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

Saki Rubaiya Talukder ,[1] Julia M Lappin,[1,2] Veronica Boland,[1] Hayden McRobbie,[1] Ryan James Courtney[1]

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[1]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia
[2]School of Psychiatry, University of New South Wales, Sydney, New South Wales, Australia

Correspondence to
Saki Rubaiya Talukder, National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia; s.talukder@unsw.edu.au

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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

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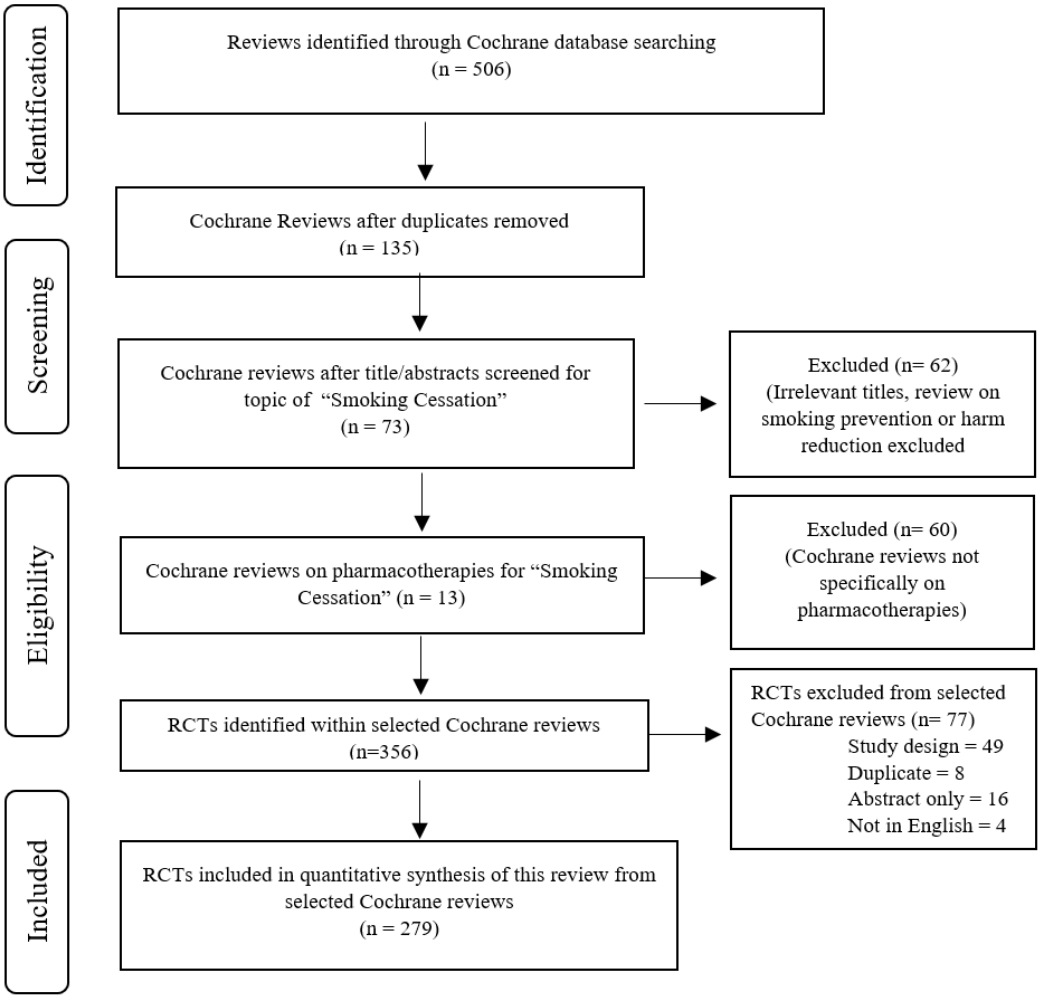

Figure 1 The PRISMA flow chart of the process of identification and eligibility of studies. Online supplemental table provides details of the 279 included RCTs. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trials.

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

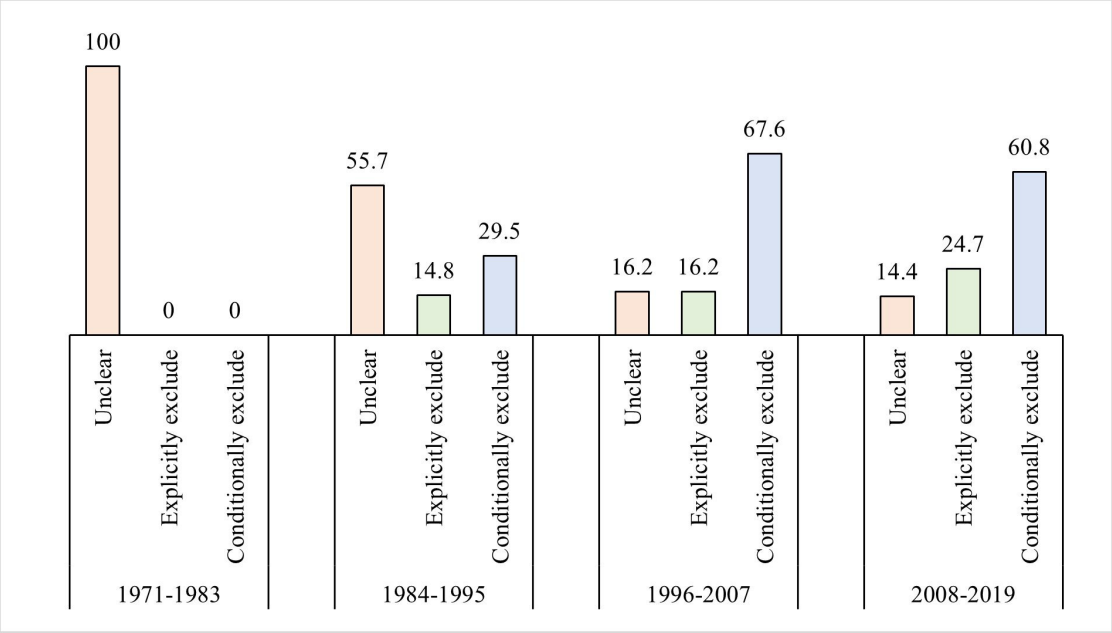

Figure 2 Proportions of selected studies with unclear exclusion criteria, criteria explicitly excluding all classes of MHDs and criteria conditionally excluding some classes of MHDs categorised by years of publication. Proportions add up to 100% within each year category. MHDs, mental health disorders.

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.

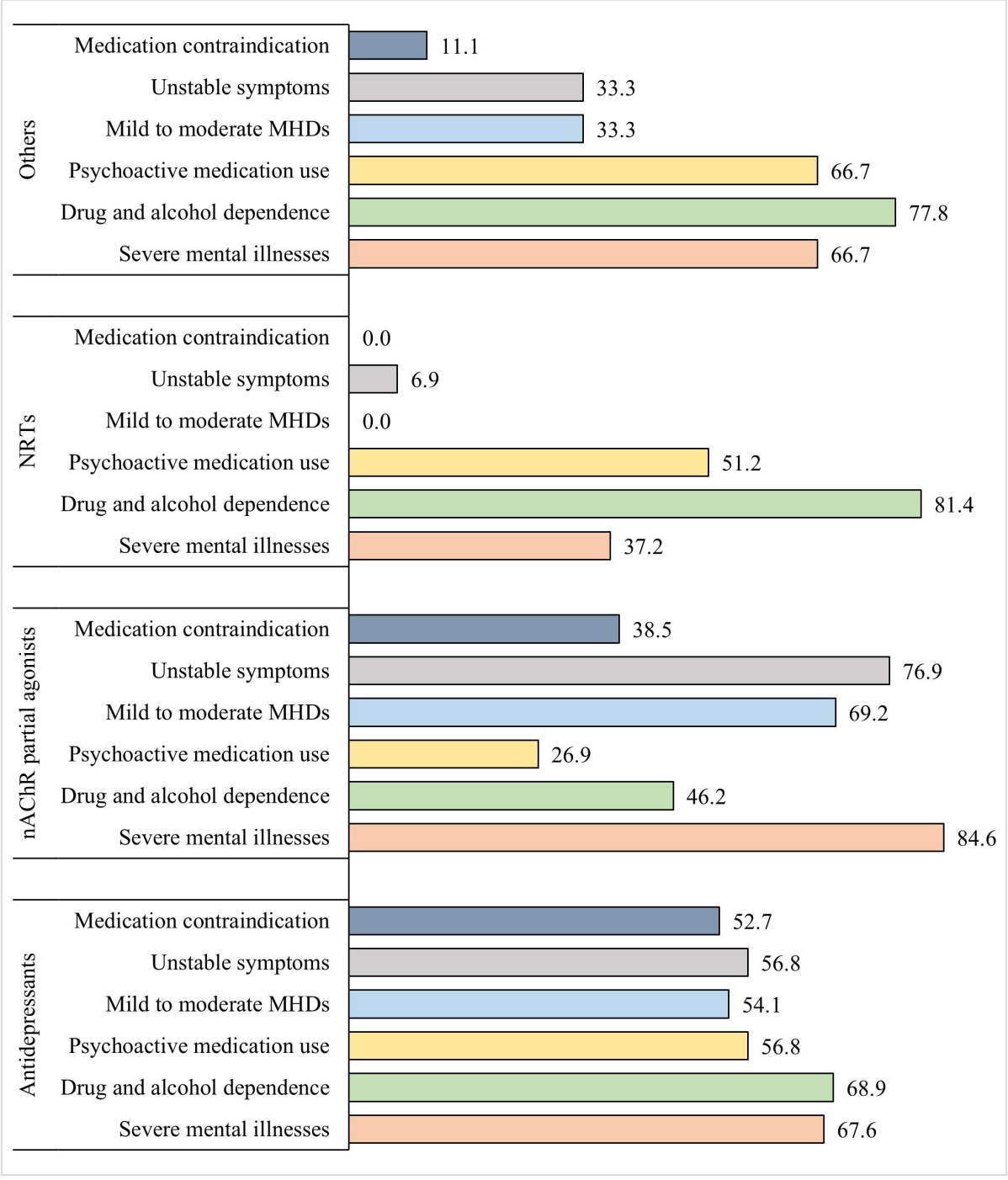

Figure 3 Exclusion criteria used in studies that conditionally excluded smokers with MHDs. Proportion of studies that conditionally excluded MHDs, % does not add up to 100 as categories are not mutually exclusive. MHDs, mental health disorders; nAChR, nicotinic acetylcholine receptor; NRTs, nicotine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

Twitter Saki Rubaiya Talukder @RubaiyaSaki

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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ORCID iD

Saki Rubaiya Talukder http://orcid.org/0000-0001-6905-0370

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