Effectiveness of pharmacotherapy for smoking cessation: Umbrella review and quality assessment of systematic reviews

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Abstract

Background: In the long term, smoking cessation can decrease the risk of cancer, stroke, and heart attacks and improve overall survival. This umbrella review aimed to assess the effect of pharmacological interventions on smoking cessation and to evaluate the methodological quality of previously conducted systematic reviews.

Methods: Databases including the Cochrane library, PubMed, MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, Scopus and Google Scholar were used to retrieve reviews. Systematic reviews that included only randomized controlled trials designed to assess pharmacotherapeutic interventions supporting abstinence from smoking were considered in this umbrella review. Each review was assessed for quality using the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) tool. Two authors (AM, AB) screened the titles and abstracts of all reviews obtained by the search strategy, assessed the full text of selected articles for inclusion and extracted data independently. Two authors (AM, AB) also performed a quality appraisal independently and Cohen's Kappa statistic was used to assess inter-rater agreement. The findings of the studies were narrated qualitatively to describe the evidence regarding the effectiveness of pharmacotherapies for smoking cessation.

Results: Nine reviews were included in this umbrella review**.** Most of the reviews included in this review reported that Nicotine Replacement Therapy (NRT), bupropion and varenicline were effective for smoking cessation. The combination of a nicotine patch with other nicotine formulations was also more effective than monotherapy. Similarly, the combination of nicotine with the non-nicotine therapy varenicline was found to be more effective than varenicline alone. However, the opioid antagonist naltrexone alone was not found to be effective for smoking cessation nor in combination with nicotine replacement therapy. The quality of reviews published after the development of the R-AMSTAR tool was higher than reviews published before the inception of the tool.

Conclusions: This review revealed that drugs approved by the US Food and Drug Administration (FDA) are effective for smoking cessation. A combination of nicotine patches with other nicotine formulations was also effective for smoking cessation compared to nicotine monotherapy. The quality of papers published after the development of the AMSTAR tool demonstrated better quality compared to papers published before the inception of the tool.

Background

In 2012, the global estimated prevalence of daily tobacco smoking among men and women aged 15 and over was 31.1% and 6.2% respectively [1]. Smoking seriously affects almost all organs in the body. Tobacco smoking can lead to many short- and long-term health effects including lung and other organ cancers, chronic bronchitis, emphysema, stroke and heart attack [2]. Tobacco smoking is responsible for 90% of all cases of lung cancer and 90% of all deaths due to chronic obstructive pulmonary disease (COPD) [3]. According to the World Health Organization, tobacco smoking kills about six million people globally per annum [4]. Second-hand smoke contains hundreds of chemicals responsible for diseases such as respiratory disorders, cancer, and cardiovascular disease. Combustible chemicals found in tobacco smoke are responsible for disorders such as cancer, cardiovascular, and pulmonary diseases, through mechanisms that involve DNA damage, inflammation, and oxidative stress [5]. Globally, second-hand smoking affects women and children more than men [6, 7]. Tobacco-related disability-adjusted life years (DALYs) account for 4% of the global burden of disease, with the burden significantly higher for developed nations [8].

Tobacco contains about 4,000 chemicals, of which nicotine is the one responsible for addictive behaviour [9]. During smoking, the nicotine components of tobacco are absorbed through respiratory mucous membranes and enter the bloodstream, and thereby the brain. Upon entering the brain, nicotine stimulates the release of epinephrine and dopamine which in turn increases blood pressure, heart rate, respiration rate and produces pleasurable feelings [3, 9].

In the long-term, smoking cessation decreases the risk of cancer, stroke and cardiovascular disease and also improves life expectancy [3, 10]. By improving natural lung function, smoking cessation can also decrease the risk of respiratory infections such as pneumonia, influenza and chronic obstructive pulmonary disease [11]. Kahler et al. and Eddy et al. have shown that smoking cessation is associated with significant reductions in risk of COPD, myocardial infarction, stroke and coronary heart disease [12, 13].

The range of available smoking cessation interventions can broadly be categorized as motivational, behavioural/psychological, or pharmacological. The World Health Organization recommends that countries prioritize different smoking cessation strategies depending on their available resources, national health system, and political will to implement the cessation strategies [14]. The World Health Organization recommends treatment of tobacco dependence as one strategy within its comprehensive tobacco-control policy, along with measures such as taxation and price policies, advertising restrictions, dissemination of information and establishment of smoke-free public places [14]. Treatment of tobacco smoking, like any other forms of substance dependence, necessitates pharmacological interventions to minimize cravings and the treatment of withdrawal symptoms associated with dependence [9]. Nicotine replacement therapies (NRT) in different formulations, such as inhalation, patches, gums, nasal sprays and lozenges, can be used for the treatment of withdrawal symptoms after smoking cessation. Since the nicotine concentration in NRT is low compared to tobacco, these therapies have a low addiction rate [3].

Amfebutamone (bupropion) represents the first non-nicotine drug used for the treatment of nicotine dependence. Amfebutamone is a nicotine receptor antagonist and inhibits the reuptake of epinephrine, dopamine and serotonin, thus reducing withdrawal symptoms [15–17]. Varenicline is a nicotine

receptor partial agonist that blocks nicotine receptors by binding into $\alpha_4\beta_2$ nicotinic acetylcholine receptors and moderately releases dopamine, thus reducing the craving and withdrawal symptoms associated with an absence of nicotine [18].

Although most of the previous trials and systematic reviews supported the effectiveness of behavioural interventions [19, 20] for smoking cessation, the findings are less consistent for pharmacological interventions. To date, many trials and systematic reviews have been conducted to assess the effectiveness of smoking cessation interventions. Thus, a sound next step in providing evidence to healthcare decision-makers is a review of existing systematic reviews [21]. Therefore, in this umbrella review, we have assessed the effectiveness of different pharmacotherapies and the methodological quality of the included reviews.

Objectives

The current umbrella review synthesised findings of previous reviews conducted to evaluate the effects of pharmacotherapies for smoking cessation and assessed the consistency of conclusions among previous systematic reviews. This umbrella review summarized the effects of pharmacological interventions reported by each review of smoking cessation, specifically addressing the following objectives:

- To summarize existing systematic reviews that assessed the effects of pharmacological interventions for smoking cessation; and
- To assess the methodological quality of previously conducted systematic reviews

Methods

Protocol registration and reporting of findings

The protocol of this review followed the guidelines of Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 922]. The protocol was registered in PROSPERO (registration number CRD42017080906), available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017080906. The findings of the systematic review were reported in accordance with the recommendation of Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) [23]. The PRISMA checklist is available as Additional File 1. The Joanna Briggs Institute Reviewers' Manual was also used to guide and organize the review processes [24].

Inclusion and exclusion criteria

Since the primary aim of the current umbrella review was to identify the effect of pharmacological interventions on smoking cessation, only reviews that include randomized control trials were reviewed. Since smoking cessation interventions are mostly targeted at adults aged 15 and over, in this umbrella review, we have included studies of young people and adults aged 15 and over who were smokers [25]. All systematic reviews that used randomized control trial studies designed to assess the effect of pharmacotherapy in any setting were included in this review. The umbrella review included only reviews for which the full text is available. The outcome variable measured in this study was smoking cessation. The control or comparison groups used were either placebo, behavioural interventions, or pharmacotherapy. The current review included only reviews that reported pooled effects of the included studies. The current review only included studies published in English.

If the review was an update of a previous review, the ost recent review data were included. Reviews that assessed combined pharmacotherapy and behavioural interventions were excluded unless the review reported the effect of pharmacotherapy separately, in which case the review was included. The summary of inclusion criteria based on population, intervention, comparator and outcome and study design (PICOS) is presented in Table 1.

Information source and search strategy

To trace related reviews, databases such as the Cochrane library, PubMed, MEDLINE, EMBASE, CINAHL, PsycINFO, Web of Science, Scopus and Google Scholar were used without limits on the publication period. Each database was searched up to September 2, 2019. Additional reviews were sought using the reference lists of the retrieved articles. Additional articles were traced from daily email alerts from the MEDLINE database throughout the review process. The search strategy was developed in consultation with a senior librarian. Different keywords/search terms were used to access reviews from the database, including "smoking cessation", "smoking abstinence", "Pharmacotherapy", "Nicotine replacement therapy (NRT)", "bupropion", "Varenicline" "combination therapy", "non-nicotine drug", "nicotine receptor partial agonist", "meta-analysis", and "Systematic review". The search strategy for Medline is found in Additional File 2.

Data collection processes

Studies not fulfilling the inclusion criteria were first excluded by reading the title, and then the abstract of the articles. Full articles were then accessed and those articles not fitting the objectives of the review were excluded. The excluded studies were recorded along with the reason for exclusion at each stage. The Cochrane data abstraction format was used to extract information from the studies. Two authors (AM, AB) conducted the following processes independently: screened the titles and abstracts of all publications obtained by the search strategy; and assessed the full text of selected articles for inclusion. Discrepancies were resolved by discussion between the authors. The data extraction form was designed to extract data relating to the objectives of the study, study design, study inclusion and exclusion criteria, number of articles and participants included, participant characteristics, intervention, control, outcome and pooled effect, among others. The data extraction form is shown in Additional File 3.

Assessment of methodological quality

Each review was assessed for quality using the Assessment of Multiple Systematic Reviews (AMSTAR) tool comprising 11 items [26]. AMSTAR has been shown to have good face and content validity and reliability to assess the quality of systematic reviews [26, 27]. However, quantitative scoring of the 11 items has been found to be problematic; therefore, we used the Revised-AMSTAR developed by Kung and colleagues to quantitatively measure the specific items [28]. According to R-AMSTAR, the maximum score for each item is 4 (high quality) and the minimum score is 1 (poor quality). The total score across the items ranges from 11 to 44. Therefore, if the total score is 11, this implies that none of the AMSTAR quality items was satisfied, while 44 denotes the satisfaction of all the criteria. Each of the 11 criteria contains sub-criteria against which the quality of each review was assessed. The numeric values of R-AMSTAR were graded as follows for comparison purposes: a cumulative score less than 20 indicated poor methodological quality, scores of 21–28 indicated fair methodological quality, scores of 29–36 indicated good methodological quality, and scores greater than 37 indicated studies with excellent methodological quality [29, 30]. The R-AMSTAR criteria are found in Additional File 4. Two independent reviewers (AM, AB) conducted the quality assessment of the included systematic reviews and any disagreement between the two reviewers was resolved by discussion. Cohen's Kappa statistic was used to assess inter-rater agreement. A kappa value below 60% indicates inadequate agreement among the raters [31].

Data synthesis

In this review, a meta-analysis was not conducted because data from individual studies are likely to be represented more than once across the systematic reviews and this could likely lead to over- or underestimation of the true effect size [21]. The required information was collected using a pretested checklist based on the objectives of the review [32]. A narrative synthesis method was employed to show the effects of different pharmacotherapies on smoking cessation. The narrative presentation included the overall effect size reported by systematic review authors along with statistical heterogeneity and methodological quality. Evidence was summarized in a table to present the types of intervention, comparators, outcome measures, number of participants, number of included primary studies, and pooled results from each review, heterogeneity, and the review author's conclusions.

Results

The search identified 211 studies from a range of databases and other sources using comprehensive and sensitive search terms. After removing duplicates, 151 studies were assessed by reading their titles and abstracts, of which 132 studies were removed as they were not relevant to the review question. Finally, 19 full text articles were assessed, of which 10 studies were excluded. Reasons for study exclusion included combined intervention with behavioural therapy [33-35], measured cost-effectiveness of pharmacological smoking cessation therapies (36), pooled effect not provided [37-39], review not published in English [40], inclusion of non-randomized controlled trials in the review [41], and inclusion of study participants under the age of 15 [42]. The PRISMA flow diagram is depicted in Figure 1.

Characteristics of included reviews

Table 2 presents the detailed characteristics of the included systematic reviews. Of the nine included reviews, three assessed the effectiveness of nicotine replacement therapy [43-45], two assessed the effect of multiple pharmacotherapy [46, 47], one compared combination therapy (NRT+ varenicline vs varenicline alone) [48], one compared opioid antagonists to placebo or an alternative therapy [49], one evaluated the effectiveness of silver acetate products (gum, lozenge, spray) [50], and one compared the combined effect of nicotine replacement therapy of different formulations [51]. In total, 142 trials were included in 9 systematic reviews (mean per review: 14.2; range: 2-86). The included reviews consisted of a total of 63,568 study participants (mean per review: 7063.1). However, data from individual studies are likely to be represented more than once across the systematic reviews. Of the included reviews, two were Cochrane reviews. Six studies included in their reviews only studies that verified smoking cessation/abstinence using biochemical methods, while three included studies which used both self-reported and biochemical techniques (Table 3).

Methodological quality of included reviews

The reviews were assessed for methodological quality using the R-AMSTAR quality appraisal tool for systematic reviews. Table 4 presents the score of each item and the overall score of specific systematic reviews. The mean and standard deviation of each R-AMSTAR item have also been shown. A high mean value showed that most reviews attained a high quality level (maximum mean value possible is 4; minimum mean value possible is 1). The R-AMSTAR score for the nine included reviews ranged from 22 to 41 with a mean of 28.8. Based on R-AMSTAR scoring, one review scored 'high' for methodological quality [46], three scored 'good' for methodological quality [44, 48, 50], and five scored 'fair' for methodological quality [43, 45, 47, 49, 51]. All of the reviews conducted before the development of R-AMSTAR scored 'fair' for methodological quality. On the other hand, except for one review, all the reviews published after the inception of R-AMSTAR scored at least 'good' for methodological quality. Six reviews scored the maximum of 4 in the 6^{th} item ("Were the characteristics of the included studies provided?"), and the 9^{th} item ("Were the methods used to combine the findings of studies appropriate?") and none of the reviews scored 4 in the 7^{th} item ("Was the scientific quality of the included studies assessed and documented?"). The inter-rater agreement of individual items ranged from 0.57 to 1.00 and the overall Kappa score was 0.77 (95% CI: 0.65 - 0.89). Except for items 4 and 11, all items scored a kappa of >0.6 (Table 5).

The effectiveness of pharmacological interventions

Nicotine replacement therapy

In one review, which included 11 randomized controlled trials involving 1,808 study participants, researchers found that pharmacotherapy significantly increased the smoking cessation rate compared to the placebo group (RR = 1.88, 95% CI: 1.35, 2.57) at 6 weeks to 18-months follow-up. Likewise the pooled effect from a sub-analysis of three trials using only NRT indicated a significant positive effect on smoking cessation rate (RR = 7.74, 95% CI: 3.00, 19.94; 3 studies, 635 participants) [46]. In the quality appraisal, this paper was scored as having 'excellent' methodological quality. Another study assessing the pooled effect from 12 randomized controlled trials ('fair' methodological quality review) supported the favourable effect of NRT on sustaining smoking cessation beyond 12 months compared to a placebo (OR = 1.99, 95% CI: 1.50, 2.64) [43].

In a review of seven studies ('fair' methodological quality review), Moore et al. found that NRT increased smoking cessation for at least six months compared with the placebo (RR = 2.06, 95% CI: 1.34, 3.15; 5 studies) [45]. The pooled effect from a review that included 70 trials (n=28,343) found that the odds of smoking cessation at one year were higher among participants using NRT compared to the control group (OR = 1.71, 95%, CI: 1.55, 1.88) [47]. In this review, the finding was consistent across all NRT formulations (gum, patch). In addition, the pooled effect of 59 trials (n=25,294) demonstrated that NRT provided support for the efficacy of smoking cessation in the short-term follow-up (3 months) compared to the control group (OR = 1.98, 95% CI: 1.77, 2.21) [47]. In the quality appraisal, this review scored a 'fair' methodological quality. Conversely, a review by Lindson et al ('good' methodological quality review) that included eight studies and 2,813 participants found no significant effects of NRT over placebo for the treatment of smoking cessation in the short-term follow-up (4 to 12 weeks) (RR = 1.05, 95% CI: 0.92, 1.19) and long-term follow-up (6 to 12 months) (RR = 1.16, 95% CI: 0.97, 1.38) [44].

Non-nicotine pharmacotherapy

The pooled effect of a study including eight randomized control trials with 1,213 study participants identified that opioid antagonist therapy had no effect on smoking cessation rate based on the 6-month reported abstinence rate (RR = 0.97; 95% CI: 0.76, 1.24). Five studies that assessed the effect of naltrexone (long-acting form of opioid antagonist) compared to placebo also showed no significant effect on smoking abstinence rate (RR = 1.00; 95% CI: 0.66, 1.51) [49]. In the quality appraisal, this review was scored as having 'fair' methodological quality.

The pooled effect of 12 trials including 5,228 participants showed bupropion was more effective for smoking cessation compared to the control group at the one-year follow-up (OR = 1.56, 95% CI: 1.10, 2.21). Moreover, bupropion was more effective than placebo at the 3-month follow-up (OR = 2.13, 95% CI: 1.72, 2.64; 11 trials) [47]. The pooled effect of 4 studies (n=2,528) found that varenicline was effective for smoking cessation compared to placebo both at long-term follow-up (1 year) (OR = 2.96, 95% CI: 2.12, 4.12) and short-term follow-up evaluation (3 months) (OR = 3.75, 95% CI: 2.65, 5.30). Similarly, varenicline was more effective than bupropion at one year follow-up (OR = 1.58, 95% CI: 1.22, 2.05; 3 trials) and three-month follow-up (OR = 1.61, 95% CI: 1.16, 2.21; 3 trials) [47]. Silver nitrate was not effective for smoking cessation compared to placebo at a minimum of 6-month follow-up (RR = 1.04, 95% CI: 0.69, 1.57; 2 trials) [50]. This review was ranked as having a 'good' methodological quality.

Combination therapy

Chang et al ('good' methodological quality review) found that study participants on a combined regimen (NRT and non-NRT) were more likely to abstain from smoking compared with those in a non-NRT (varenicline) only treatment group, both during the short-term (measured at 4-12 months before treatment completion; OR = 1.50, 95% CI: 1.14, 1.97; 3 trials) and long-term (measured at the end of 2-24 months after treatment completion; OR = 1.62, 95% CI: 1.18, 2.23; 2 trials) [48]. Combining naltrexone and NRT did not favour smoking cessation compared to the placebo group based on the 6-month reported abstinence rate (RR = 0.95, 95% CI: 0.70, 1.30; 4 studies) [49].

In a 'fair' methodological quality review that included 2,204 study participants from 5 trials, a combination therapy of nicotine replacement patches with other nicotine formulation drugs (nicotine gum or nicotine inhaler or nicotine nasal spray) was found to be more effective than monotherapy at 3 months (RR = 1.42, 95% CI: 1.21, 1.67; 4 trials), at 6 months (RR = 1.54, 95% CI: 1.19, 2.00; 4 trials) and at the 12-month follow-up (RR = 1.58, 95% CI: 1.25, 1.99; 4 trials) [51].

Discussion

In this umbrella review, we aimed to assess the effect of different pharmacotherapies on smoking cessation. Most of the included reviews found supportive evidence for NRT being an efficacious treatment for withdrawal symptoms associated with nicotine dependence. Nicotine replacement therapy in different formulations are used as a first line drug for the treatment of nicotine addiction in many settings [52]. Non-nicotine pharmacotherapy such as bupropion and varenicline were also found to be effective for smoking cessation. Reviews also revealed that the combination of NRT and varenicline was more effective for smoking cessation compared with varenicline alone. Moreover, a combination of different formulations of NRT (gum, nasal spray) with nicotine patches was more effective than nicotine patch monotherapy. Evidence suggests that the use of other formulations of NRT (gum, inhaler, spray) in combination with nicotine patches helps to supplement blood nicotine concentrations at times of craving or risk of smoking relapse [52]. NRT, bupropion and varenicline are drugs approved by the US Food and Drug Administration and other countries for the treatment of smoking cessation [53].

The severity of nicotine dependence is one factor that can affect the effectiveness of pharmacotherapies for smoking cessation. Some researchers found that the rate of smoking cessation was lower among study participants who smoked a greater number of cigarettes per day compared to those

who smoked fewer cigarettes per day [9, 54]. The level of treatment compliance is also an important factor in attaining and sustaining smoking abstinence [12, 55].

In a systematic review of the reviews, researchers found that compared to NRT alone, a combination of non-pharmacological interventions such as brief counselling and pharmacotherapy has been more effective for smoking cessation [56]. Moreover, behavioural interventions have been recommended to prevent relapse and to sustain smoking cessation achieved by pharmacotherapy [57]. Therefore, combining counselling and pharmacotherapy could be more efficacious for smoking cessation.

Overall, the quality of the systematic reviews included in the current umbrella review was rated as 'fair' to 'excellent', and no reviews were scored as having 'poor' quality. The maximum R-AMSTAR mean quality score across the 10 systematic reviews was high for item six ("Were the characteristics of the included studies provided?") and item nine ("Were the methods used to combine the findings of studies appropriate?"). In the previous systematic review of reviews, these items were also well addressed by review authors [30, 58, 59]. Duplicate selection of articles to be included in a systematic review can decrease the chance of missing articles. In the current review, item 2 ("Duplicate study selection and data extraction") was poorly addressed by most of the included reviews.

Formulating a review protocol is an important step prior to conducting a systematic review. This is in order to determine whether the review was conducted as per the plan and if not, to justify reasons for amending the plan [60]. In almost all of the included reviews, no statement about the protocol registration and/or publication was stated under the first criteria ("Was an "a priori" design provided?"). This finding was consistent with a previous review undertaking a quality assessment of systematic reviews in paediatric surgery [61]. Clinicians and decision-makers need to assure themselves that the basic approaches and methods used to collect and combine the findings of individual studies are relevant and sound before using the evidence for patient care and policy development. The observed quality improvement in the reviews published after the development of R-AMSTAR demonstrated the importance of encouraging review authors to adhere to guidelines that advance excellence in conducting systematic reviews. Improving the methodological quality of systematic reviews is fundamental to to precisely inform clinical decision-making [62].

There are several limitations of this review that should be acknowledged. First, the timing of the outcome measure was not consistent across the included reviews. Some of the studies measured short-term effects or long-term effects, while others measured both. Since the data were not retrieved from the primary studies, we were restricted by the evidence reported by the review authors with respect to aspects including the explanation of the intervention, method, outcome, and conclusions. Despite duplicate study selection, subjectivity in data extraction and quality appraisal are not totally avoidable. Another limitation of this review was the restriction of the review to articles published in English. Despite these limitations, this umbrella review considered only systematic reviews that included primary studies with a randomized controlled trial design. Article selection, data abstraction, and quality appraisal were also conducted in duplicate, minimizing selection bias.

Conclusions

In this review, NRT, bupropion and varenicline were found to be effective for smoking cessation. Likewise, the combination of a nicotine patch with other nicotine formulations and combination of nicotine with non-nicotine pharmacotherapy were found to be effective for smoking cessation compared to nicotine monotherapy. Silver nitrate was not found to be effective for smoking cessation. The quality of reviews published after the development of R-AMSTAR were of higher quality than reviews published before the inception of the tool. We recommend future studies and subsequent reviews to identify other factors that could affect the effectiveness of pharmacotherapy for smoking cessation. We also recommend review authors adopt and follow the AMSTAR tool to improve the methodological and reporting quality of systematic reviews. The findings of the current review will improve clinical decision-making and can be used as a baseline for future studies.

Declarations

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Availability of data

Not applicable

Authors' contributions

AS developed the review protocol and CC, DL and EH reviewed the protocol. AS and AB identified, screened and extracted data from articles. AS and AB conducted quality assessment of the articles. AS wrote the findings. CC, DL and EH revised and reviewed the articles. All authors approved the final submission of the paper.

Ethics approval and consent for participants

Not applicable

Consent for publication: Not applicable

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Abbreviations

NRT: Nicotine replacement therapy; COPD: Chronic obstructive pulmonary disease; PRISMA: Preferred reporting items for systematic review and meta-analysis; PROSPERO: International prospective register of systematic reviews; AMSTAR: Assessment of multiple systematic reviews; R-AMSTAR: Revised Assessment of multiple systematic reviews; RR: Relative risk; OR: Odds ratio.

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Tables

Table 1: Population, intervention, comparator, outcome and study design (PICOS) elements

PICOS elements	Criteria
Population	Young people and adults aged 15 years and over who were smokers.
Intervention	Reviews assessed only the effect of pharmacotherapy on smoking cessation were included. Reviews, which assessed combined pharmacotherapy and behavioural interventions, were excluded.
Comparator	The control may be either standard care or placebo, behavioural intervention or no intervention.
Outcome	Systematic reviews that were designed to assess abstinence from smoking were considered in this umbrella review.
Study design	Reviews that include only randomized control trials.

e 2: Characteristics of included reviews

ew ors /ear	Number of trials included/number of participants	Review questions/ objectives	Outcome measures/intervention	Inclusion criteria	Summary findings	Authors comments
lonio ,	35 RCT, (11 assessed pharmacotherapy)/ 5796 (1808 pharmacotherapy)	To assess whether interventions for smoking cessation are related with smoking abstinence for people in concurrent treatment for or in recovery from alcohol dependence	smoking abstinence/ pharmacotherapy of NRT and non-NRT	· No exclusions based on language of publication or publication status · The study included adults aged 15 years and over who were treated for alcohol dependence	· Pharmacotherapy increased smoking abstinence (RR = 1.88, 95% CI: 1.35, 2.57; 11 studies, 1,808 participants, low quality evidence) · When the analysis was restricted to those studies evaluating only NRT, the treatment effect remained significant (RR = 7.74, 95% CI: 3.00, 19.94; 3 studies, 635 participants)	Overall, the results suggest that smoking cessation interventions incorporating pharmacotherapy should be incorporated into clinical practice
ıg et 015	3 trials/ 904 participants	To examine the effectiveness of varenicline combined with NRT for smoking cessation	Smoking abstinence rates/ Combination therapy (NRT+ varenicline) vs. varenicline + placebo patch	Only published RCTs with an adult population aged 18 and more were included	· The results demonstrated a significant increase in the smoking abstinence rate during early measurement in the combined wing compared with varenicline only treatment (OR = 1.50, 95% CI: 1.14, 1.97; 3 trials) and for late outcome measure (OR = 1.62, 95% CI:1.18, 2.23; 2 trials)	Larger RCTs are needed to make more robust conclusions
d et 014	8 trials/ 1,213 participants	To assess the effectiveness of opioid antagonists in helping long-term smoking cessation	smoking abstinence /comparing opioid antagonists to placebo or an alternative therapy for smoking cessation	Adult smokers that reported data on abstinence for a minimum of 6 months	· Eight trials gave no evidence of a treatment effect (RR = 0.97; 95% CI: 0.76, 1.24) · For the 4 studies that examined naltrexone versus placebo as an adjunct to NRT (n=768), the pooled estimate was RR = 0.95; 95% CI: 0.70, 1.30.	The findings indicate no beneficial effect of naltrexone alone or as an adjunct to NRT on smoking abstinence
et 006	12/ 4,792 participants (2,408 NRT, 2,384 control)	To evaluate if the outcome of a single treatment episode with NRT enhances smoking cessation over many years	Smoking cessation at the time of follow-up /Nicotine replacement therapy	Studies with a final follow-up of more than one year after the start of treatment and only study arms of standard recommended	· Pooled effect provided evidence for the efficacy of NRT in sustaining smoking cessation beyond 12 months (OR = 1.99, 95%CI: 1.50, 2.64)—fixed	NRT has a permanent effect on smoking cessation

				doses of NRT were included	effect gives the same result	
aster ,	2 trials / 976 participants	To determine the efficacy of silver acetate products (gum, lozenge, spray) in helping smoking cessation	Sustained abstinence from smoking at 6 to 12 months/ silver acetate	RCTs of silver acetate for smoking cessation with reports of smoking status at least 6 months after the beginning of treatment	· The pooled estimate for the risk ratio for quitting was RR = 1.04, 95% CI: 0.69; 2 trials	Silver acetate has no role in promoting smoking cessation
son ,	8 trials/ 2,813 (1,403 intervention vs. 1410 control)	To update the nicotine preloading efficacy	Short-term abstinence and long-term abstinence at least six months after quit day / nicotine replacement therapy (NRT) whilst smoking, prior to quitting (preloading)	Only RCTs, participants were cigarette smokers attempting to quit, and if abstinence was reported at a 6-month follow-up or later. Mean age of study participants was 42 years	· There was a very weak positive effect of preloading on short-term abstinence (RR = 1.05, 95% CI: 0.92, 1.19) · The pooled effect on long-term abstinence was not significant (RR = 1.16, 95% CI: 0.97, 1.38)	The review found weak non-significant effect of nicotine pre-loading on smoking abstinence
re et 009	7 trials/ 2,767participants	To identify the efficacy and safety of nicotine replacement therapy for smoking cessation	Six months' sustained abstinence starting any time before the end of treatment/ Gum or inhaler nicotine replacement therapy	· Only RCTs were eligible The population comprised smokers who were unable or unwilling to stop abruptly	· The proportion of smokers achieving sustained abstinence at six months with nicotine replacement therapy was double that of the placebo group (RR = 2.06, 95% CI: 1.34, 3.15; 5 studies) · The proportion of smokers achieving sustained abstinence at the end of follow-up was RR = 1.72, 95% CI: 1.31, 2.26; 7 studies	Nicotine replacement therapy is an effective intervention in achieving sustained smoking abstinence
et al.,	NRT=70 trials/28,343 participants, Bupropion=12 trials/ 5,228 participants, Varenicline=4 trials/ 2,528 participants	To evaluate the effectiveness of pharmacotherapy for smoking cessation	Smoking cessation at 1 year short-term smoking cessation (3 months) / Any RCT of NRT of any delivery method, bupropion or varenicline	Chemical confirmation of smoking cessation randomised controlled trials	· Smoking cessation favoured NRT over controls at one year (OR = 1.71, 95% CI: 1.55, 1.88) · Smoking cessation favoured NRT over controls at 3 months (59 trials, n = 25,294 participants, OR = 1.98, 95% CI: 1.77–2.21)	NRT, bupropion and varenicline all provide therapeutic effects in assisting with smoking cessation

					· Bupropion was effective for smoking cessation compared to control at one year (12 trials/ 5,228 participants; OR = 1.56, 95% CI: 1.10, 2.2, P = 0.01). · NRT was superior to bupropion for smoking cessation at one year (2 trials, n=548, OR = 1.14, 95% CI: 0.20, 6.42) · Varenicline was effective for smoking cessation compared to placebo both at long-term (1 year) (OR = 2.96, 95% CI: 2.12, 4.12; 4 trials, n=2,528) and short-term evaluation (OR = 3.75, 95% CI: 2.65, 5.30; 4 trial, n=2,528) · Varenicline was more effective than bupropion at one year (OR = 1.58, 95% CI: 1.22, 2.05) and three months (3 trials, OR = 1.61, 95% CI: 1.16, 2.21)	
ı. et 008	5 trials/2,204 participants	To determine whether combination therapy for smoking cessation with first line agents is more effective than monotherapy	Abstinence at 3, 6 and 12 month of follow up/ Clinical trials evaluating combination therapy using first line agents (all trials include nicotine replacement patches along with one other agent)	· Double blind randomized placebo controlled trial · Study duration of one year or more · Sample size ≥200 · Using first line smoking cessation therapies	· Comparing the combination and single agent therapy at 3 months, the rate of abstinence was RR = 1.42, 95% CI: 1.21, 1.67 (4 trials) · Comparing the combination and single agent therapy at 6 months, the rate of abstinence was RR = 1.54, 95% CI: 1.19, 2.00 (4 trials) · Comparing the combination and single agent therapy at 12 months, the rate of abstinence was RR = 1.58, 95%	The author recommended future research to consider optimal therapy combination, duration of therapy and preferred agent for special population

					CI 1.25, 1.99 (4 trials)	

Table 3: Methods of smoking cessation validation and quality assessment tool used and reported heterogeneity of the reviews

Author and year	Validation of smoking cessation of included review	Quality assessment tool and source	Reported heterogeneity of the reviews
Apollonio et al., 2016	Self-reported tobacco use or biochemical validation	Cochrane risk of assessment tool	I^2 = 64% for overall pharmacotherapy
Chang et al., 2015	Biochemical verification	Jadad score	I^2 = 0% for early outcome measure and 54% for late outcome measures
David et al., 2014	Self-reported or biochemical verification	Cochrane risk of assessment tool	I^2 = 0%
Etter et al., 2006	Biochemically verified abstinence	Not stated	Q statistics was 18.7 (p=0.08)—No evidence of heterogeneity
Lancaster et al., 2012	Biochemically verified abstinence	Cochrane risk of assessment tool	I^2 = 0.0%
Lindson et al., 2011	Biochemically verified abstinence and/or self-report	Cochrane risk of assessment tool	For short-term abstinence I^2 of 69% and for long-term abstinence I^2 of 39%
Moore al., 2009	Biochemical (exhaled carbon monoxide)	Standard guidelines of NHS Centre for Reviews and Dissemination	I^2= 52.4%
Wu. et al., 2006	Biochemically verified	Cochrane risk of assessment tool	I^2 = 20.5 to 71.5%
Shah et al., 2008	Biochemically verified	Not stated	I^2 = 0% to 37%

Table 4: Systematic review quality (N=9).

R-AMSTAR items [a]	Apollonio et al., 2016	Chang et al., 2015	David et al., 2014	Etter. et al, 2006	Lancaster et al., 2012	Lindson et al., 2011	Moore et al., 2009	Wu et al., 2006	Shah et al., 2008	Mean (SD)	Median
1	4	3	3	2	4	3	3	3	3	3.1 (0.60)	3
2	4	1	1	2	2	2	3	2	1	1.9 (1.05)	2
3	4	4	3	1	4	4	3	4	2	3.3 (1.01)	4
4	4	2	1	1	1	1	1	3	2	1.8 (1.09)	1
5	4	1	3	2	4	1	4	1	2	2.4 (1.3)	2
6	4	4	4	2	4	4	4	3	2	3.4 (0.88)	4
7	3	3	2	1	2	2	2	1	1	1.9 (0.78)	2
8	4	4	2	1	2	3	2	1	2	2.3 (1.11)	2
9	4	4	4	4	3	4	3	3	4	3.6 (0.50)	4
10	3	4	1	4	1	3	1	1	1	2.1 (1.36)	1
11	3	3	2	2	4	3	2	3	3	2.8 (0.66)	3
Total Score	41	33	26	22	31	30	28	25	23	28.8 (5.86)	28
Methodological quality	excellent	good	fair	fair	good	good	fair	fair	fair	-	-

[a] = 1: Was an ''a priori'' design provided? 2: Was there duplicate study selection and data extraction? 3: Was a comprehensive literature search performed? 4: Was the status of publication (i.e., grey literature) used as an inclusion criterion? 5: Was a list of studies (included and excluded) provided? 6: Were the characteristics of the included studies provided? 7: Was the scientific quality of the included studies assessed and documented? 8: Was the scientific quality of the included studies used appropriately in formulating conclusions? 9: Were the methods used to combine the findings of studies appropriate? 10: Was the likelihood of publication bias assessed? 11: Was the conflict of interest included?

Table 5: Assessment of inter-rater agreement for AMSTAR tool

Items	Kappa (k)	95% CI
Was an ‘‘a priori’’ design provided	0.61	0.30 to 0.91
Was there duplicate study selection and data extraction?	0.78	0.40 to1.00
Was a comprehensive literature search performed?	0.68	0.32 to 1.00
Was the status of publication (i.e., grey literature) used as an inclusion criterion?	0.59	0.31 to 0.87
Was a list of studies (included and excluded) provided?	0.70	0.47 to 0.93
Were the characteristics of the included studies provided?	0.62	0.30 to 0.94
Was the scientific quality of the included studies assessed and documented?	0.88	0.67 to 1.00
Was the scientific quality of the included studies used appropriately in formulating conclusions?	0.73	0.497 to 0.97
Were the methods used to combine the findings of studies appropriate?	0.78	0.39 to 1.00
Was the likelihood of publication bias assessed?	1.00	1.00 to 1.00
Was the conflict of interest included?	0.57	0.27 to 0.87
Overall score	**0.77**	**0.65 to 0.89**

Figures

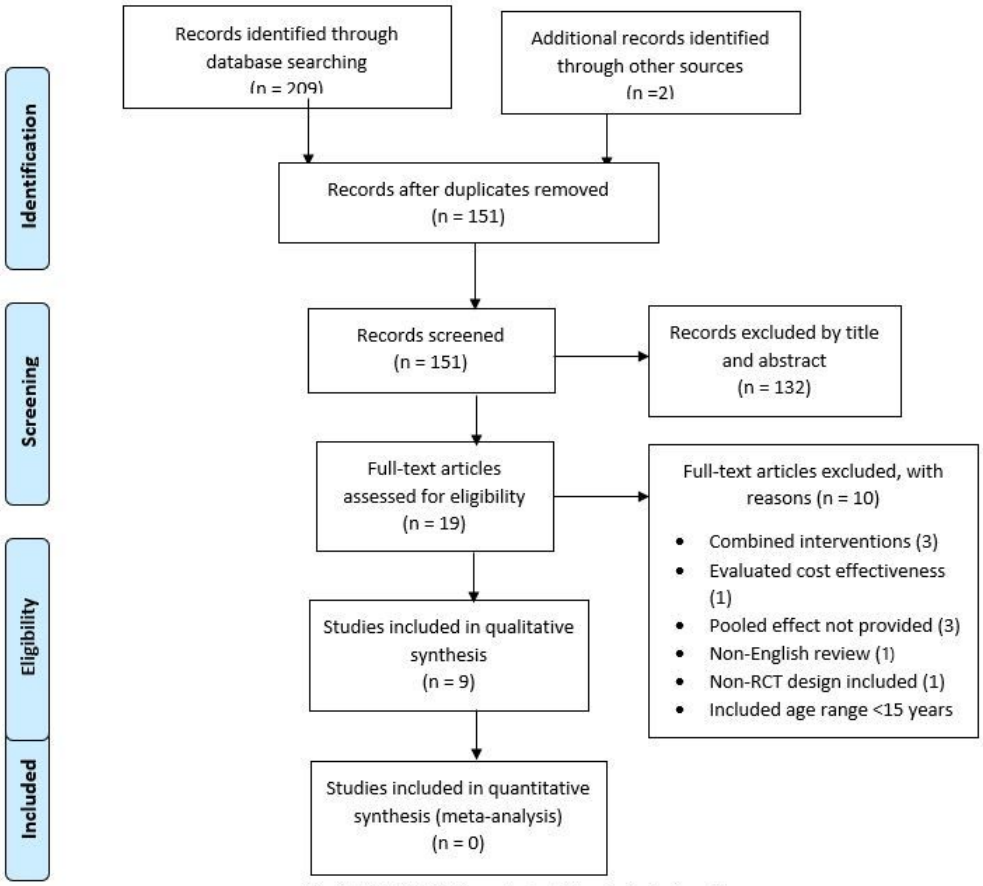

Fig 1: PRISMA flowchart of the included reviews

Figure 1

PRISMA flowchart of the included reviews

Supplementary Files

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