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Efficacy of pharmacological intervention for smokeless tobacco cessation in adults: a systematic review and meta-analysis

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Abstract

Background & Objectives Smokeless tobacco (SLT) use is a global burden, and its long-term use can result in health issues like oral cancers, oral potentially malignant disorders, etc. This review assessed the effectiveness of behavioural and pharmacological interventions for SLT cessation, adding new dimensions to the evidence found earlier in the literature, including recent trials.

Search methods Four electronic databases were used in the search: PubMed, Scopus, Cochrane, and Web-of-Science. Study Selection included randomized control trials (RCTs) comparing pharmacological and behavioural interventions with or without placebo to help users quit SLT with 3 & 6 months follow-up. Two review writers who separately evaluated abstracts for possible inclusion extracted data from included trials. Mantel-Haenszel's random-effect method was used to assess pooled effects for trial subgroups. Furthermore, the effectiveness of the intervention was evaluated from the reported odds ratios, confidence intervals and quit rates.

Results Nineteen, consisting of 4575 participants, fulfilled the requirements to be listed in the review. A significant difference was observed at 6 months for pharmacological versus behavioural intervention with a low heterogeneity at a 95% confidence interval. Pooling the fifteen pharmacotherapy-versus-behavioural modification studies in adults, we discovered that pharmacotherapy had a statistically significant impact on raising quit rates by the conclusion of the follow-up period (OR 1.21, 95% CI 1.03 to 1.43; 3271 participants) with low heterogeneity ($I^2 = 19\%$).

Conclusion Worldwide, there has been minimal data on interventions for SLT cessation, yet the pharmacological interventional methods have been found to be comparatively effective than behavioural intervention. Adequate awareness, health care professionals training, and law implementation are necessary to achieve habit cessation.

Clinical trial number Not Applicable. The present systematic review is registered in PROSPERO's International Prospective Register of Systematic Reviews (registration number CRD42023399178 dated 13th Feb 2023).

Keywords Smokeless tobacco, Nicotine replacement therapy, Varenicline, Bupropion, Randomized controlled trial, Cessation, Tobacco cessation, Behaviour modification

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Text box 1. Contributions to the literature

- There is limited literature contributing to the use, types and therapies for cessation of smokeless tobacco.
- Unlike the smoking form of tobacco, studies and trials are few, making it necessary to form policies across nations that are consuming smokeless tobacco.
- Behaviour modification along with pharmacological interventions are essential for smokeless tobacco cessation seeing the overindulgence of smokeless tobacco.

Introduction

Tobacco is one of the leading preventable causes of death and illness in the world. Tobacco expose could be by cigarette smoking, second-hand exposure to smoke, smoking of other combustible products, smokeless tobacco (SLT) and electronic nicotine delivery products.Smokeless tobacco products contain tobacco that is placed in the oral or nasal cavity, but it is not combusted/ burned. It is consumed globally and is available in a wide variety of forms. It can be unprocessed, raw, or sun-dried, processed with the addition of various agents which can be either chewed, sucked, or applied to gums and teeth [1]. It is a global health concern and is widely used in Southeast Asian countries. Long-term use of smokeless tobacco can result in health issues such as cancer, cardiovascular and cerebrovascular illness, periodontal disease, and tobacco dependence [2].

In India, khaini or tobacco-lime mixture (12%) is the most used SLT product, followed by gutkha (8%) and betel quid with tobacco (6%) and tobacco dentifrice (5%) [3]. India is second in terms of tobacco consumption and is among the top manufacturers, according to the Global Adult Tobacco Survey-2 (GATS-2). In South Asia, there are over 267 million tobacco users, of which 199 million (or two-thirds) use SLT. The prevalence of SLT in India is 21.4%, which is twice as high as the rate of smoking (10.7%). 70% of the world's smokeless tobacco-related deaths (2,30,000 annually) occur in India and South Asia [2].

Smoking cessation has been extensively studied throughout time, and the prevalence of smokeless tobacco use needs evidence-based treatment protocols for SLT cessation and dependency. There is little evidence on tobacco cessation and control in the South Asian context with a very few descriptions in the literature of experimental trials looking into strategies for treating SLT use when compared to smoking cessation. According to the guidelines of article 14 as reported in the global progress report, tobacco cessation consists of several dimensions, including behavior modification (BM), nicotine replacement therapy (NRT), and pharmacotherapy consisting of bupropion and varenicline, which should ensure the full involvement of health care professionals [4].

Objective

The objective of this research was to conduct a systematic review to determine and evaluate the current outcome measures for the assessment of SLT cessation using different pharmaceutical medications in comparison to behavioural support with or without a placebo. The aim was to achieve the following goals:

1. A database of outcome measures that have been used or are being developed for use in SLT cessation interventions has been created through a systematic evaluation of the literature.
2. Evaluation of outcome measures to pinpoint and emphasize those that were created and assessed with the use of excellent, extremely thorough methodologies.
3. Development of a framework for SLT cessation outcome measures, classified as.
    a. Primary outcome: Abstinence rates.
    b. Secondary outcomes: SLT use history (frequency & duration), SLT dependence, quit attempts, adverse events of pharmacotherapy.

Materials and methods

To search the literature, we developed a research question by the Participants, Interventions, Control, and Outcome (PICO) concept as well as the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) standards [5]. The research question was: "What is the efficacy of pharmacotherapy in comparison to behavioural modifications for the intervention of smokeless tobacco in adults?"

The present systematic review is registered in the International Prospective Register of Systematic Reviews maintained by PROSPERO, the National Institute for Health Research (registration number CRD42023399178).

Inclusion criteria

The studies have been selected based on the following PICO components. Only English language literature was included.

- Participants: SLT consumers of the adult population (> 18 years of age).
- Intervention: Pharmacological agents (bupropion, varenicline, NRTs i.e., nicotine patches, gums, and lozenges).
- Comparator: BM with/without placebo.
- Outcomes:

- Primary outcomes: complete abstinence of all tobacco or SLT reported for 3 and 6 months from the beginning of the intervention was used for meta-analysis. Biochemical validation was not assessed for all the included studies.
- Secondary outcomes: tobacco dependence, quit attempts, continuous and prolonged abstinence. Adverse effects were also evaluated.
- Study design (S): Randomized controlled trials (RCTs).

Exclusion criteria

Studies or articles with letters to the editor, case series, editorials, editorial review papers, animal studies, in vitro research, uncontrolled trials, and monographs were omitted. Old published data, unavailability of complete reports, study protocols, and information with lack of clarity in the abstracts were excluded.

There was no review protocol, and no amendments to any information provided at registration.

Data extraction

The research papers that were pertinent to this review were assessed individually. The complete texts of the selected studies were evaluated, co-relating them to the inclusion criteria. The papers were assessed separately by two independent authors, and any differences in the incompetence of the included studies were confirmed through discussions. The preliminary studies were re-evaluated for any missed-out studies by examining the references. After the primary assessment, the clinical studies or publications according to inclusion criteria were excluded for further analysis. For every study, the authors, country where the study was carried out, design of the study, type of intervention used, age, number, and gender of participants were included, and treatment duration, clinical parameters, recall period, and outcomes were noted. Each study was then assessed for any bias by two independent reviewers as per the recommendations of the CONSORT "(Consolidated Standards of Reporting Trials)" statement.

Data analysis

The intention-to-treat principle was used to extract all binary outcomes, and participants who were absent from the analyses were presumed to be either tobacco users or to have encountered any adverse event. Mantel-Haenszel (M-H) test with random-effects model was used for the study using Review Manager 5.4.1. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the dichotomous outcome (i.e. abstinence) for each included study. The odds ratio was calculated as follows: (total number of participants randomized to the intervention group/number of participants in the intervention group who achieve abstinence) / (total number of participants randomized to the control group who achieve abstinence / total number of people randomized to the control group). Studies were evaluated to determine whether to pool data and whether they employed equivalent interventions and measured similar results. When we did choose to pool data, the I^2 statistic was used to evaluate statistical heterogeneity [6]. Evidence of significant heterogeneity was defined as a value higher than 50%.

Quality of included studies

We used the "Risk of bias" table in Review Manager 5.4.1 to assess the quality of the included studies according to the *Cochrane Handbook for Systematic Reviews of Interventions* [26]. We assessed based on various criteria such as selection bias, performance bias, detection bias, attrition bias, and reporting bias for each study. The overall risk of bias was graded as high when one or more criteria were not met, moderate when one or more criteria were partly met, and low when all criteria were met. Out of the nineteen studies [7–25] included in this review, a high risk of performance bias in three trials [13, 17, 25] and reporting bias was identified in two trials [12, 13], and an unknown risk of other biases was present in numerous others.

The term "criteria met" has been referred to as selection bias, performance bias, detection bias, attrition bias, and reporting bias for each study and the quality of each study has been classified as high, medium or low based on the assessment of the biases mentioned above using the "risk of bias table" in Review Manager 5.4.1.

Deviations from protocol

We intended to conduct subgroup analyses wherever it was practical to do so to investigate whether the following factors affected the differences in intervention effects: treatment intensity (e.g., number of visits), history of drug use, history of use of pharmaceutical agents, dependency on tobacco; and exposure to SLT products in the participant's environment. However, it was not possible because of the lack of optimal evidence required for the analyses.

Results

Study selection

One thousand five hundred ninety-four study articles were identified using electronic search in four databases such as PubMed (439), Scopus (962), Cochrane [19], and Web of Science (170) by using various amalgamations of the keywords [MeSh]: smokeless tobacco, behavioural modifications, placebo, pharmacotherapy, and nicotine replacement therapy; and 458 duplicates were removed. 1088 articles were excluded based on their abstracts, and

35 full text articles were reviewed. After analyzing critically, 16 articles were excluded based on the type of the study, and only 19 articles [7–25] were entitled to this systematic review (Figure 1–3).

Quality of included studies

Out of the nineteen studies [7–25] included in this review, seven studies [8, 9, 10, 14, 17, 21, 24] were found to have unclear risk and twelve studies [7, 11, 12, 13, 15, 16, 18, 19, 20, 22, 23, 25] were assessed as low risk while looking into random sequence generation in selection bias; similarly eight studies [9, 13, 14, 17, 20, 21, 22, 24] were found to have unclear risk and eleven studies [7, 8, 10, 11, 12, 15, 16, 18, 19, 23, 25] were assessed as low risk in case of allocation concealment in selection bias; a high risk of performance bias was found in three trials [13, 17, 25], five studies [8, 9, 20, 21, 24] were found to have unclear risk and eleven studies [7, 10, 11, 12, 14, 15, 16, 18, 19, 22, 23] were assessed as low risk. Most of the studies didn't include enough details on outcome assessment, thus posing an unclear risk of detection bias; only four studies [9, 12, 22, 25] were assessed with low risk. Six studies [8, 17, 20, 22, 23, 24] were assessed to have unclear risk, whereas thirteen trials [7, 9, 10, 11, 12, 13, 14, 15, 16, 18, 19, 21, 25] were found to have low risk. In reporting bias, a high risk was identified in two trials [12, 13], an unknown risk was present in seven trials [8, 9, 10, 16, 20, 22, 23, 25] and low risk in nine trials [7, 11, 14, 15, 17, 18, 19, 21, 24]. The quality of the studies included was mostly found to be moderate to high based on the above findings. Only 4 [12, 13, 17, 25] of the 19 trials were found to have high risk in two categories of risk of biases, which were believed to degrade the quality of the studies.

Qualitative analysis

Nineteen eligible studies (RCTs) [7–25] were included in this review. Most of them were conducted in the USA and some of them in India, Bangladesh, Pakistan, and Norway & Sweden. There was a total of 4575 participants in all the included studies out of which 95%were male and only 5% were female. The participants in the study ranged from 18 to 76 years, with a mean age of 37 years. The participants used SLT 4 times/week on average for about 14 years. There were three studies each which used bupropion [10, 11, 22] and varenicline [18, 19, 24] as intervention for SLT cessation, three studies [7, 8, 25] used nicotine gum, four studies [9, 12, 16, 23] used nicotine patch and six studies [14, 15, 16, 18, 21, 22] used nicotine lozenge as intervention for SLT cessation in adults. The treatment period in two studies [7, 23] was 6 weeks; 7 weeks, 8 weeks, 10 weeks, and 12 weeks in one study [22], four studies [8, 12, 13, 16, 25], one study [9], and 10 studies [11, 12, 15, 16, 18, 19, 20, 21, 22, 25] respectively. The participants in most of the studies were followed up to 3 and 6 months, and only three studies [8, 9, 11], were followed up to 12 months (Table 1).

Meta-analysis

A meta-analysis was performed with the studies that were included for the abstinence of 3 and 6 months of SLT abstinence, and a forest plot was plotted for each analysis performed. Several sub-group analyses were conducted for each pharmacological agent at the respective treatment endpoints, along with the forest plots for all the analyses (Table 2).

Sixteen studies [9–11, 13–25] as well as fifteen studies [8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 23, 25] were included to estimate the abstinence rates between pharmacotherapy and BM, respectively on the 7-day point prevalence (PPA) at the end of 3 and 6 months. The association was found to be 54% higher with pharmacotherapy than BM (OR 1.54 [1.28, 1.85]; $p < 0.00001$; $I^2 = 37\%$) at 3 months and 21% higher with pharmacotherapy than BM (OR 1.21 [1.03, 1.43]; $p = 0.02$; $I^2 = 19\%$) at 6 months (Figs. 4 and 5).

Three studies [10, 11, 22] using bupropion and three studies using varenicline [18, 19, 24]were entitled to estimate the abstinence rates between various pharmacotherapies and BM at the respective treatment endpoints. The association was found to be 18% higher with bupropion than BM (OR 1.18 [0.51, 2.73]; $p = 0.70$; $I^2 = 67\%$) and 99% higher with varenicline than BM (OR 1.99 [1.48, 2.68]; $p < 0.00001$; $I^2 = 0\%$) at the treatment endpoints. Similarly, three studies [7, 8, 25] using nicotine gum, four studies using nicotine patches [9, 12, 16, 23], and three studies using nicotine lozenge [13, 14, 15, 17, 20, 21]were entitled to estimate the abstinence rates between pharmacotherapies and BM at the respective treatment endpoints. The association was found to be 64% higher with nicotine gum than BM (OR 1.64 [0.82, 3.37]; $p = 0.16$; $I^2 = 59\%$), 46% higher with nicotine patch than BM (OR 1.46 [1.07, 1.98]; $p = 0.02$; $I^2 = 0\%$) and 41% higher with nicotine lozenge than BM (OR 1.41 [1.08, 1.83]; $p = 0.01$; $I^2 = 30\%$) at the treatment endpoints (Figs. 6, 7, 8, 9 and 10).

A significant difference was observed at 6 months for pharmacological versus behavioural intervention with a low heterogeneity at a 95% confidence interval. Pooling the fifteen pharmacotherapy-versus-behavioural modification studies [8, 9, 10, 11, 12, 14, 15, 16, 17, 18, 19, 20, 21, 23, 25] in adults, we discovered that pharmacotherapy had a statistically significant impact on raising quit rates by the conclusion of the follow-up period(OR 1.21, 95% CI 1.03 to 1.43; 3271 participants) with low heterogeneity ($I^2 = 19\%$).

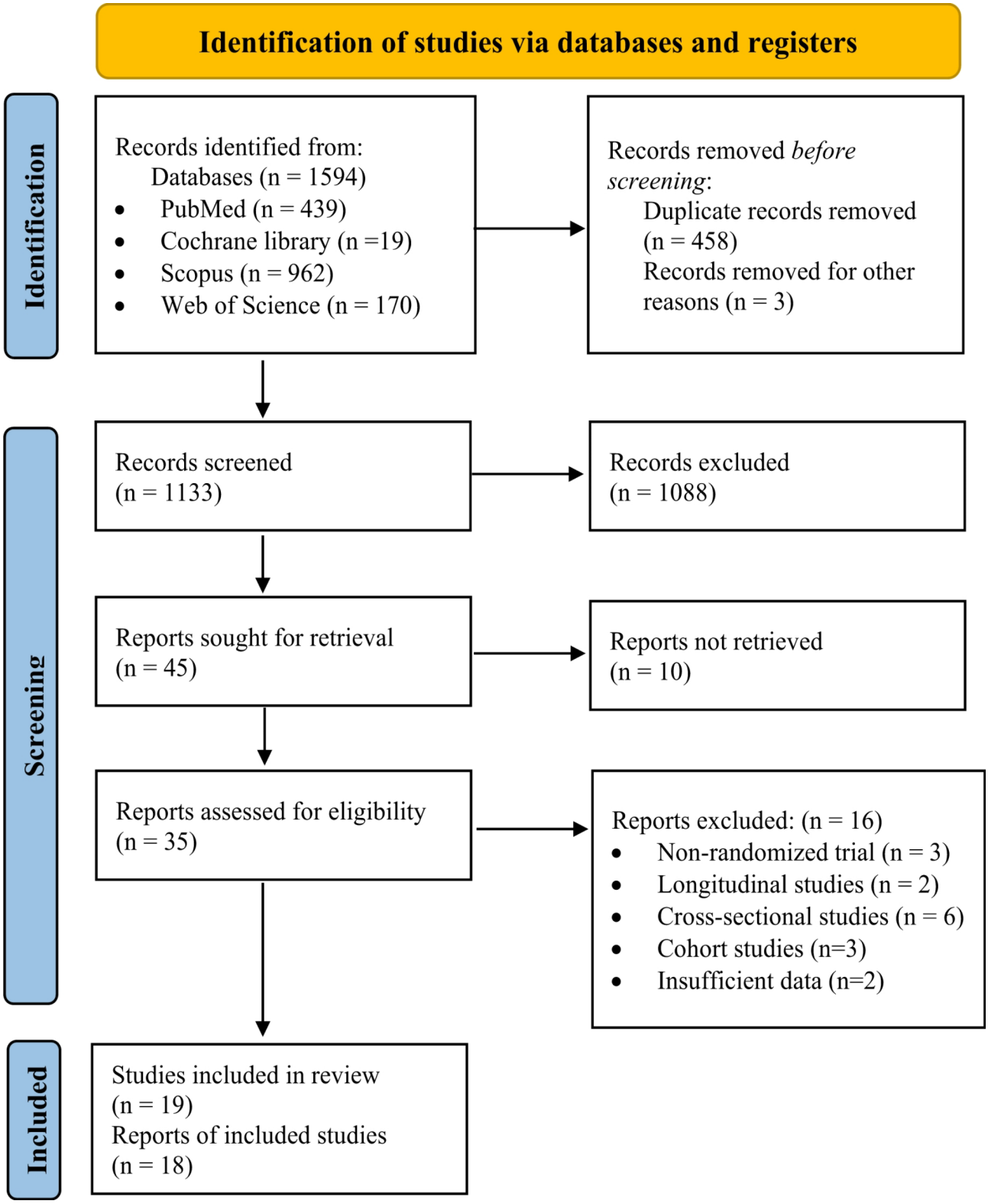

Fig. 1 Prisma flow chart

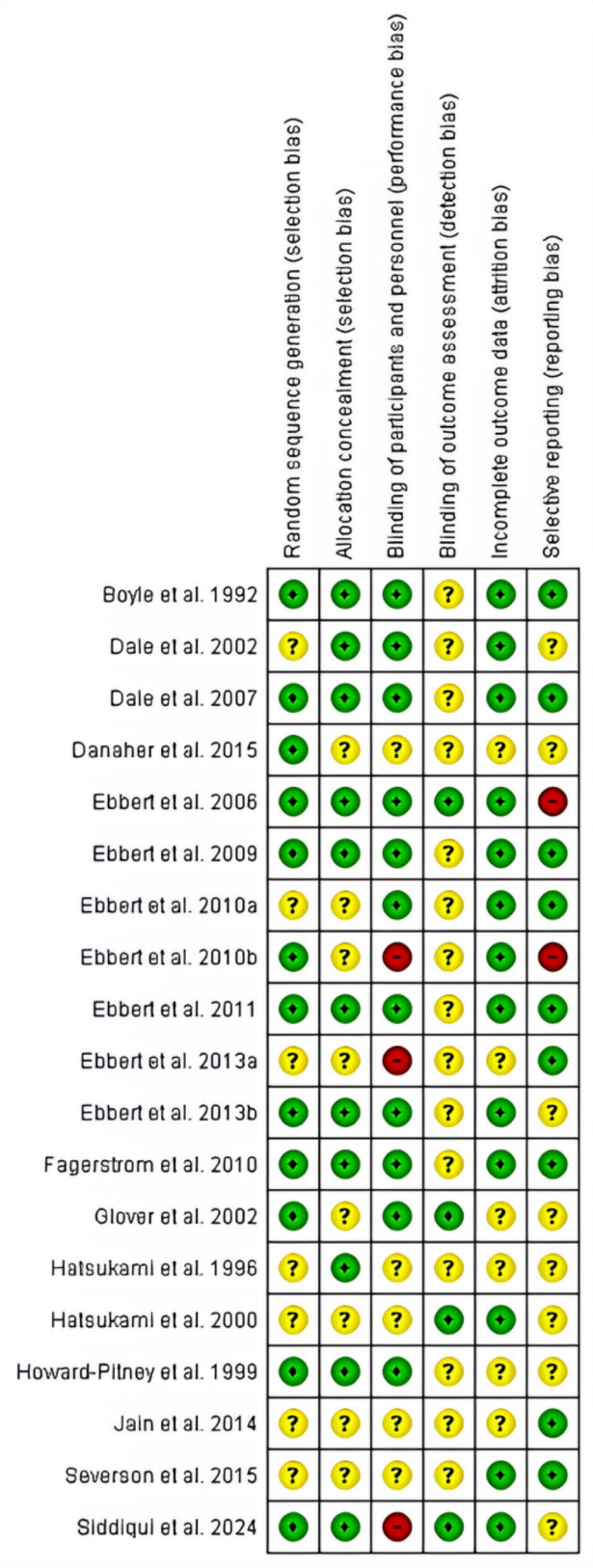

Fig. 2 Risk of bias plot

Discussion

SLT is of many different kinds that are consumed globally and is a significant global health concern [27]. A multitude of techniques have been used to create SLT products (finely ground/shredded tobacco or powdered tobacco) [28]. Numerous additives are added to SLT products; some are used for flavour (such as sugar, nuts, spices, and oils), while others are added to raise the pH and, consequently, the amount of un-protonated nicotine (such as sodium and ammonium carbonate, or alkaline buffers) [29]. Nicotine that has not been protonated or ionized is easier to absorb than nicotine that has been protonated [30].

Long-term use of SLT can result in health issues such as cancer, periodontal disease, cerebrovascular and cardiovascular disease, and tobacco addictions [31].The strategies that can assist an SLT user in quitting include self-help books, BM, and medication assistance [32]. Pharmacological agents such as NRTs (nicotine gum, patch, and lozenge), varenicline, andbupropion are considered as aids for cessation of SLT. However, there is very little evidence to support the statement.

In this review, there were 19 trials [7–25] evaluating pharmacotherapy. Bupropion was tested in three small studies [10, 11, 22]; no effect was found, but the CIs do not rule out a slight benefit. A statistically significant treatment impact was revealed by thirteen NRT trials [7–25] involving gum, patches, and lozenges. The effectiveness of nicotine gum appears to be the main driver of this effect. According to three studies [18, 19, 24], among SLT users, varenicline improves long-term SLT abstinence rates by roughly 35% when compared to a placebo. However, compared to a placebo, varenicline boosts abstinence rates in cigarette users by 31% (RR 2.31, 95% CI 2.01 to 2.66 [33]). When compared to trialsthat included smokers (e.g., 13.2% [34] and 10.5% [35], the prolonged abstinence rates ofthe control groups in SLT trials were higher at six months (31.6% [18]and 34% [19]). This could be related to the fact that SLT users have limited access to treatment, which has led to the high effectiveness of behavioural therapies included in the study's control groups.

The current systematic review indicates the effectiveness ofpharmacotherapy as an intervention forSLT cessation.Eighteen research papers [8–25] were able to undergo meta-analysis due to the heterogeneity of data across different research.A noteworthy distinction was recognized in the point prevalence abstinence rates between the pharmacological intervention and the behavioural intervention at 3 months.

A significant difference was observed at 6 months for pharmacological versus behavioural intervention with a low heterogeneity at a 95% confidence interval. Pooling the fifteen pharmacotherapy-versus-behavioural

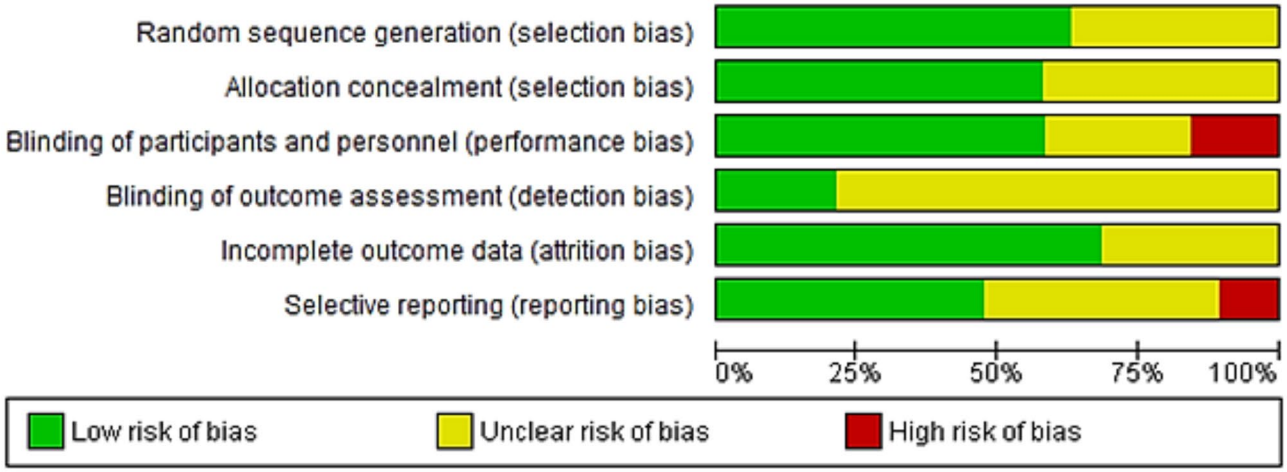

Fig. 3 Summary of review authors' judgments for risk of bias items

modification studies [9, 10, 11, 12, 13, 15, 16, 17, 18, 19, 20, 21, 22, 24, 26] in adults, we discovered that pharmacotherapy had a statistically significant impact on raising quit rates by the conclusion of the follow-up period(OR 1.21, 95% CI 1.03 to 1.43; 3271 participants) with low heterogeneity ($I^2 = 19\%$).

Our results are generally in line with earlier reviews [36, 37]. We discovered from the evidence that, when compared to a placebo, almost all recognized doses of tobacco cessation medications enhanced the likelihood of prolonged abstinence. When compared to a placebo (control), Bupropion was shown to increase the chance of quitting (from the quit date or PPA). However, this effect was only seen in our analyses of the 7-day PPA and "any abstinence" outcomes, not for continuous or prolonged outcomes.Additionally, our outcomes were similar to that of the most recent pertinent Cochranesystematic review [36]: Consistent with our results, prior analyses also discovered evidence supporting the notion that NRT monotherapy enhanced the likelihood of cessation in comparison to varenicline and bupropion but found conflicting data on the likelihood of stopping between varenicline and bupropion. Amongst NRT, nicotine gums were found to be more effective in SLT cessation, followed by nicotine patches and then nicotine lozenges, due to lesser evidence on the efficacy of the lozenges. They [37] did not stratify their results but we did by performing sub-group analyses for every pharmacological drug. The outcomes of the reviews' rankings of tobacco cessation programs were consistent. In contrast to a recent Cochranereview [36], we were unable to locate compelling evidence that the high effectiveness of behavioural interventions offered in the control arms of these studies was due to the limited treatment availability for SLT users. Unlike a recent review [36], we discovered evidence showing pharmacotherapeutic agents have proven to be a better method of SLT cessation, but we also agree that more evidence is required for this method to be declared as the robust one.

According to included trials, individuals trying to cut back on SLT are more likely to succeed in doing so if they use medication than a placebo. There is not enough data to determine whether alternative harm reduction strategies can lessen the harm that SLT causes. Since the groups receiving pharmacotherapy had higher cessation rates, no indication of using medication to aid in reduction discouraged persons from trying to stop using SLT.

At the longest time-mastered point, the level of SLT abstinence was assessed. This could have led to underestimating the intervention's impact on shorter-term quit efforts. However, this is reasonable because all the related health benefits of quitting SLT require long-term abstinence from using SLT.

Strengths & limitations

To verify the effectiveness of each pharmaceutical agent in SLT cessation at the treatment endpoints, we have included a variety of subgroup analyses in this review. That clearly explains how each pharmacological intervention functions for SLT cessation.

We intended to conduct subgroup analyses wherever it was practical to do so to investigate whether the following factors affected the differences in intervention effects: treatment intensity (e.g., number of visits), history of drug use, history of use of pharmaceutical agents, dependency on tobacco; and exposure to SLT products in the participant's environment.

Unfortunately, the lack of research and data for each comparison made this impossible. Many included studies did not disclose details regarding our secondary outcomes, such as the proportion of participants who attempted to quit. It is a significant finding as it may have clarified whether low rates of relapse following effective cessation are due to people not attending therapy

Table 1 Details of the smokeless tobacco cessation with interventional randomized controlled trials

Author	Year	Country	Sample size	Male	Female	Pharmacological group (Mean)				Behavioural group (Mean)				Intervention	Primary outcome	Time interval
						Age	Dips/day	Tins/Week	Years of slt use	Age	Dips/Day	tins/Week	Years of slt use			
Boyle et al.	1992	USA	100	97	3	32.2	11.2	-	12.2	32.2	11.4	-	12.1	Nicotine gum	Point prevalence abstinence	6 weeks
Hatsukami et al.	1996	USA	210	210	0	-	-	-	-	-	-	-	-	Nicotine gum	Point prevalence abstinence	4 weeks, 8 weeks, 1 month, 3 months, 6 months & 12 months
Howard-Pitney et al.	1999	USA	410	410	0	36.3	-	3.9	-	34.7	-	4.1	-	Nicotine patch	Point prevalence abstinence	10 days, 3 months & 6 months
Hatsukami et al.	2000	USA	402	398	4	-	-	-	-	-	-	-	-	Nicotine patch	Point prevalence & Continuous abstinence	10 weeks, 1 month, 3 months, 6 months & 12 months
Dale et al.	2002	USA	68	67	1	37.1	14.7	3.1	17.4	35.8	11.8	3.5	16.8	Bupropion SR	Point prevalence & Continuous abstinence	4 weeks, 6 weeks, 8 weeks, 3 months & 6 months
Glover et al.	2002	USA	70	70	0	36	-	-	-	36.4	-	-	-	Bupropion SR	Point prevalence abstinence	8 weeks & 3 months
Ebbert et al.	2006	USA	42	42	0	38	12.4	5.5	16.1	34.1	11.3	5.4	16.8	Nicotine patch	Point prevalence & Continuous abstinence	8 weeks & 3 months
Dale et al.	2007	USA	225	225	0	37.9	-	4.3	16.7	38.4	-	4.3	15.8	Bupropion SR	Point prevalence, Continuous & Prolonged abstinence	3 months, 6 months & 12 months
Ebbert et al.	2009	USA	270	264	6	36.6	-	4.1	18.7	36.5	-	4.0	19.4	Nicotine lozenge	Point prevalence & Prolonged abstinence	3 months & 6 months
Fagerstrom et al.	2010	Norway & Sweden	432	385	47	43.9	15.4	-	20.3	43.9	15.9	-	21.7	Varenicline	Point prevalence & Continuous abstinence	3 months & 6 months
Ebbert et al.	2010	USA	60	60	0	42.4	-	3.9	16.2	43.6	-	3.7	19.3	Nicotine lozenge	Point prevalence & Prolonged abstinence	3 months & 6 months
Ebbert et al.	2010	USA	102	102	0	35	10.1	4.3	-	35.3	9.3	4.1	-	Nicotine lozenge	Point prevalence abstinence	8 weeks & 3 months

Table 1 (continued)

Author	Year	Country	Sample size	Male	Female	Pharmacological group (Mean)				Behavioural group (Mean)				Intervention	Primary outcome	Time interval
						Age	Dips/day	Tins/Week	Years of slt use	Age	Dips/Day	tins/Week	Years of slt use			
Ebbert et al.	2011	USA	76	76	0	40.7	-	4.0	19.1	41	-	3.2	18.5	Varenicline	Point prevalence & Prolonged abstinence	3 months & 6 months
Ebbert et al.	2013	USA	81	78	3	37.8	7.6	3.2	14.1	37.5	9.7	4.0	15.3	Nicotine lozenge	Point prevalence abstinence	4 weeks, 8 weeks, 3 months & 6 months
Ebbert et al.	2013	USA	52	52	0	39.2	-	4.6	19.2	35.3	-	4.0	16.8	Nicotine patch	Point prevalence & Prolonged abstinence	8weeks, 3 months & 6 months
Jain et al.	2014	India	237	230	7	34.7	13	-	10.9	33.8	12.3	-	11.4	Varenicline	Point prevalence abstinence	3 months
Danaher et al.	2015	USA	407	397	10	35.31	-	-	13.9	35.07	-	-	15.4	Nicotine lozenge	Point prevalence abstinence	3 months & 6 months
Severson et al.	2015	USA	1067	1041	26	35.8	-	-	15.5	35.3	-	-	14.8	Nicotine lozenge	Point prevalence abstinence	3 months & 6 months
Siddiqui et al.	2024	Bangladesh, India, and Pakistan	264	140	124	35.2	-	-	-	34.5	-	-	-	Nicotine gum	Point prevalence abstinence	6 weeks,3 months & 6 months

Table 2 Summary of meta-analysis of the included studies

Outcome or Subgroup	Studies	Participants	Statistical method	Effect estimate
1.1 Abstinence at 3 months	16	3533	Odds Ratio (M-H, Random, 95% CI)	1.54 [1.28, 1.85]
2.1 Abstinence at 6 months	15	3271	Odds Ratio (M-H, Random, 95% CI)	1.21 [1.03, 1.43]
3.1 Abstinence at treatment endpoints(bupropion SR)	3	363	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.51, 2.73]
4.1 Abstinence at treatment endpoints (varenicline)	3	744	Odds Ratio (M-H, Random, 95% CI)	1.99 [1.48, 2.68]
5.1 Abstinence at treatment endpoints (nicotine gum)	3	337	Odds Ratio (M-H, Random, 95% CI)	1.64 [0.82, 3.37]
6.1 Abstinence at treatment endpoints (nicotine patch	4	706	Odds Ratio (M-H, Random, 95% CI)	1.46 [1.07, 1.98]
7.1 Abstinence at treatment endpoints(nicotine lozenge)	6	1630	Odds Ratio (M-H, Random, 95% CI)	1.41 [1.08, 1.83]

* M-H = Mantel Haenszel method, Random = Random effects model, CI = Confidence Interval

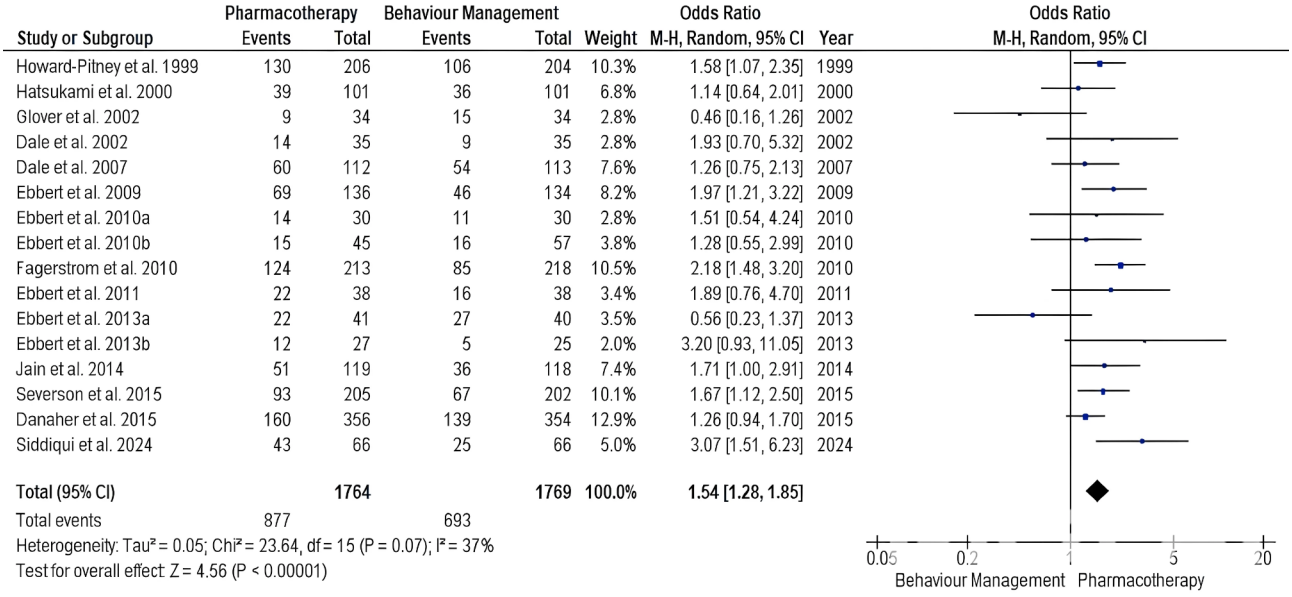

Fig. 4 Abstinence rates of pharmacotherapy vs. behavioural management at 3 months

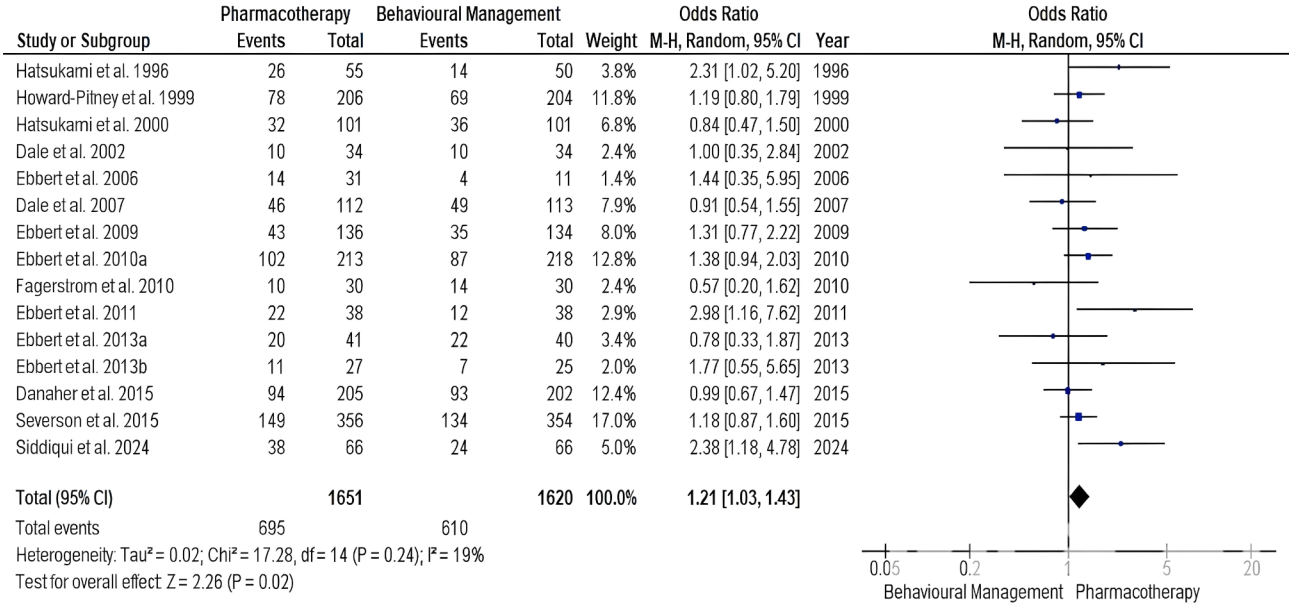

Fig. 5 Abstinence rates of pharmacotherapy vs. behavioural management at 6 months

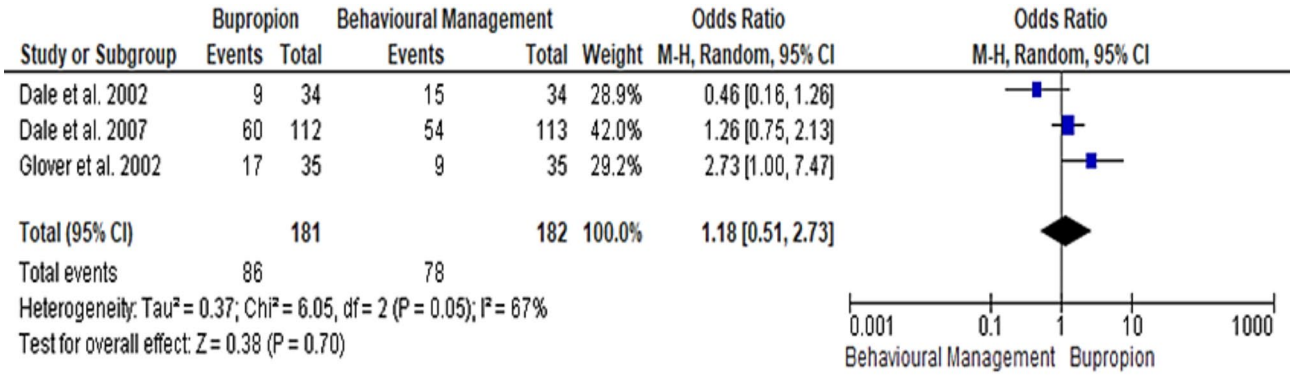

Fig. 6 Abstinence rates of bupropion vs. behavioural management at treatment endpoints

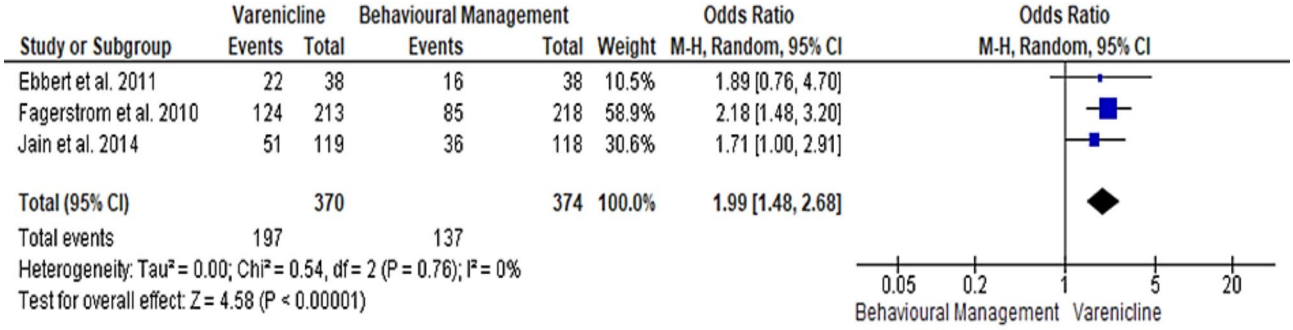

Fig. 7 Abstinence rates varenicline vs. behavioural management at treatment endpoints

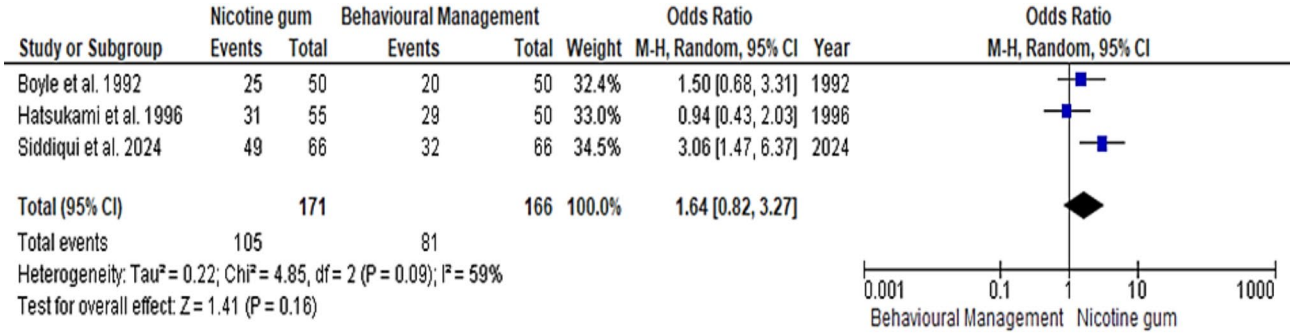

Fig. 8 Abstinence rates of nicotine gum vs. behavioural management at treatment endpoints

from the beginning or relapsing after quitting—the exact targeting of relapse prevention or engagement in later sessions. Two studies for reporting and three for performance bias were found to be at high risk while analyzing the studies contributing to the declining quality. However, data quality could have been better in the included studies as there was a considerable research gap among the various types of pharmacological interventions, and more studies are required to determine the efficacy.

Conclusion

Regardless of these limitations, this study strengthens the evidence foundation supporting using varenicline, bupropion, and NRT monotherapies as first-line alternatives for stopping SLT, which aligns with current guidelines. It should also assure patients, clinicians, and legislators that most treatments are safe. Intervention-based research on SLT cessation requires international assistance, particularly in low-income countries with inadequate resources to help SLT users quit. Varenicline may be prescribed because it appears to increase tobacco abstinence among American SLT and Swedish snus users. Although there

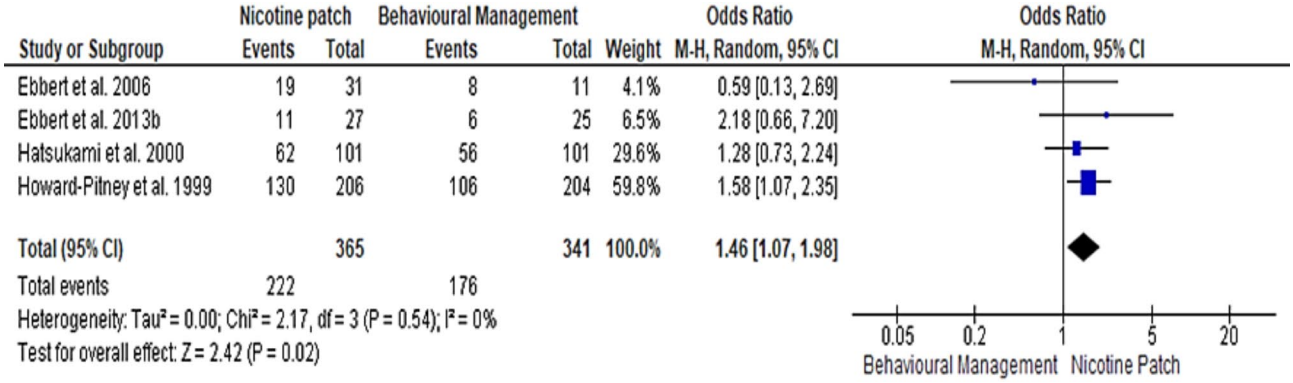

Fig. 9 Abstinence rates of nicotine patch vs. behavioural management at treatment endpoints

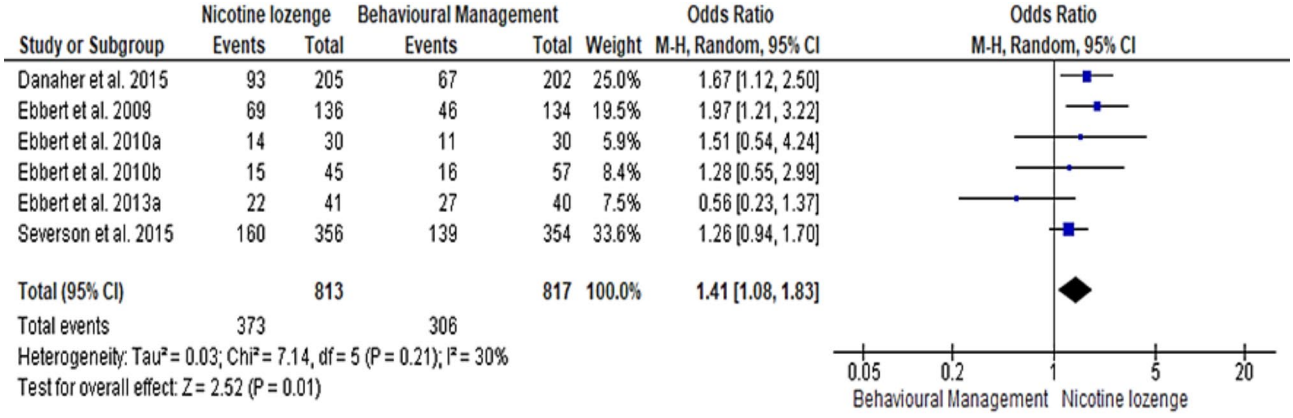

Fig. 10 Abstinence rates nicotine lozenge vs. behavioural management at treatment endpoints

are no placebo controls, the nicotine lozenge increases SLT abstinence rates, suggesting doubt about the impact.

Compared to cigarette smokers trying to quit, the effectiveness of nicotine gum is lower in the case of users of SLT. Some evidence supports the successful application of bupropion SR in treating SLT usage. It is beneficial to conduct more studies to examine the efficacy of pharmaceutical treatment in conjunction with counselling or psychological therapies. To guarantee the thoroughness of reporting within studies and enhance consistency across studies, researchers should ensure that safety data are reported in trials comprehensively.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13690-025-01593-5.

Supplementary Material 1

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Author contributions
SP, SRP, AND SaP designed the work, SP AND SRP acquired the data, and SP AND SaP did the analysis. SRP AND, SaP, AND SRM interpreted data, RP, BKC, SRP, SP, and SRM drafted the work, SP, SRP, SaP, SRM, RP, and BKC substantively revised the manuscript.Finally, all authors approved the version to be published, agreed on the journal to which the article had been submitted, and agreed to be accountable for all aspects of the work.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This section is not applicable because this study is a systematic review and meta-analysis.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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