking cessation medication contraindications and warnings/precautions relating to mental illness

Group of medication	Name of medication	Contraindications and/or warnings and precautions listed in product summary that relate to mental illness
Antidepressants (Atypical antidepressants)	Bupropion	Contraindications • Undergoing abrupt withdrawal of alcohol or other medicinal products that are associated with an increased risk of seizure on withdrawal (e.g., benzodiazepines) • Current or previous diagnosis of bulimia or anorexia nervosa • Concomitant use of monoamine oxidase inhibitors • History of bipolar disorder Special warnings • Bupropion should be used with caution in people taking medication that are known to lower seizure threshold. This includes most antidepressant and antipsychotic medications • Care should be taken when using bupropion in people with a history of mental illness, due to the greater possibility of neuropsychiatric events Source: https://www.medicines.org.uk/emc/medicine/2948/#gref
Antidepressants (Atypical antidepressants)	Venlafaxine	Contraindications • None reported Special warning • Venlafaxine should be used with caution in people who have a history of, or if someone in their family has had, mania or bipolar disorder, aggressive behaviour Source: https://www.medicines.org.uk/emc/product/4487/pil#gref
Antidepressants Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine	Contraindications • Concomitant use of non-selective monoamine oxidase inhibitors Special warnings • Fluoxetine should be taken with caution in people who suffer from epilepsy or had a fit in the past, as it may increase the likelihood of an epileptic fit • Care should be taken when using fluoxetine in people with a history of mental illness known as mania or hypomania Source: https://www.medicines.org.uk/emc/files/pil.5787.pdf
Antidepressants Selective serotonin reuptake inhibitors (SSRIs)	Paroxetine	Contraindications • Concomitant use of monoamine oxidase inhibitors or have taken them at any time within the last two weeks. • Concomitant use of anti-psychotic medicines called thioridazine or pimozide. Special warnings: • Paroxetine should be taken with caution in people who have epilepsy or history of fits or seizures • Care should be taken in people with history of mania or having a treatment for severe depression called electro convulsive therapy (ECT) • Caution should be followed if taking medicines that may increase the risk of bleeding, including antipsychotics such as perphenazine or clozapine, tricyclic antidepressants, such as clomipramine Source: https://www.medicines.org.uk/emc/files/pil.8486.pdf
Antidepressants Selective serotonin reuptake inhibitors (SSRIs)	Sertraline	Contraindications • Concomitant use of monoamine oxidase inhibitors • Concomitant use of monoamine oxidase inhibitors called pimozide (a medicine for mental disorders such as psychosis) Special warnings: • Caution should be taken in people with epilepsy (fit) or a history of seizures • Sertraline should be used with caution in people who have suffered from manic depressive illness (bipolar disorder) or schizophrenia. Also, among people have or have previously had suicidal ideation Source: https://www.medicines.org.uk/emc/files/pil.4348.pdf

Antidepressants Tricyclic antidepressants (TCAs)	Nortriptyline	Contraindications • Suffering from mania (abnormally raised mood) • Concomitant use, or have taken in the last two weeks, monoamine oxidase inhibitors Special warnings: • Nortriptyline should be taken with caution in people who are suicidal or aggressive, are agitated, overactive or suffer from schizophrenia, and have a history of epilepsy • Caution should be followed in people who are undergoing electroconvulsive therapy and had an allergic reaction to another tricyclic antidepressant in the past Source: https://www.medicines.org.uk/emc/files/pil.2423.pdf
Antidepressants Monoamine oxidase inhibitors (MAOIs)	Selegiline	Contraindications • Taking any antidepressants. Antidepressants should be stopped a number of weeks before taking Eldepryl, • taking any monoamine oxidase (MAO) inhibitors e.g., the antibiotic linezolid Special warnings: • Selegiline (Eldepryl) should be taken with caution if patient is being treated for any mental illness, anxiety or sleep problems • Care should be taken in people taking Levodopa, as it can cause agitation and uncontrollable movements. • Caution should be followed in people with history of any unusual urges and/or behaviours (such as excessive gambling or excessively sexual behaviour) Source: https://www.medicines.org.uk/emc/files/pil.2251.pdf
Antidepressants Monoamine oxidase inhibitors (MAOIs)	Moclobemide	Contraindications • Suffering from a severe mental problem that may make you confused, lose contact with reality or become unable to think and judge clearly. • Concomitant use or have recently stopped taking any other medicines to treat depression or anxiety, such as fluoxetine, paroxetine or clomipramine. Special warnings: • Moclobemide (Manerix) should be taken with caution in people suffering from bipolar disorder or manic depression, or have ever had suicidal ideation Source: https://www.medicines.org.uk/emc/files/pil.6661.pdf
Antidepressants Extracts of St. John's wort	St. John's wort	Contraindications • Diagnosis of depression Source: https://www.medicines.org.uk/emc/files/pil.9038.pdf
Antidepressants Dietary supplement	S-Adenosyl-L-Methionine (SAMe)	Contraindications • Diagnosis of bipolar disorder, as SAMe may worsen symptoms of mania) Special warnings: • Precautions must be followed among people who are taking Levodopa to treat Parkinson's disease, taking antidepressants, as SAMe increase levels of serotonin Source: https://files.nccih.nih.gov/s3fs-public/SAMe_08-11-2015.pdf
nAChR partial agonist	Cytisine	Contraindications • None reported Special warnings: • Cytisine (Desmoxan) should be taken with caution in people suffering from schizophrenia and epilepsy Source: https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/Desmoxan.pdf
nAChR partial agonist	Varenicline	Contraindications • None reported Special warnings: • Champix should be taken with caution, as there have been reports of depression, suicidal ideation and behaviour and suicide attempts in patients taking this medication. If someone develops agitation, depressed mood, changes in behaviour after taking CHAMPIX or develop suicidal thoughts or behaviours, should stop taking Champix and contact the doctor immediately for treatment assessment. • Care should be taken among people who have experienced seizures or have epilepsy Source: https://www.medicines.org.uk/emc/files/pil.266.pdf
NRT	Nicotine Gum	Contraindications • None reported Special warnings: • None reported Source: https://www.aafp.org/dam/AAFP/documents/patient_care/tobacco/pharmacologic-guide.pdf
NRT	Nicotine Lozenges and Transdermal Patch	Contraindications • None reported Special warnings: • None reported Source: https://www.aafp.org/dam/AAFP/documents/patient_care/tobacco/pharmacologic-guide.pdf
NRT	Nasal Spray	Contraindications • None reported Special warnings: • None reported Source: https://www.aafp.org/dam/AAFP/documents/patient_care/tobacco/pharmacologic-guide.pdf

NRT	Oral Inhaler	Contraindications • None reported Special warnings: • None reported Source: https://www.aafp.org/dam/AAFP/documents/patient_care/tobacco/pharmacologic-guide.pdf
Opioid antagonist	Naltrexone	Contraindications • Receiving opioid analgesics, currently dependent, in acute opioid withdrawal Special warnings: • Precautions must be followed while taking naltrexone in patients with substance abuse with or without concomitant depression, as it may increase the risk of suicide. This risk is not abated by treatment with naltrexone hydrochloride Source: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-01168-1
Cannabinoid receptor antagonist	Rimonabant	Contraindications • Suffering from major depressive illness and/or taking anti-depressive treatment Special warnings: • Rimonabant (Acomplia) should be taken with caution in people with a history of depressive disorders/mood alterations, uncontrolled psychiatric illness, and seizures Source: https://www.ema.europa.eu/en/documents/product-information/acomplia-epar-product-information_en.pdf
Anxiolytics	Buspirone Beta-blockers Oxprenolol Metoprolol	Contraindications • Epilepsy Special warnings: • Should be taken with caution in people taking benzodiazepine e.g., nitrazepam or temazepam or another common sedative or hypnotic medicine, or have had drug dependence Source: https://www.medicines.org.uk/emc/files/pil.5735.pdf
	Diazepam	Contraindications • Phobic or obsessional states; chronic psychosis, hyperkinesis (paradoxical reactions may occur) • depression or those with anxiety and depression as suicide may be precipitated in such patients. Special warnings: • Should be taken with caution in people taking alcohol and/or CNS depressants • Extreme caution should be used in prescribing diazepam to patients with personality disorders Source: https://www.medicines.org.uk/emc/product/4524/smpc#gref
Nicotine acetylcholine receptor antagonist	Mecamylamine	Contraindications • None reported Special warnings: • None reported Source: https://www.emedicinehealth.com/drug-mecamylamine/article_em.htm
Alpha-agonist hypotensive	Clonidine	Contraindications • None reported Special warnings: • Should be taken with caution, as sudden cessation of clonidine treatment has, in some cases, resulted in symptoms such as nervousness, agitation, headache, and tremor accompanied or followed by a rapid rise in blood pressure and elevated catecholamine concentrations in the plasma Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017407s034lbl.pdf

Table 2: Cochrane reviews included in this review to identify RCTs on smoking cessation using pharmacotherapies and RCTs within the Cochrane reviews

Treatment	1st Author	Review Year	Title of Review	Number of RCTs included in each Cochrane review (n = 359)	Number of RCTs included in this review from each Cochrane review (n= 279)
Antidepressants	Hughes, J. R.	2014	Antidepressants for smoking cessation	90	80
Anxiolytics	Hughes, J. R.	2000	Anxiolytics for smoking cessation	7	5
Clonidine	Gourlay, S. G.	2004	Clonidine for smoking cessation	6	4
Electronic cigarettes	Hartmann-Boyce, J.	2016	Electronic cigarettes for smoking cessation	24	2
Lobeline	Stead, L. F.	2012	Lobeline for smoking cessation	0	0

Mecamylamine	Lancaster, T.	1998	Mecamylamine (a nicotine antagonist) for smoking cessation	2	2
Nicobrevin	Stead, L. F.	2006	Nicobrevin for smoking cessation	0	0
Nicotine receptor partial agonists	Cahill, K.	2016	Nicotine receptor partial agonists for smoking cessation	44	39
Nicotine vaccines	Hartmann-Boyce, J.	2012	Nicotine vaccines for smoking cessation	4	4
Nicotine Replacement Therapy	Hartmann-Boyce, J.	2018	Nicotine replacement therapy versus control for smoking cessation	136	120
Opioid antagonists	David, S. P.	2013	Opioid antagonists for smoking cessation	8	7
Rimonabant	Cahill, K.	2011	Cannabinoid type 1 receptor antagonists for smoking cessation	3	3
Silver acetate	Lancaster, T.	2012	Silver Acetate for Smoking Cessation	2	2
Search updated in December 2020					
Antidepressants	Howes, S.	2020	Antidepressants for smoking cessation	33	11

Table 3: Number of included RCTs by the medication being tested

Group of treatment	Name of Medication	Number of RCTs (n = 279)
Antidepressants	Bupropion	65
	Fluoxetine	6
	Paroxetine	1
	Venlafaxine	1
	Sertraline	1
	Nortriptyline	7
	Selegiline	5
	Moclobemide	1
	St John's-wort	3
	S-Adenosyl methionine (SAMe)	1
nAChR partial agonist	Dianicline	1
	Cytisine	4
	Varenicline	34
NRT	Single NRT product	111
	Combination/choice of NRT products	9
Other	Rimonabant	3
	Silver acetate	2
	Buspirone	3
	Clonidine	4
	Diazepam	1
	Mecamylamine	2
	Beta-blockers	1
	Naltrexone	7
	NEC (nicotine EC)	2
	Nicotine vaccine	4

Table 4: RCTs included in this review grouped by medication type

Author & Year	Treatment group	Medication type	Comparison group	Exclusion criteria related to mental illness	Does the exclusion criteria mention Population with MHDs?	Reviewers' Decision on MHDs exclusion/inclusion based on information provided in published article
Ahluwalia 2002	Antidepressants	Bupropion	Placebo	• current use of psychoactive medication • in drug treatment during the past 6 months • being treated for depression	Yes	Conditionally include
Aubin 2004	Antidepressants	Bupropion	Placebo	• diagnosis of anorexia nervosa or bulimia, bipolar affective disorder, panic disorder or psychosis • recent history of alcohol severe problems • substance abuse or dependence • current major depression	Yes	Conditionally include
Aveyard 2008	Antidepressants	Nortriptyline	Placebo	• a contraindication or caution to nortriptyline or contraindication to nicotine replacement therapy and those taking a drug that interacted with nortriptyline	Yes	Conditionally include
Berlin 1995	Antidepressants	Moclobemide	Placebo	• DSM-III-R criteria for psychoactive substance use disorders: alcohol dependence or abuse or drug dependence or abuse (with the exception of nicotine dependence) • actual episodes of major depression, dysthymia, anxiety disorders, or psychotic episodes; or if they took antidepressants, anxiolytics	Yes	Conditionally include
Biberman 2003	Antidepressants	Selegiline	Placebo	• major physical or mental disorder • abuse of alcohol or use of illegal drug within the preceding year	Yes	Conditionally include
Blondal 1999	Antidepressants	Fluoxetine	Placebo + NRT	• current and past (in the preceding 2 years) treatment with an antidepressant were excluded • current abuse of alcohol	Yes	Conditionally include
Brown 2007	Antidepressants	Bupropion	Placebo	• current Axis I disorder according to the 4th edition • DSM-IV diagnosis of past-year psychoactive substance abuse or dependence • current use of psychotropic medication or medication that may interact adversely with bupropion • current weekly (or more frequent) psychotherapy • eating disorder; or panic disorder.”	Yes	Explicitly exclude
Brown 2013	Antidepressants	Fluoxetine	No Placebo	• current MDD or other Axis I disorder • psychoactive substance abuse or dependence (excluding nicotine dependence) within the past year • current use of psychotropic medication, • use of AD medication within the past 6 months • current suicidal risk	Yes	Explicitly exclude
Cinciripini 2005	Antidepressants	Venlafaxine	Placebo	• currently taking psychoactive medication • current substance abuse, or other psychiatric disorders	Yes	Explicitly exclude
Cinciripini 2013	Antidepressants	Bupropion	Placebo	• currently taking psychotropic medication • lifetime history of a psychotic disorder	Yes	Explicitly exclude

				• psychiatric hospitalization within the last year • current psychiatric disorder (including substance abuse except for smoking) • scoring moderate or higher on the suicidality subscale of the Mini-International Neuropsychiatric Interview • contraindications to the use of varenicline (e.g., severe renal impairment) or bupropion SR (e.g., history of seizures).”		
Collins 2004	Antidepressants	Bupropion	Placebo	• currently used psychotropic medications • history of Diagnostic and Statistical Manual of Mental Disorders Axis I psychiatric disorder • contraindications for bupropion	Yes	Explicitly exclude
Covey 2002	Antidepressants	Sertraline	Placebo	• use of a psychotropic medication • major depression, alcohol or drug dependence, panic disorder, posttraumatic stress disorder, anorexia nervosa, or bulimia nervosa within the past 6 months • lifetime diagnosis of bipolar disorder, antisocial or schizotypal personality disorder, severe borderline personality disorder, obsessive-compulsive disorder, or psychosis including schizophrenia	Yes	Conditionally include
Covey 2007	Antidepressants	Bupropion	Placebo + NRT	• use of psychoactive medications • psychiatric conditions including current major depressive disorder • dependence on alcohol or drugs within the past yea • life-time history of bipolar disorder or any psychotic illness	Yes	Conditionally include
Cox 2012	Antidepressants	Bupropion	Placebo	• use of psychoactive medications • history of alcohol or substance abuse within the past year; current drinking of 14 or more alcoholic drinks per week and/or drinking five or more drinks on one occasion two or more times in the past month • history of bulimia or anorexia nervosa	Yes	Conditionally include
Croghan 2007	Antidepressants	Bupropion	Placebo	• history of bulimia/anorexia nervosa • chemical dependence on any drug other than nicotine in the past year • use of antipsychotics, antidepressants	Yes	Conditionally include
Da Costa 2002	Antidepressants	Nortriptyline	Placebo	• mental deficiency	Yes	Conditionally include
Dalsgarð 2004	Antidepressants	Bupropion	Placebo	• history of or current major depression reported by participant	Yes	Conditionally include
Eisenberg 2013	Antidepressants	Bupropion	Placebo	• use of anti-depressants, anti-psychotics • current diagnosis of major depression (requiring medication), bipolar disease, or dementia • history of suicidal events (previous suicide attempt, suicidal ideation) or family history of suicide; History of anorexia nervosa or bulimia • use of any illegal drugs in the past year (e.g., opiates, cocaine, heroin)	Yes	Conditionally include
Evins 2001	Antidepressants	Bupropion	Placebo	• acute exacerbation of psychosis • active co-morbid substance abuse, or bulimia • current but not past major depressive episode	Yes	Conditionally include
Evins 2005	Antidepressants	Bupropion	Placebo	• unstable symptoms and an unstable dose of antipsychotic medication for 30 days • meet Diagnostic and Statistical Manual of Mental Disorders • history of bulimia, and history of mania or substance abuse disorder other than nicotine or caffeine within 6 months of enrolment	Yes	Conditionally include
Evins 2007	Antidepressants	Bupropion	Placebo + NRT	• unstable psychiatric symptoms and antipsychotic dose for 30 days or more	Yes	Conditionally include

				• current major depressive disorder • substance use disorder other than nicotine or caffeine within 6 months of screening • bulimia		
Fossati 2007	Antidepressants	Bupropion	Placebo	• use of antidepressants and antipsychotics • a medical history of eating disorders	Yes	Conditionally include
Gariti 2009	Antidepressants	Bupropion	Placebo + NRT	• not in reasonably good health, including being psychiatrically unstable • history of psychosis, mania (Bipolar 1), eating disorder • substance abuse/dependence within the past 6 months or current use of cocaine • current use of an anti-depressant was also exclusionary • Severe anxiety disorders and depressive disorders	Yes	Conditionally include
George 2002	Antidepressants	Bupropion	Placebo	• unstable schizophrenia or schizoaffective disorder • not on stable doses of their antipsychotic drugs for at least one month prior to randomization and continued antipsychotic treatment during the trial • evidence of alcohol or illicit drug abuse or dependence in the 3 months prior to screening evaluation • psychiatric instability including active suicidal or homicidal ideation, unstable medical disorders and inability to give informed consent	Yes	Conditionally include
George 2003	Antidepressants	Selegiline	Placebo	• lifetime history of schizophrenia, bipolar disorder, panic disorder, and posttraumatic stress disorder were excluded from the trial • past history of major depression • use of antidepressant medications or sympathomimetic agents (e.g., phenylephrine, methylphenidate) • history of alcohol/drug abuse or dependence (except nicotine or caffeine) in the 6 months before study enrolment	Yes	Conditionally include
George 2008	Antidepressants	Bupropion	Placebo + NRT	• positive urine drug screen, or evidence of alcohol or illicit drug abuse or dependence in the 3 months prior to screening evaluation • history of seizure disorders • psychiatric instability including active suicidal or homicidal ideation, unstable medical disorders and inability to give informed consent	Yes	Conditionally include
Gonzales 2001	Antidepressants	Bupropion	Placebo	• history of bulimia or anorexia nervosa • had a current diagnosis of major depression	Yes	Conditionally include
Grant 2007	Antidepressants	Bupropion	Placebo + NRT	• history of schizophrenia or bipolar affective disorder • current use of any of the following medications: tricyclic antidepressants, monoamine oxidase inhibitors, fluoxetine, antipsychotics, benzodiazepines, protriptyline, theophylline or any investigational drug in the previous four weeks	Yes	Conditionally include
Haggsträm 2006	Antidepressants	Bupropion & Nortriptyline	Placebo	• serious or unstable clinical or psychiatric disorders (including history of severe depression) • alcohol or any other drug abuse	Yes	Conditionally include
Hall 1998	Antidepressants	Nortriptyline	Placebo	• met the criteria for MDD within 3 months of the baseline were excluded and referred for depression treatment • use of prescribed psychotropic drugs	Yes	Conditionally include
Hall 2002	Antidepressants	Bupropion & Nortriptyline	Placebo	• bulimia • bipolar disease, current major depressive disorder (MDD)	Yes	Conditionally include

				• treatment for alcohol or other drug use within 6 months • psychiatric hospitalization within 1 year • use of any psychiatric medication • suicidal or psychotic symptoms		
Hall 2004	Antidepressants	Nortriptyline	Placebo	• bulimia • bipolar disease, current major depressive disorder (MDD) • treatment for alcohol or other drug use within 6 months • psychiatric hospitalization within 1 year • use of any psychiatric medication • suicidal or psychotic symptoms	Yes	Conditionally include
Hall 2011	Antidepressants	Bupropion	Placebo	• lifetime bipolar disorder, current major depression disorder • current use of any psychiatric medication • suicidal or psychotic symptoms • treatment of drug or alcohol use within the prior 6 months • psychiatric hospitalization within the prior year	Yes	Conditionally include
Hatsukami 2004	Antidepressants	Bupropion	Placebo	• eating disorders • concurrent drug therapy (e.g., psychoactive drugs, theophylline) • symptoms of depression at the time of enrolment (Beck Depression Inventory score 7 and verified by clinical impression) • history or current diagnosis of other serious psychiatric illness (e.g., panic disorder, psychosis, bipolar disorder) • history of alcohol or other substance abuse in the year before enrolment."	Yes	Conditionally include
Hays 2001	Antidepressants	Bupropion	Placebo	• history or current diagnosis of anorexia nervosa or bulimia • presence of an unstable medical or psychiatric condition • current use of psychotropic medications • current use of any behavioural therapy for smoking cessation • current major depression	Yes	Conditionally include
Hays 2009	Antidepressants	Bupropion	Placebo	• current diagnosis of anorexia nervosa or bulimia • presence of an unstable medical or psychiatric condition • current use of psychotropic medications • current (within the past 3 months) DSM - IV diagnosis of a major depressive disorder	Yes	Conditionally include
Hertzberg 2001	Antidepressants	Bupropion	Placebo	• use psychotropic medication or an unstable psychotropic regimen (same dosage and drug for at least 6 months before the study)."	Yes	Conditionally include
Holt 2005	Antidepressants	Bupropion	Placebo	• anorexia or bulimia • pregnant or lactating; history of alcohol or drug abuse	Yes	Conditionally include
Hurt 1997	Antidepressants	Bupropion	Placebo	• history or current diagnosis of anorexia nervosa or bulimia • presence of an unstable medical or psychiatric condition • history of dependence on alcohol or a non-nicotine substance within the past year • current use of psychotropic medications • current depression as assessed by the physician	Yes	Conditionally include
Hurt 2003	Antidepressants	Bupropion	Placebo	• current (1 month) major psychiatric disorder or use of major psychiatric medications • active alcoholism or drug dependence	Yes	Conditionally include

				• history of anorexia or bulimia		
Jorenby 1999	Antidepressants	Bupropion	Placebo	• current diagnosis of major depressive episode or a history of panic disorder, psychosis, bipolar disorder, or eating disorders • abuse of alcohol or a non–nicotine-containing drug within the preceding year • use of a psychoactive drug within the week before enrolment	Yes	Conditionally include
Jorenby 2006	Antidepressants	Bupropion	Placebo	• contraindications for use of bupropion (diagnosis of eating disorder) • serious or unstable disease within the previous 6 months • history of alcohol or other drug abuse or dependence in the previous 12 months (nicotine excepted) • treatment for major depression in the previous 12months • history of or current panic disorder, psychosis, or bipolar disorder	Yes	Conditionally include
Kahn 2012	Antidepressants	Selegiline	Placebo	• current diagnosis of major depressive disorder or other neuropsychiatric disorders that required current contraindicated pharmacological treatment	Yes	Conditionally include
Kalman 2011	Antidepressants	Bupropion	Placebo + NRT	• diagnosis of schizophrenia • current psychotic episode	Yes	Conditionally include
Killen 2000	Antidepressants	Paroxetine	Placebo + NRT	• history of bipolar disorder, schizophrenia • receiving active treatment for or reported current depression or substance abuse • taking antidepressants, psychotropics, or other drugs that could interact with paroxetine resulting in potentially adverse consequences	Yes	Conditionally include
Killen 2004	Antidepressants	Bupropion	Placebo + NRT	• potential participants received a comprehensive history and physical exam conducted by a study physician and an assessment of past and current depression and current drug use. No further details provided	No	Unclear
Killen 2006	Antidepressants	Bupropion	Placebo	• bipolar disorder, schizophrenia • receiving active treatment for or reporting current depression or substance abuse	Yes	Conditionally include
Killen 2010	Antidepressants	Selegiline	Placebo	• bipolar disorder, schizophrenia • active treatment for or reporting current depression or substance abuse • use of medications contraindicated for use with selegiline	Yes	Conditionally include
Levine 2010	Antidepressants	Bupropion	Placebo	• current major depressive disorder or suicidality • drug or alcohol dependence within the past year • psychotic disorders • use of medications contraindicated with bupropion	Yes	Conditionally include
McCarthy 2008	Antidepressants	Bupropion	Placebo	• bipolar disorder, psychosis, current depression • contraindications to bupropion SR use • history of eating disorders • current heavy drinking	Yes	Conditionally include
Muramoto 2007	Antidepressants	Bupropion	Placebo	• history or current diagnosis or treatment of panic disorder, psychosis, bipolar disorder, or eating disorder • substance abuse or dependence in the 3 months preceding the study • current clinical depression or ADHD • any psychoactive drug treatment within 4 weeks of the study treatment phase	Yes	Conditionally include
Myles 2004	Antidepressants	Bupropion	Placebo	• any medical condition or drug therapy that was considered likely to interact with bupropion	Yes	Conditionally include

				• major depression or psychosis • alcoholism or substance abuse		
Niaura 2002	Antidepressants	Fluoxetine	Placebo	• use of psychotropic medication or current psychiatric illness • alcohol or drug abuse in the past year • suicidal ideation • history of bipolar disorder	Yes	Explicitly exclude
Parsons 2009	Antidepressants	St John's-wort	Placebo	• history of an eating disorder • severe mental illness • regular use of illegal drugs or alcohol dependence within the past 6 months • currently depressed or taking antidepressant medication	Yes	Conditionally include
Piper 2007	Antidepressants	Bupropion	Placebo	• any mental health issues that would prevent them from participating in or completing the study. No further details provided	No	Unclear
Planer 2011	Antidepressants	Bupropion	Placebo	• clinical depression or was prescribed antidepressants • had been diagnosed as having anorexia nervosa and/or bulimia	Yes	Conditionally include
Prochazka 1998	Antidepressants	Nortriptyline	Placebo	• current major depression or other significant psychiatric disorder • alcohol or drug dependence • contraindication or allergy to nortriptyline	Yes	Conditionally include
Prochazka 2004	Antidepressants	Nortriptyline	Placebo	• current major depression or other significant psychiatric disorder • alcohol or drug dependence • contraindication or allergy to nortriptyline	Yes	Conditionally include
Richmond 2013	Antidepressants	Nortriptyline	Placebo	• mental illness (major depressive disorder, bipolar disorder; threats of suicide or repeated deliberate self-harm; current psychotic disorder) • current use of antidepressant or antipsychotic medication • current major depression	Yes	Conditionally include
Rigotti 2006	Antidepressants	Bupropion	Placebo	• contraindication to bupropion • heavy alcohol use (3 drinks/day) • major depression, psychosis	Yes	Conditionally include
Rovina 2009	Antidepressants	Bupropion	Placebo	• history or current diagnosis of anorexia nervosa or bulimia • presence of an unstable medical or psychiatric condition • history of dependence on alcohol or a non-nicotine substance within the past year • current use of psychotropic medications, fluoxetine, clonidine, buspirone or doxepin • current depression, as assessed by the psychiatrist of the program	Yes	Conditionally include
Saules 2004	Antidepressants	Fluoxetine	Placebo	• acute psychiatric crisis • met criteria for a psychiatric disorder within the past six months • currently taking psychiatric medications	Yes	Explicitly exclude
Schmitz 2007	Antidepressants	Bupropion	Placebo	• anorexia nervosa, or bulimia • presence of a current psychiatric disorder or serious medical condition • dependence on alcohol or other illicit substances • concurrent drug therapy or psychotherapy for smoking cessation	Yes	Explicitly exclude
Schnoll 2010	Antidepressants	Bupropion	Placebo	• Axis I psychiatric conditions and medical conditions	Yes	Explicitly exclude
Siddiqi 2013	Antidepressants	Bupropion	Placebo	• not reported	No	Unclear
Simon 2004	Antidepressants	Bupropion	Placebo	• contraindications to bupropion or NRT • serious psychiatric illnesses, including major depression	Yes	Conditionally include

				• recent history of alcohol abuse within the prior 3 months		
Simon 2009	Antidepressants	Bupropion	Placebo	• contraindications to bupropion • serious unstable psychiatric illness (defined by frequent mental health visits or changing psychiatric medication regimens) • history of drug abuse within the prior 3 months	Yes	Conditionally include
Smith 2009	Antidepressants	Bupropion	NRT	• bipolar disorder, psychosis, bulimia, or anorexia nervosa • serious thoughts of self-harm in the previous 2 weeks • drug or alcohol dependence in the past 6 months	Yes	Conditionally include
Sood 2010	Antidepressants	St John's-wort	Placebo	• met diagnostic criteria for current major depressive disorder • lifetime history of bipolar disorder or schizophrenia • currently (past 30 days) using antipsychotic or antidepressant medicines • a recent history (past 3 months) of alcohol abuse or dependence • a recent history of drug abuse • currently taking medications known to interact with SJW including all serotonergic drugs (serotonin reuptake inhibitors, tricyclic antidepressants, tramadol, venlafaxine, tryptophan, and buspirone)	Yes	Conditionally include
Sood 2012	Antidepressants	S-Adenosyl methionine (SAMe)	Placebo	• clinically significant levels of current depression • lifetime diagnosis of bipolar disorder, schizophrenia, or dementia • an unstable medical condition • currently (past 30 days) using antipsychotics or antidepressants • recent history (past 3 months) of alcohol abuse or dependence • had a recent history (past 3 months) of drug abuse	Yes	Conditionally include
Spring 2007	Antidepressants	Fluoxetine	Placebo	• lifetime history of MDD or as having at least one past episode of MDD • currently depressed or an MDD episode within the past 6 months • current episode of Axis I disorder (other than nicotine dependence) • history of seizures, psychosis, or bipolar disorder • use of psychotropic medication within the past month • medically unstable conditions	Yes	Conditionally include
Stapleton 2013	Antidepressants	Bupropion	Placebo	• contraindication to bupropion or NRT according to the summary of product characteristics (SpC)	Yes	Conditionally include
Swan 2003	Antidepressants	Bupropion	Placebo	• current use of medications contraindicated for use with bupropion SR or known to lower seizure threshold • history of or current diagnosis of anorexia nervosa or bulimia • current depression • recent high frequency or binge drinking, abuse of other substances including recreational/street drugs	Yes	Conditionally include
Tashkin 2001	Antidepressants	Bupropion	Placebo	• any serious or unstable medical disorders for which bupropion SR was contraindicated • current diagnosis of major depression	Yes	Conditionally include
Tonnesen 2003	Antidepressants	Bupropion	Placebo	• psychiatric disease • currently depressed, or had a history or current diagnosis of bulimia, anorexia nervosa, panic disorder, psychosis or bipolar disorder	Yes	Conditionally include
Tonstad 2003	Antidepressants	Bupropion	Placebo	• history or current diagnosis of bulimia or anorexia nervosa • history or current diagnosis of panic disorder, psychosis, or bipolar disorder • current depression	Yes	Conditionally include

Wagena 2005	Antidepressants	Bupropion & Nortriptyline	Placebo	• use of psychoactive medication at the time of assessment • any serious or unstable medical disorders for which bupropion SR or nortriptyline was contraindicated	Yes	Conditionally include
Weinberger 2010	Antidepressants	Selegiline	Placebo	• evidence of alcohol or other drug abuse or dependence in the previous 6 months • met DSM-IV criteria for a current diagnosis of major depressive disorder, panic disorder or post-traumatic stress disorder • met DSM-IV criteria for a current or past diagnosis of bipolar disorder or schizophrenia • unstable medical disorders • inability to give informed consent • use of antidepressant medication, or other medications (e.g., meperidine) which might interact with SEL	Yes	Conditionally include
Wittchen 2011	Antidepressants	Bupropion	Placebo	• current diagnosis of major depressive episode • history of panic disorder, psychosis, bipolar disorder, or eating disorder • abuse of alcohol or a non-nicotine containing drug within the preceding year • concurrent use of tricyclics, selective serotonin re-uptake inhibitors (SSRIs), serotonin- norepinephrine re-uptake inhibitors (SNRIs), neuroleptics or monoamine oxidase (MAO) inhibitors	Yes	Conditionally include
Zellweger 2005	Antidepressants	Bupropion	Placebo	• history or current diagnosis of bulimia, anorexia nervosa, panic disorder, psychosis, or bipolar disorder • current depression	Yes	Conditionally include
Cinciripini 1995 L + H	Other	Buspirone	Placebo	• current history of a psychiatric disorder or use of psychotropic medications	Yes	Explicitly exclude
Dow 1984	Other	Beta-blockers 1. Oxprenolol 2. Metoprolol	Placebo	• not reported	No	Unclear
Hao 1988	Other	Diazepam	Placebo	• not reported	No	Unclear
Hilleman 1994	Other	Buspirone	NRT	• history of psychiatric illness, alcoholism or drug addiction	Yes	Explicitly exclude
Schneider 1996	Other	Buspirone	Placebo	• use of psychoactive drugs, or a history of diagnosed anxiety and depression	Yes	Conditionally include
Glassman 1988	Other	Clonidine	Placebo	• drug or alcohol abuse, schizophrenia, and current major depression	Yes	Conditionally include
Glassman 1993	Other	Clonidine	Placebo	• drug or alcohol abuse, schizophrenia, and current major depression • current use of any antidepressant drug • history of major depressive disorder had to have been free of symptoms for at least 6 months and to have taken no antidepressant medication for at least 6 weeks	Yes	Conditionally include
Hilleman 1993	Other	Clonidine	Placebo	• unstable disease states • history of psychiatric illness, alcoholism, or drug addiction	Yes	Explicitly exclude
Niaura 1996	Other	Clonidine	Placebo	• current treatment for a psychiatric disorder (excluding nicotine dependence)	Yes	Explicitly exclude
Bullen 2013	Other	NEC (nicotine EC)	Placebo	• not reported	No	Unclear
Caponnetto 2013a	Other	NEC (nicotine EC)	Placebo	• regular psychotropic medicine use • current or past history of alcohol abuse	Yes	Conditionally include
Rose 1994	Other	Mecamylamine + Nicotine patch	Placebo + NRT	• alcohol or drug abuse • use of psychotropic medications	Yes	Explicitly exclude

Rose 1996	Other	Mecamylamine	Placebo + NRT	• not reported	No	Unclear
Scharfenberg 1971	nAChR partial agonist	Cytisine	Placebo	• not reported	No	Unclear
Vinnikov 2008	nAChR partial agonist	Cytisine	Placebo	• serious or unstable disorders • contraindication for cytisine use • schizophrenia	Yes	Conditionally include
West 2011	nAChR partial agonist	Cytisine	Placebo	• diagnosis of a current psychiatric disorder or a medical condition that was contraindicated according to the cytisine label	Yes	Explicitly exclude
Walker 2014	nAChR partial agonist	Cytisine	NRT	• schizophrenia	Yes	Conditionally include
Tonstad 2011	nAChR partial agonist	Dianicline	Placebo	• current psychotic disorder or major depressive episode based on DSM-IV	Yes	Conditionally include
Anthenelli 2013	nAChR partial agonist	Varenicline	Placebo	• current or past diagnosis of dementia, schizophrenia, schizoaffective disorder, or other psychotic disorder, bipolar I disorder, bipolar II disorder • antisocial, schizotypal, or any other personality disorder severe enough to compromise their ability to comply with the study requirement	Yes	Conditionally include
Aubin 2008	nAChR partial agonist	Varenicline	NRT	• diagnoses of or treatment for depression or other psychological disorder • drug or alcohol dependence within the previous 12 months	Yes	Explicitly exclude
Baker 2016	nAChR partial agonist	Varenicline	NRT	• prior suicide attempts within the last 5 years or current suicidal ideation • diagnosis of or treatment for psychoses within the last 10 years • moderately severe depression via the Patient Health Questionnaire18 • current use of bupropion	Yes	Explicitly exclude
Bolliger 2011	nAChR partial agonist	Varenicline	Placebo	• diagnosis of, or treatment for, depression during the previous 12 months • history of or current psychosis, panic disorder, or bipolar disorder • use of bupropion, clonidine, or nortriptyline within the previous 6 months	Yes	Conditionally include
Carson 2014	nAChR partial agonist	Varenicline	No Placebo	• acute or pre-existing psychiatric illnesses including depression uncontrolled with medication • past history psychosis or suicidal ideation	Yes	Conditionally include
Chengappa 2014	nAChR partial agonist	Varenicline	Placebo	• history of psychiatric emergency room visits or hospitalization, suicidal attempts, or aggressive or violent acts • Comorbid psychiatric condition diagnosed within the last three months was excluded.”	Yes	Conditionally include
Cinciripini 2013	nAChR partial agonist	Varenicline	Placebo	• currently taking psychotropic medication • lifetime history of a psychotic disorder • psychiatric hospitalization within the last year • current psychiatric disorder (including substance abuse except for smoking) • scoring moderate or higher on the suicidality subscale of the Mini-International Neuropsychiatric Interview • contraindications to the use of varenicline (e.g., severe renal impairment) or bupropion SR (e.g., history of seizures).”	Yes	Explicitly exclude
De Dios 2012	nAChR partial agonist	Varenicline	Placebo	• history of a suicide attempt/s • chronic or acute severe psychiatric disorder that will interfere with participation • substance dependence other than nicotine dependence.”	Yes	Explicitly exclude
Ebbert 2015	nAChR partial agonist	Varenicline	Placebo	• history of a suicide attempt or suicidal behaviour in the previous 2 years	Yes	Conditionally include

				• major depressive or anxiety disorder assessed by a physician as severe (lifetime or current) or unstable (ie, medication dose change or exacerbations in the last6months) • lifetime diagnosis of psychosis, panic disorder, posttraumatic stress disorder, or schizophrenia • alcohol or substance abuse in the last 12 months		
Eisenberg 2016	nAChR partial agonist	Varenicline	Placebo	• excessive alcohol use, current use of marijuana or noncigarette tobacco products • history of neuropsychiatric disorders including suicidal attempts or suicidal ideation, family history of suicide, panic disorder, psychosis, bipolar disorder, dementia, bulimia, anorexia • recent or recurring depression	Yes	Conditionally include
Evins 2014	nAChR partial agonist	Varenicline	Placebo	• suicidal or homicidal ideation • hospitalization for suicidality in the prior 12 months • active substance use disorder, or major depressive episode in the prior 6 months	Yes	Conditionally include
Gonzales 2006	nAChR partial agonist	Varenicline/ Bupropion	Placebo	• any serious or unstable disease within 6 months • major depressive disorder within the past year requiring treatment • history of panic disorder, psychosis, bipolar disorder, or eating disorders; alcohol or drug abuse/ dependency within the past year • use of clonidine, or nortriptyline within the month prior to enrolment	Yes	Conditionally include
Gonzales 2014	nAChR partial agonist	Varenicline	Placebo	• history of a suicide attempt or any suicidal behaviour in the past 2 years or current suicidal ideation • self-reported current depression • diagnosis of depression or treatment with antidepressants during the previous 12 months recorded in medical history • lifetime diagnosis of psychosis, panic disorder, other anxiety disorders, or bipolar disorder • active alcohol or substance abuse/dependence (except nicotine) within the past 12 months • any severe medical or psychiatric condition or laboratory abnormality that would make the participant inappropriate for the study	Yes	Conditionally include
Jorenby 2006	nAChR partial agonist	Varenicline	Placebo	• contraindications for use of bupropion (e.g., history of seizure, diagnosis of eating disorder) • use of a monoamine oxidase inhibitor in the prior 14 days • serious or unstable disease within the previous 6 months • history of alcohol or other drug abuse or dependence in the previous 12 months • treatment for major depression in the previous 12months • history of or current panic disorder, psychosis, or bipolar disorder	Yes	Conditionally include
Nahvi 2014a	nAChR partial agonist	Varenicline	Placebo	• current major depressive or manic episode • current psychotic disorder, • past-year suicide attempt or psychiatric hospitalization, or current suicidal ideation with plan or intent	Yes	Conditionally include
Nakamura 2007	nAChR partial agonist	Varenicline	Placebo	• neurologic and psychiatric disorder	Yes	Explicitly exclude

NCT00828113	nAChR partial agonist	Varenicline	Placebo	• current or history of psychotic disorder • current major depressive disorder • history of suicidal ideation in the previous 3 months • unstable medical condition	Yes	Conditionally include
NCT01347112	nAChR partial agonist	Varenicline	Placebo	• current moderate or severe depression • current non-specific suicidal thoughts, or have a lifetime history of a suicidal attempt • current (past 30 days) major depressive disorder or has a history of another psychiatric disorder such as psychosis or bipolar disorder	Yes	Conditionally include
Niaura 2008	nAChR partial agonist	Varenicline	Placebo	• history of psychiatric, pulmonary, renal, or cardiovascular disease • history of depression, panic disorder, psychosis, or bipolar disorder • non-nicotine drug or alcohol dependence within 12 months before study enrolment	Yes	Explicitly exclude
Nides 2006	nAChR partial agonist	Varenicline/ Bupropion	Placebo	• active depression requiring treatment • history of panic disorder, psychosis, bipolar disorder, eating disorders • alcohol or drug abuse/dependency within the previous year	Yes	Conditionally include
Oncken 2006	nAChR partial agonist	Varenicline	Placebo	• major depression within the prior year • panic disorder, psychosis, or bipolar disorder • use of bupropion within the previous 3 months • drug or alcohol abuse or dependence within the past year	Yes	Conditionally include
Rennard 2012	nAChR partial agonist	Varenicline	Placebo	• use of bupropion, clonidine, or nortriptyline within the past 3 months • serious or unstable psychiatric disorders in the past 6 months or on the basis of medical history • current depression or depression diagnosed or treated within the past 12 months • history of suicidal ideation or suicidal behaviour in the past 5 years • history of or present psychosis, panic attacks, or anxiety disorders, or bipolar disorder • history of drug (except nicotine) or alcohol abuse/dependence	Yes	Conditionally include
Rigotti 2010	nAChR partial agonist	Varenicline	Placebo	• diagnosis of depression; treatment with antidepressants in the past year • history of psychosis, panic disorder, or bipolar disorder • drug or alcohol abuse or dependence in the past year • use of bupropion, clonidine, or nortriptyline in the past month.”	Yes	Conditionally include
Rose 2013	nAChR partial agonist	Varenicline /Bupropion	NRT	• current psychiatric disease (with the exception of anxiety disorders, OCD and ADHD; Suicidal ideation (within the past 10 years) • lifetime occurrence of attempted suicide • current depression • psychiatric medications including antidepressants, anti-psychotics	Yes	Conditionally include
Steinberg 2011	nAChR partial agonist	Varenicline	Placebo	• mental illness requiring antipsychotic medications • currently using bupropion, nortriptyline • active substance abuse • deemed clinically unstable	Yes	Conditionally include
Tashkin 2011	nAChR partial agonist	Varenicline	Placebo	• unstable or uncontrolled medical conditions • diagnosis of depression or treatment with antidepressants in the past year • drug or alcohol abuse (other than nicotine) in the past year • history of psychosis, panic disorder, or bipolar disorder	Yes	Conditionally include

Tsai 2007	nAChR partial agonist	Varenicline	Placebo	• past or present history of a serious or unstable clinical disease requiring treatment including neurologic or psychiatric disorders • history of drug (except nicotine) or alcohol abuse	Yes	Explicitly exclude
Tsukahara 2010	nAChR partial agonist	Varenicline	NRT	• drug or alcohol dependence • psychological disorders	Yes	Explicitly exclude
Wang 2009	nAChR partial agonist	Varenicline	Placebo	• diagnosed with, or treated for, depression during the previous 12 months • history of psychosis, panic disorder, bipolar disorder	Yes	Conditionally include
Westergaard 2015	nAChR partial agonist	Varenicline	Placebo	• not reported	No	Unclear
Williams 2007	nAChR partial agonist	Varenicline	Placebo	• use of antidepressants, antipsychotic agents, naltrexone	Yes	Conditionally include
Williams 2012	nAChR partial agonist	Varenicline	Placebo	• psychiatric hospitalization • serious suicidal ideation/behaviour • history of drug or alcohol abuse/dependence	Yes	Conditionally include
Wong 2012	nAChR partial agonist	Varenicline	Placebo	• psychiatric disorders.”	Yes	Explicitly exclude
Cornuz 2008	Other	NIC002 (formerly Nicotine-Qβ)	Placebo	• current diagnosis or a history of major depressive episodes, of panic attacks, psychosis, bipolar or eating disorders • use of bupropion within 6 months before study enrolment or at the time of screening • abuse of alcohol or other recreational drugs • use of a psychoactive drug (excluding sleeping pills) within one month before enrolment	Yes	Conditionally include
Hatsukami 2011	Other	NicVAX [3'AmNic-rEPA]	Placebo	• not reported	No	Unclear
NCT00836199 2011	Other	NicVAX [3'AmNic-rEPA]	Placebo	• history of drug or alcohol abuse or dependence within 12 months • psychiatric disease	Yes	Explicitly exclude
NCT01102114 2010	Other	NicVAX [3'AmNic-rEPA]	Placebo	• history of drug or alcohol abuse or dependence within 12 months • psychiatric disease	Yes	Explicitly exclude
Abelin 1989	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Ahluwalia 1998	NRT	Nicotine patch	Placebo	• self-reported alcohol or drug dependency	Yes	Conditionally include
Ahluwalia 2006	NRT	Nicotine gum (2 mg),	Placebo	• not reported	No	Unclear
Anthenelli (EAGLES) 2016	nAChR partial agonist	Varenicline, Bupropion, Nicotine patch	Placebo	• clinical exacerbation of psychotic, anxiety, mood disorders, Axis I and Axis II disorders in the prior 6 months • not on stable treatment (medication and dose) for ≥ 3 months (if on treatment) • judged to be at imminent risk of self-injurious or suicidal behaviour	Yes	Conditionally include
Areechon 1988	NRT	Nicotine Gum	Placebo	• not reported	No	Unclear
Blondal 1997	NRT	Nicotine nasal spray	Placebo	• current abuse of alcohol or other drugs	Yes	Conditionally include
Br Thor Society 1983	NRT	nicotine chewing gum	Placebo	• psychiatric disorder contraindicating smoking withdrawal	No	Unclear

Buchkremer 1988	NRT	Nicotine patch + behavioural therapy	Placebo	• not reported	No	Unclear
Campbell 1987	NRT	Nicotine gum (2 mg)	Placebo	• not reported	No	Unclear
Campbell 1991	NRT	Nicotine gum 2 to 4 mg	Placebo	• organic psychosis • drug and alcohol abuse	Yes	Conditionally include
Campbell 1996	NRT	Nicotine patch (21 mg	Placebo	• mental disturbances	Yes	Explicitly exclude
Cinciripini 1996	NRT	Nicotine patch (21 mg	No Placebo	• uncontrolled systemic illnesses • recent history (within 1 year) of diagnosed major depression or treatment with antidepressants	Yes	Conditionally include
Clavel 1985	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Clavel-Chapelon 1992	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Coleman 2012	NRT	Nicotine patch	Placebo	• chemical or alcohol dependence	Yes	Conditionally include
Cooper 2005	NRT	Nicotine gum	Placebo	• currently taking antidepressant medication or receiving psychiatric or alcohol/drug abuse treatment. • history of depression still in treatment	Yes	Conditionally include
Cummins 2016	NRT	Nicotine patch	No Placebo	• not enough information provided	No	Unclear
Cunningham 2016	NRT	Nicotine patch	No Placebo	• not reported	No	Unclear
Daughton 1991	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Daughton 1998	NRT	Nicotine patch	Placebo	• current use of psychotropic drugs • recent history of drug or alcohol abuse (within 1 year of the study)	Yes	Conditionally include
Davidson 1998	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Ehrsam 1991	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Fagerström 1982	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Fagerström 1984	NRT	Nicotine gum	No Placebo	• psychologically imbalanced or in the midst of a crisis	Yes	Conditionally include
Fee 1982	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Fiore 1994a	NRT	Nicotine patch	Placebo	• regular use of psychotropic drugs • current symptomatic psychiatric disorder • alcohol or other drug abuse	Yes	Explicitly exclude
Fiore 1994b	NRT	Nicotine patch	Placebo	• regular use of psychotropic drugs • alcohol or dmg abuse; chronic dermatologic disorders • current symptomatic psychiatric disorder	Yes	Explicitly exclude
Fortmann 1995	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Fraser 2014	NRT	Nicotine lozenge	No Placebo	• not reported	No	Unclear
Gallagher 2007	NRT	NRT patch	No Placebo	• acute decompensation/exacerbation of psychiatric symptomatology that precluded the ability to participate, • active, significant substance use in the last 30 days	Yes	Conditionally include
Garvey 2000	NRT	Nicotine gum	Placebo	• not reported	No	Unclear

Gilbert 1989	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Glavas 2003	NRT	Nicotine patch	Placebo	• drug dependence • major psychiatric disorders	Yes	Conditionally include
Glover 2002	NRT	Nicotine sublingual tablet	Placebo	• regular use of psychotropic medication • alcohol or any other drug abuse during the previous 12 months	Yes	Conditionally include
Graham 2017	NRT	Nicotine patch	No Placebo	• not reported	No	Unclear
Gross 1995	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Hall 1985	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Hall 1987	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Hall 1996	NRT	Nicotine gum	Placebo	• current major depression	Yes	Conditionally include
Hand 2002	NRT	Nicotine patch + inhaler	No Placebo	• alcoholism, drug dependency • active psychiatric illness	Yes	Explicitly exclude
Harackiewicz 1988	NRT	Nicotine Gum	No Placebo	• not reported	No	Unclear
Hasan 2014	NRT	Patch and gum	No Placebo	• history of substance abuse • major psychiatric disorder included schizophrenia, bipolar and personality disorders	Yes	Conditionally include
Hays 1999	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Herrera 1995	NRT	Nicotine Gum	Placebo	• use of any psychotropic medications • abuse alcohol or any other drugs	Yes	Conditionally include
Heydari 2012	NRT	Nicotine patch	No Placebo	• not reported	No	Unclear
Heydari 2013	NRT	Patch, Gum and Lozenges	No Placebo	• mental or physical illness	Yes	Explicitly exclude
Hjalmarson 1984	NRT	Nicotine gum	Placebo	• psychosis, mental retardation, and alcohol abuse	Yes	Conditionally include
Hjalmarson 1994	NRT	Nicotine nasal spray	Placebo	• current use of any psychotropic medication • current abuse of alcohol or any other drug	Yes	Conditionally include
Hjalmarson 1997	NRT	Nicotine inhaler	Placebo	• regular treatment with psychotropic drugs • abuse of alcohol or any other drugs during the last 12 months	Yes	Conditionally include
Huber 1988	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Hughes 1989	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Hughes 1990	NRT	Nicotine gum	Placebo	• contraindication to nicotine gum • history of drug abuse, drug dependence • history of psychiatric disorder	Yes	Explicitly exclude
Hughes 1999	NRT	Nicotine Patch	Placebo	• use of psychotropic	Yes	Conditionally include
Hughes 2003	NRT	Nicotine patch	Placebo	• past alcohol dependence but no alcohol or illicit drug intake for last 30 days • current major psychiatric disorder and not taking a psychoactive medication	Yes	Conditionally include
Hurt 1990	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Hurt 1994	NRT	Nicotine patch	Placebo	• active chemical dependence on alcohol • current psychiatric disorder, • current use of clonidine, buspirone hydrochloride, doxepin hydrochloride, or fluoxetine	Yes	Explicitly exclude
ICRF 1994	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Jamrozik 1984	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Jarvis 1982	NRT	Nicotine gum	Placebo	• not reported	No	Unclear

Jensen 1991	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Jorenby 1999	NRT	Nicotine patch	Placebo	• current diagnosis of major depressive episode • history of panic disorder, psychosis, bipolar disorder, or eating disorders • abuse of alcohol or a non–nicotine-containing drug within the preceding year • use of a psychoactive drug within the week before enrolment • clinical depression	Yes	Conditionally include
Joseph 1996	NRT	Nicotine patch	Placebo	• presence of unstable psychiatric illness • unstable disorder involving the use of alcohol or controlled substances	Yes	Conditionally include
Killen 1984	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Killen 1990	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Killen 1997	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Kornitzer 1995	NRT	Nicotine patch	Placebo	• regular use of psychotropic medication • abuse of alcohol or any other drug	Yes	Conditionally include
Kralikova 2009	NRT	Nicotine gum or inhaler	Placebo	• psychiatric treatment or use of medication • alcohol or other drug problems	Yes	Conditionally include
Leischow 1996	NRT	Nicotine Inhaler	Placebo	• regular use of psychotropic drugs • alcohol or drug abuse	Yes	Conditionally include
Lerman 2015	NRT	Nicotine patch	Placebo	• history of substance misuse treatment • current use of cocaine or methamphetamine, or more than 25 alcoholic drinks per week • history of DSM-IV Axis 1 psychiatric disorder • suicide risk score on the MINI International Neuropsychiatric Interview (MINI) of more than 1 • current major depression; current use of antipsychotics (e.g., monoamine oxidase inhibitors, tricyclic antidepressants)	Yes	Conditionally include
Lewis 1998	NRT	Nicotine patch	Placebo	• drug and alcohol abuse within 6 month of admission • history of major psychiatric illnesses	Yes	Conditionally include
Malcolm 1980	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
McGovern 1992	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Molyneux 2003	NRT	Choice of NRT	No Placebo	• admission for psychiatric care • history of alcohol and/or illicit drug abuse in the last 12 months	Yes	Conditionally include
Moolchan 2005	NRT	Nicotine patch + gum	Placebo	• drug or alcohol dependence other than nicotine • current mania, psychosis, and acute depression	Yes	Conditionally include
NCT00534404	NRT	Nicotine patch	No Placebo	• not reported	No	Unclear
Nebot 1992	NRT	Nicotine gum	No Placebo	• addiction to legal or illegal drugs	Yes	Conditionally include
Niaura 1994	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Niaura 1999	NRT	Nicotine gum	No Placebo	• treatment for any psychiatric disorder in the past year • using recreational drugs	Yes	Explicitly exclude
Ockene 1991	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Oncken 2007	NRT	Nicotine patch	Placebo	• Axis I psychiatric diagnosis that required clinical attention (e.g., current major depression or substance dependence other than nicotine) • chronic treatment with bupropion for depression was not exclusionary	Yes	Conditionally include
Oncken 2008	NRT	Nicotine gum	Placebo	• evidence of cognitive or mental health problems (e.g., diagnosis of mental disorder in chart or interviewer or support specialist suspected problems)	Yes	Explicitly exclude

				• evidence of possible drug or alcohol addiction		
Ortega 2011	NRT	Nicotine patch or gum	No Placebo	• pathologies related to psychiatry or neurology	Yes	Explicitly exclude
Otero 2006	NRT	Nicotine patch	No Placebo	• lifetime mental disorders • alcohol and other drugs dependence	Yes	Explicitly exclude
Page 1986	NRT	Nicotine Gum	No Placebo	• not reported	No	Unclear
Paoletti 1996	NRT	Nicotine patch	Placebo	• past or current history of psychiatric disorders • currently taking daily psychiatric medications	Yes	Explicitly exclude
Piper 2009	NRT	Choice of NRT/Bupropion	Placebo	• current psychosis or schizophrenia diagnosis • contraindications for any of the study medications • high alcohol consumption (6 drinks per day on 6 or 7 days of the week) • bipolar disorder, an eating disorder	Yes	Conditionally include
Pirie 1992	NRT	Nicotine Gum	No Placebo	• substance abuse in the past 6 months	Yes	Conditionally include
Pollak 2007	NRT	Nicotine patch, gum, lozenge	No Placebo	• cognitive or mental health problems (e.g., diagnosis of mental disorder in chart or interviewer or support specialist suspected problems) • possible drug or alcohol addiction	Yes	Explicitly exclude
Prapavessis 2007	NRT	Nicotine patch	No Placebo	• psychological problems"	Yes	Explicitly exclude
Puska 1979	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Richmond 1993	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Richmond 1994	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Russell 1983	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Sachs 1993	NRT	Nicotine patch	Placebo	• current regular use of psychotropic medications • current or past alcohol or other drug abuse	Yes	Conditionally include
Scherphof 2014	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Schneider 1983a	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Schneider 1983b	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Schneider 1995	NRT	Nicotine nasal spray	Placebo	• use of psychoactive medication • past or current drug abuse • psychiatric conditions	Yes	Explicitly exclude
Schneider 1996	NRT	Nicotine inhaler	Placebo	• psychiatric conditions or diagnoses • psychoactive medication • past or current drug abuse	Yes	Explicitly exclude
Segnan 1991	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Shiffman 2002 (2 mg)	NRT	Nicotine lozenge	Placebo	• not reported	No	Unclear
Shiffman 2002 (4 mg)	NRT	Nicotine lozenge	Placebo	• not reported	No	Unclear
Shiffman 2009 (2 mg)	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Shiffman 2009 (4 mg)	NRT	Nicotine gum	Placebo	• not reported	No	Unclear
Stapleton 1995	NRT	Nicotine patch	Placebo	• current psychotropic medication	Yes	Conditionally include

Stein 2013	NRT	Nicotine patch + gum	Placebo	• self-reported psychiatric history	Yes	Explicitly exclude
Sutherland 1992	NRT	Nicotine nasal spray	Placebo	• current use of psychotropic medication • current abuse of alcohol or other drugs	Yes	Conditionally include
Sønderskov 1997	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
TNSG 1991	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Tuisku 2016	NRT	Nicotine patch	Placebo	• current drug or alcohol abuse	Yes	Conditionally include
Tønnesen 1988	NRT	Nicotine gum	Placebo	• alcohol abuse • major psychiatric disorders	Yes	Conditionally include
Tønnesen 1991	NRT	Nicotine patch	Placebo	• regular use of psychiatric drugs • alcohol or drug abuse	Yes	Conditionally include
Tønnesen 1993	NRT	Nicotine inhaler	Placebo	• regular use of psychotropic drugs • abuse of alcohol or any other drugs	Yes	Conditionally include
Tønnesen 2000	NRT	Nicotine patch	Placebo	• regular use of psychotropic drugs • abuse of alcohol or any other drugs	Yes	Conditionally include
Tønnesen 2006	NRT	Nicotine lozenges	Placebo	• not reported	No	Unclear
Tønnesen 2012	NRT	Nicotine spray	Placebo	• suspected alcohol or drug abuse • psychiatric condition	Yes	Explicitly exclude
Wallstrom 2000	NRT	Nicotine lozenges	Placebo	• use of psychotropic medication	Yes	Conditionally include
Ward 2013	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Westman 1993	NRT	Nicotine patch	Placebo	• major psychiatric disorders requiring medication	Yes	Conditionally include
Wisborg 2000	NRT	Nicotine patch	Placebo	• not reported	No	Unclear
Zelman 1992	NRT	Nicotine gum	No Placebo	• not reported	No	Unclear
Baltieri 2009	Other	Naltrexone	Placebo	• current diagnosis of dependence or abuse of other substances except nicotine • concomitant psychiatric disorders that might require specific drug treatment • clinical history of mental retardation	Yes	Conditionally include
Covey 1999	Other	Naltrexone	Placebo	• current psychiatric disorder including major depression • drugs or alcohol abuse or dependence • history of a psychotic illness	Yes	Conditionally include
King 2006	Other	Naltrexone + Nicotine Patch	Placebo + NRT	• current or recent past major medical or psychiatric disorder • use of psychotropic medications in the previous year	Yes	Explicitly exclude
King 2012	Other	Naltrexone + Nicotine Patch	Placebo + NRT	• past-year history of a major medical or psychiatric disorder • substance dependence (except nicotine) • lifetime diagnosis of opioid abuse or dependence • use of opioids psychotropic medications	Yes	Explicitly exclude
O'Malley 2006	Other	Naltrexone + Nicotine Patch	Placebo	• past-year history of a major medical or psychiatric disorder • substance dependence (except nicotine) • lifetime diagnosis of opioid abuse or dependence • use of opioids psychotropic medications	Yes	Conditionally include
Toll 2010a	Other	Naltrexone	Placebo	• current alcohol or drug dependence other than nicotine dependence • serious current neurologic, psychiatric, suicidal risk or medical illness • use of any psychotropic drug or on any drug with a psychotropic component [except those who were on a stable dose of a Selective	Yes	Explicitly exclude

				Serotonin Reuptake Inhibitor for at least 2 months for the indications of Major Depressive Disorder, Premenstrual Syndrome or Premenstrual Dysphoric Disorder]		
Wong 1999	Other	Naltrexone	Placebo	• contraindication for the use of either naltrexone or nicotine patch therapy • history of depression, were currently depressed • had other psychiatric conditions requiring medication	Yes	Conditionally include
STRATUS-EU 2006	Other	(i) Rimonabant 5 mg (ii) Rimonabant 20 mg	Placebo	• not reported	No	Unclear
STRATUS-US 2006	Other	(i) Rimonabant 5 mg (ii) Rimonabant 20 mg	Placebo	• not reported	No	Unclear
STRATUS-WW 2005	Other	(i) Rimonabant 5 mg (ii) Rimonabant 20 mg	Placebo	• not reported	No	Unclear
Hymowitz 1996	Other	2.5mg silver acetate lozenge	Placebo	• not reported	No	Unclear
Jensen 1990	Other	6mg Silver acetate chewing gum, up to six pieces daily	Placebo + NRT	• not reported	No	Unclear
Following studies are included after search updated in December 2020						
Barnes 2006	Antidepressants	St John's Wort, 300 mg per day	St John's Wort, 300 mg twice per day	• history of dependence on alcohol or a non-nicotine substance within the past year • current diagnosis of major depressive episode • history of panic disorder, psychosis, bipolar disorder or eating disorders • current use of antidepressant agents	Yes	Conditionally include
Benli 2017	Antidepressants	Bupropion	Varenicline	• current treatment for previously known psychiatric disease	Yes	Explicitly exclude
Cinciripini 2018	Antidepressants	Bupropion	Varenicline	• currently taking psychotropic medication • having a current psychiatric disorder, psychiatric hospitalization within the last year • life-time history of a psychotic disorder • scoring moderate or higher on the suicidality scale of the Mini International Neuropsychiatric Interview (MINI)	Yes	Explicitly exclude
CTRI/2013/07/003830	Antidepressants	Bupropion	No Placebo	• past psychiatric illness”	Yes	Conditionally include
Ebbert 2014	Antidepressants	Bupropion	Varenicline	• history of psychosis, bipolar disorder, bulimia, or anorexia nervosa • current depression (moderate or severe) • active substance abuse other than nicotine • current use (previous 14 days) of antipsychotics, monoamine oxidase inhibitors, or drugs with bupropion SR interactions • recent antidepressant dose change (previous 3 months)	Yes	Conditionally include
Gilbert 2019	Antidepressants	Bupropion	Placebo	• current use of psychoactive drugs or medications	Yes	Conditionally include

				• alcohol use 28 alcoholic drinks per week • bulimia or anorexia • current diagnoses of a mood, bipolar, or psychotic disorder		
Moreno-Coutino 2015	Antidepressants	Bupropion	NRT	• use or abuse of another psychoactive substance (including psychiatric medications) • diagnosis of mental disorders and conditions • contraindications to bupropion	Yes	Explicitly exclude
NCT00132821	Antidepressants	Bupropion	NRT	• met DSM-IV criteria for dependence on substances other than nicotine and caffeine • substance abuse within the year prior to enrolment • history of DSM-IV diagnosis of schizophrenia, bipolar disorder, obsessive compulsive disorder, or chronic depression • current diagnosis of major depression • currently diagnosed with a sleep disorder, anorexia or bulimia • use of medications contraindicated with bupropion • high frequency alcohol use or binge drinking in the month prior to enrolment	Yes	Conditionally include
NCT00308763	Antidepressants	Bupropion	NRT	• history of substance abuse, including alcohol use in excess of 14 drinks a week • history of anorexia or bulimia • presence of an unstable psychiatric illness • current use of a psychotropic medication, including antidepressant medications	Yes	Conditionally include
NCT00578669	Antidepressants	Fluoxetine	Placebo	• current Axis I disorder, including Major Depressive Disorder • psychoactive substance abuse or dependence within past year • current use of psychotropic medication • use of antidepressant medication within past 6 months • current suicidal risk	Yes	Explicitly exclude
Rose 2014	Antidepressants	Bupropion	Varenicline	• not reported	No	Unclear