

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. The methodological quality of the included reviews was assessed using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool, which contains 16 domains. 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. The findings of the studies were narrated qualitatively to describe the evidence regarding the effectiveness of pharmacotherapies for smoking cessation.

Results: Ten reviews were included in this umbrella review . Most of the reviews included in this review reported that Nicotine Replacement Therapy (NRT), bupropion and varenicline and cytisine 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. Based on the AMSTAR 2 rating, one review scored high quality, two scored moderate quality, four scored low quality, and three scored critically low quality.

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.

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 was associated with significant reductions in risk of myocardial infarction, stroke and coronary heart disease [12, 13]. *In the long term, smoking cessation is an effective intervention to reverse the course of atherosclerosis.*

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, 22]. 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) [23]. 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) [24]. 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 [25].

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 [26]. 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 standard care or placebo, no intervention, or alternative 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 most 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 (DB). 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 JBI data abstraction format was used to extract information from the

studies. Two authors (AM, AB) screen the titles and abstracts of all publications obtained by the search strategy, and assessed the full text of selected articles for inclusion and extracted and checked data independently. 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

Methodological quality of the included reviews was assessed using the Assessment of Multiple Systematic Reviews 2 (an update of AMSTAR) tool, which contains 16 domains [27]. The tool includes 10 items from the original AMSTAR tool. Two items were created by splitting a single item from the original AMSTAR tool [28]. In total, four domains were added in AMSTAR 2 which were not found in the original tool. The response option for most domains consists of “yes” and “no” while some domains contain the third option “partial yes”. AMSTAR has been shown to have good inter-rater reliability to assess the quality of systematic reviews. From the 16 AMSTAR tool items, 7 were critical domains upon which the quality rating of individual systematic reviews depends. Based on the overall score, the quality of each systematic review was rated as high, moderate, low and critically low. Table 2 presents the criteria to rate the quality of systematic reviews. The AMSTAR 2 checklist is found in Additional File 4. Scores for each item were reported separately for each systematic review. The quality assessment of the included systematic review was conducted by two independent reviewers (AM, AB) and any disagreement between the two reviewers was resolved with discussion or the aid of another reviewer (CC). Studies were not excluded based on their quality, but the assessment serves to judge the strength of evidence generated by the included studies.

The following are items in AMSTAR 2 (The full version is found in additional file 4)

1. **Did the research questions and inclusion criteria for the review include the components of PICO?**
2. **Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?**
3. **Did the review authors explain their selection of the study designs for inclusion in the review?**
4. **Did the review authors use a comprehensive literature search strategy?**
5. **Did the review authors perform study selection in duplicate?**
6. **Did the review authors perform data extraction in duplicate?**
7. **Did the review authors provide a list of excluded studies and justify the exclusions?**
8. **Did the review authors describe the included studies in adequate detail?**
9. **Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies?**
10. **Did the review authors report on the sources of funding for the studies included in the review?**
11. **If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**
12. **If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**
13. **Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**
14. **Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**
15. **If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**
16. **Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**

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 [29]. 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.

To calculate the degree of overlap, we calculated the Corrected Covered Area (CCA) by dividing the frequency of repeated occurrence of index publication in other reviews by the product of index publications and reviews, less the number of index publications. The CCA was rated as follows: CCA less than 5 was rated as slight overlap, 6-10 was considered a moderate overlap, 11-15 a high degree of overlap and greater than 15 as a very high degree of overlap [30].

$$CA = \frac{N-r}{rc-r}, \text{ where}$$

N is the number of included publications (including double counting);

r is the number of rows (number of index publications)

c is the number of column (number of reviews)

Results

The search identified 218 studies from a range of databases and other sources using comprehensive and sensitive search terms. After removing duplicates, 156 studies were assessed by reading their titles and abstracts, of which 136 studies were removed as they were not relevant to the review question. Finally, 20 full text articles were assessed, of which 10 studies were excluded. Reasons for study exclusion included combined intervention with behavioural therapy [31-33], measured cost-effectiveness of pharmacological smoking cessation therapies [34], pooled effect not provided [35-37], review not published in English [38], inclusion of non-randomized controlled trials in the review [39], and inclusion of study participants under the age of 15 [40]. The PRISMA flow diagram is depicted in Figure 1.

Characteristics of included reviews

Table 3 presents the detailed characteristics of the included systematic reviews. Of the nine included reviews, three assessed the effectiveness of nicotine replacement therapy [41-43], two assessed the effect of multiple pharmacotherapy [44, 45], one compared combination therapy (NRT+ varenicline vs varenicline alone) [46], one compared opioid antagonists to placebo or an alternative therapy [47], one evaluated the effectiveness of silver acetate products (gum, lozenge, spray) [48], one compared the combined effect of nicotine replacement therapy of different formulations [49] and one assessed the effectiveness of cytisine [50]. In total, 149 trials were included in 10 systematic reviews (mean per review: 14.2; range: 2-86). The calculated corrected covered area (CCA) was 8.3%, which indicated moderate overlaps of primary publication in the included reviews. The included reviews consisted of a total of 67,588 study participants (mean per review: 6758.8). 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 four included studies which used both self-reported and biochemical techniques (Table 4).

Methodological quality of included reviews

The reviews were assessed for methodological quality using the AMSTAR 2 quality appraisal tool for systematic reviews. Table 5 presents the score of each item for specific systematic reviews. Based on the AMSTAR 2 rating, one review scored high quality, two scored moderate quality, four scored low quality, and three scored critically low quality. Among the 16 AMSTAR 2 domains assessed except for two reviews, all the other reviews failed to develop or report the presence of written protocol (item 2). Of the ten reviews included only one review **reported on the sources of funding for the studies included in the review (item 10)**. On the other hand, all reviews satisfied items related **to the selection of the study designs for inclusion in the review (item 3) and report potential sources of conflict of interest and funding (item 16)**.

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) [44]. In the quality appraisal, this paper was scored as having 'high' methodological quality.

In a review of seven studies ('moderate' 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) [43]. Another study assessing the pooled effect from 12 randomized controlled trials ('low' 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) [41].

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) [45]. 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) [45]. In the quality appraisal, this review scored a 'critically low' methodological quality. Conversely, a review by Lindson et al ('critically low' 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) [42].

Varenicline and bupropion

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)[45]. 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) [45].

Combination therapy

Chang et al ('low' 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) [46]. 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) [47].

In a 'critically low' 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) [49].

Other therapies

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) [47]. In the quality appraisal, this review was scored as having 'low' methodological quality. 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) [48]. This review was ranked as having a 'low' methodological quality. A review that includes 7 trials (4020 participants) found that cytisine was effective for smoking cessation at 3weeks to 2years of follow-up (RR= 1.57, 95% CI: 1.42 to 1.74) compared to placebo. The pooled effect of two high-quality reviews also confirmed the effectiveness of cytisine for smoking cessation at 6months of follow-up compared to placebo (RR =3.29. 95% CI: 1.84 to 5.90) [50]. This review was ranked as having a 'moderate' methodological quality.

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 [51]. Non-nicotine pharmacotherapy such as bupropion varenicline and cytisine 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 [51]. NRT, bupropion and varenicline are second-line drugs approved by the US Food and Drug Administration and other countries for the treatment of smoking cessation [52]. Some randomized trial studies reported the superiority of cytisine for smoking cessation compared to NRT [53]. Cytisine is cheapest compared to smoking cessation drugs such as NRT, bupropion, and varenicline [54].

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, 55]. The level of treatment compliance is also an important factor in attaining and sustaining smoking abstinence [12, 56].

Findings from previous systematic reviews and reviews of reviews demonstrated the effectiveness of behavioural interventions for smoking cessation [19, 20]. Moreover, studies have found the effectiveness of combined pharmacological and behavioural interventions for smoking cessation [57]. 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 [58]. Moreover, behavioural interventions have been recommended to prevent relapse and to sustain smoking cessation achieved by pharmacotherapy [59]. Therefore, combining counselling and pharmacotherapy could be more efficacious for smoking cessation. A Cochrane systematic review with low-quality evidence that include two primary randomized controlled trials found that e-cigarette use helped with smoking cessation [60]. However, the findings regarding the effectiveness of e-cigarette for smoking cessation were inconsistent.

Overall, the quality of the systematic reviews included in the current umbrella review was rated as 'critically low' to 'high'. The majority of the included reviews scored 'low' and 'critically low' methodological quality. All of the reviews included in the current umbrella review have published before the development of the updated AMSTAR tool (AMSTAR 2). Therefore, the authors of the reviews could not be able to follow the AMSTAR 2 checklist in conducting the reviews. Future reviews should follow the AMSTAR 2 checklist and guideline to produce quality evidence that informs policy. The majority of the reviews addressed item 11 (Appropriateness of meta-analytical methods). In the previous systematic review of reviews, these items were also well addressed by review authors [61-63]. Duplicate selection of articles to be included in a systematic review can decrease the chance of missing articles. In the current review, item 5 ("Duplicate study selection") and item 6 ("Duplicate data extraction") was well 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 [64, 65]. In almost all of the included reviews, no statement about the protocol registration and/or publication was stated under the second 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 [66]. 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 poor methodological quality 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 precisely inform clinical decision-making [67].

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 varenicline and cytisine 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 the reviews included in this umbrella review ranges from high to critically low. 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 2 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.

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; RR: Relative risk; OR: Odds ratio.

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

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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, no intervention. or alternative pharmacotherapy.
Outcome	The outcome variable measured in this study was smoking cessation.
Study design	Reviews that include only randomized control trials.

Table 2: Quality rating criteria

Quality rating	Criteria	AMSTAR 2 critical domains
High	No or one non-critical weakness	<ul style="list-style-type: none"> · Protocol registered before commencement of the review (item 2) · Adequacy of the literature search (item 4) · Justification for excluding individual studies (item 7) · Risk of bias from individual studies being included in the review (item 9) · Appropriateness of meta-analytical methods (item 11) · Consideration of risk of bias when interpreting the results of the review (item 13) · Assessment of presence and likely impact of publication bias (item 15)
Moderate	More than one non-critical weakness	
Low	One critical flaws with or without non-critical weakness	
Critically low	More than one critical flaw with or without non-critical weakness	

3: Characteristics of included reviews

Review year	Number of trials included/number of participants	Review questions/objectives	Outcome measures/intervention	Inclusion criteria	Summary findings	Authors comments
2010	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	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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
2015	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	<ul style="list-style-type: none"> The results demonstrated a significant increase in the smoking abstinence rate during early measurement in the combined group 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
2014	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	<ul style="list-style-type: none"> 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
2006	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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 preloading 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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) Bupropion was effective for smoking cessation compared to 	NRT, bupropion and varenicline all provide therapeutic effects in assisting with smoking cessation

					<p>control at one year (12 trials/ 5,228 participants; OR = 1.56, 95% CI: 1.10, 2.2, P = 0.01).</p> <ul style="list-style-type: none"> 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) 	
Li et al 2008	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)	<ul style="list-style-type: none"> Double blind randomized placebo controlled trial Study duration of one year or more Sample size ≥ 200 Using first line smoking cessation therapies 	<ul style="list-style-type: none"> 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% CI 1.25, 1.99 (4 trials) 	The author recommended future research to consider optimal therapy combination, duration of therapy and preferred agent for special population
Li et al 2013	7 trials/4020 participants (2141)	To assess the efficacy of cytisine in	Smoking quit rate/ Cytisine therapy	<ul style="list-style-type: none"> only RCTs are eligible 	<ul style="list-style-type: none"> Cytisine is an effective treatment for 	Cytisine is an effective treatment for

intervention and 1879 control)	smoking cessation.			smoking cessation compared to placebo ((RR= 1.57, 95% CI: 1.42 to 1.74) at 3 to 2 years follow-up. Data from two high-quality studies shown that Cytisine is effective at 6 months follow-up (RR =3.29. 95% CI: 1.84 to 5.90).	smoking cessation
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Table 4: Methods of smoking cessation validation and quality assessment tool used and reported heterogeneity of the reviews

Authors and year	Validation of smoking cessation of included review	Quality assessment tool and source	Meta-analysis model	Reported effect size	Reported heterogeneity of the reviews
Apollonio et al., 2016	Self-reported tobacco use or biochemical validation	Cochrane risk of assessment tool	Fixed effect	RR	$I^2 = 64\%$ for overall pharmacotherapy
Chang et al., 2015	Biochemical verification	Jadad score	Fixed effect	OR	$I^2 = 0\%$ for early outcome measure and 54% for late outcome measures
David et al., 2014	Self-reported or biochemical verification	Cochrane risk of assessment tool	Fixed effect	RR	$I^2 = 0\%$
Etter et al., 2006	Biochemically verified abstinence	Not stated	Random effect	OR	Q statistics was 18.7 (p=0.08)—No evidence of heterogeneity
Lancaster et al., 2012	Biochemically verified abstinence	Cochrane risk of assessment tool	Fixed effect	RR	$I^2 = 0.0\%$
Lindson et al., 2011	Biochemically verified abstinence and/or self-report	Cochrane risk of assessment tool	Fixed-effect	RR	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	Fixed-effect	RR	$I^2 = 52.4\%$
Wu. et al., 2006	Biochemically verified	Cochrane risk of assessment tool	Random effect	RR	$I^2 = 20.5$ to 71.5%
Shah et al., 2008	Biochemically verified	Not stated	Random effect	OR	$I^2 = 0\%$ to 37%
Hajek P et al.,2013	Self-reported or Biochemically verified	National Institute for Health and Clinical Excellence (NICE) Check list	Fixed-effect	RR	$I^2 = 14$ to 76 %

Table 5: Systematic review quality (N=9).

AMSTAR 2 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	Hajek P et al.,2013
Q1	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Q2*	PY	N	N	N	PY	N	N	N	N	N
Q3	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Q4*	Y	Y	N	N	Y	N	PY	N	N	PY
Q5	Y	Y	Y	N	Y	N	Y	Y	N	Y
Q6	Y	Y	Y	Y	Y	N	Y	Y	N	Y
Q7*	Y	N	Y	Y	Y	N	Y	N	Y	N
Q8	Y	Y	PY	PY	PY	PY	PY	N	N	PY
Q9*	Y	Y	PY	N	PY	PY	Y	PY	N	PY
Q10	Y	N	N	N	N	N	N	N	N	N
Q11*	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Q12	Y	Y	N	N	N	N	Y	Y	N	Y
Q13*	Y	N	Y	N	N	Y	Y	N	N	Y
Q14	Y	Y	Y	Y	Y	Y	Y	Y	N	N
Q15*	Y	Y	N	Y	N	Y	Y	Y	N	N
Q16	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Quality of review	High	Low	Low	Low	Low	Critically Low	Moderate	Critically Low	Critically Low	Moderate

Items: Q1) Did the research questions and inclusion criteria for the review include the components of PICO? Q2) Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Q3) Did the review authors explain their selection of the study designs for inclusion in the review? Q4) did the review authors use a comprehensive literature search strategy? Q5) Did the review authors perform study selection in duplicate? Q6) Did the review authors perform data extraction in duplicate? Q7) Did the review authors provide a list of excluded studies and justify the exclusions? Q8) did the review authors describe the included studies in adequate detail? Q9) Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies? Q10) Did the review authors report on the sources of funding for the studies included in the review? Q11) If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? Q12) If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis? Q13) Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? Q14) Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review? Q15) If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? Q16) Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

* Critical domains.

AMSTAR= Assessing the Methodological Quality of Systematic Reviews; Y=Yes; N=No; PY=partial yes;

Figures

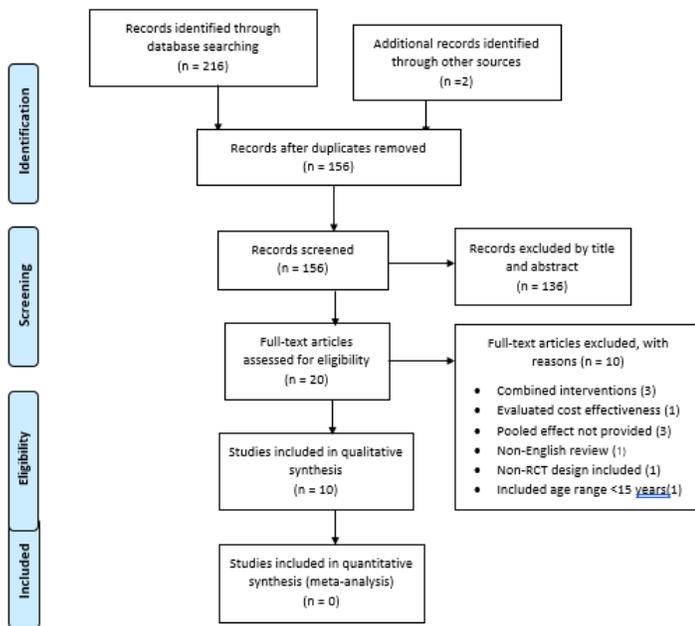


Figure 1

PRISMA flowchart of the included reviews

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