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META ANALYSIS

Therapies for Smoking Cessation: A Meta-analysis of Double-blind Randomized Controlled Trials

Dipika Dabas

ABSTRACT

Background: Several placebo-controlled randomized trials have shown a substantial effect of many products used for smoking cessation. The trials have revealed results by performing either a direct or indirect comparisons. The present meta-analysis is an endeavor to compare the effect of the currently available and widely used seven pharmacological interventions as an aid to smoking cessation.

Methods: The databases like MEDLINE, EMBASE and the Cochrane reviewed published trials were investigated and further screened to meet the inclusion criteria. For example, only double-blind randomized controlled trials were included who have validated the results of abstinence at 6 and 12 months biochemically.

Results: A total of 69 trials were identified with a total number of 32,908 participants. Out of seven therapies chosen for the analysis, six were found to be more effective than placebo, the odds ratio (OR) for varenicline was 2.41, 95% CI 1.91–3.12, for nicotine spray (OR) 2.37, 95% CI 1.12–5.13, bupropion with (OR) 2.07, 95% CI 1.73–2.55, transdermal nicotine patch (OR) 2.07, 95% CI 1.69–2.62, nicotine tablet (OR) 2.06, 95% CI 169–2.62, and for gum (OR) 1.71, 95% CI 1.35–2.21. Though OR of 2.71 in case of nicotine inhaler favors its effectiveness over placebo, but this result remained inconclusive as the 95% CI, in this case, includes unity (0.95–5.43). On the contrary, when all the seven interventions were analyzed by putting them all together, all of them were found to be effective than a placebo. When varenicline was compared against bupropion (control arm), the former was found to be superior in its effect on smoking cessation than the latter with (OR 2.18, 95 CI% 1.09–4.08).

Interpretation: The interventional products used for smoking abstinence for 6 and 12 months, namely varenicline, bupropion, and 5 nicotine replacement therapies like nicotine gum, inhaler, transdermal patch, tablet, and lozenges were all found to be effective than placebo.

Keywords: Double blind, Nicotine spray, Smoking, Therapy.

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Senior Manager

Department of Health, Research and Wellness, Vipul MedCorp, Gurugram, Haryana, India

Corresponding Author: Dipika Dabas, Senior Manager, Department of Health, Research and Wellness, Vipul MedCorp, Gurugram, Haryana, India, e-mail: dipikadabas@gmail.com

INTRODUCTION

Smoking is considered the prime cause of preventable mortality.[49] Although smoking cessation is a challenging task, yet researcher fraternity strives and put considerable effort into identifying various tools to help smokers in quitting smoking habits.[41] Out of every two chronic smokers, one is expected to die because of smoking-related health consequences.[10] The prevalence rate of smoking in Maori (adults 15 years and above) is very high (46%).

Maori women as compared to Maori men have a higher rate of smoking (50% in females and 40% in men) and the smoking rate in Maori women of childbearing age (15–39 years) is even higher (61%).[44] Furthermore, this incidence has not declined over time among Maoris as compared to the decline observed in the general population.[44] Thus, the interventions for smoke prevention in Maoris need to be addressed for nicotine dependence which must include an all-time support and an effective way of delivery of smoking cessation program which is culturally appropriate and also ensures the inclusion of all the members of the whanau.[20] Hence, giving Maoris a choice of alternative treatment options is the dire need of the era.[34] Smoking cessation has a potential effect on the reduction of morbidity and healthcare costs related to the treatment of smoking-induced conditions.[41]

Nowadays, several pharmacological therapies are available as an aid for the cessation of smoking habits like bupropion, varenicline, and nicotine replacement therapy (NRT).[41]

NRT is the most commonly used intervention used for smoking cessation, and it is one of the frequently available over the counter (OTC) product for the consumers.[53] It is also recommended as one of the safest interventional therapy to not only the general population but also to the high-risk groups like pregnant and lactating women, adolescence and smokers with cardiovascular anomalies.[42] The cessation rate, improved by NRT at a duration of one year is roughly 70% with 1.70 odds ratio and 95 confidence interval (CI) as 1.55–1.88.[21,42,53] Under NRT, several formulations namely transdermal patch, nasal sprays, tablets, gum, inhaler, and lozenges have been marketed. It works by a mechanism wherein it replaces nicotine which is either obtained by smoking or by other means and thus helps in dealing with the withdrawal

symptoms and cravings that are generated as a result of quitting smoking.

More recently, varenicline has been demonstrated as an effective agent with a unique mechanism of action for improving the rates of smoke cessation.[18,32,47,58,]

Varenicline stimulates dopamine and thus reduces craving and withdrawal symptoms. The nicotine receptors are also blocked by this drug which then prevents the release of dopamine which is associated with the consumption of nicotine.[47,48]

Another agent, bupropion is gaining attention nowadays as an antidepressant therapy for assisting in smoking cessation.[48] There is a lack of consensus among clinicians and researchers in finding the safest and the most effective therapy as some view varenicline while other refer NRT as the most effective aid for the smoking cessation. Consequently, there is a need to compare the effectiveness of all these interventions available as an aid for the cessation of smoking.

The meta-analysis of placebo-controlled randomized trials is being undertaken for viewing the effectiveness of 7 pharmacological interventions that have been approved and are being currently in use. Thus the objective of this article is first, to compare directly varenicline and bupropion by analyzing the trials which used these therapies as treatment arms; secondly, to undertake an analysis to compare all the seven interventions by viewing the results of individual studies.

METHODS

Search Strategy

The databases like MEDLINE, EMBASE as well as Cochrane library were searched and the report of 7 interventional studies in the English language was identified for this analysis. The keywords like "smoking", "varenicline", "bupropion", nicotine inhaler", "nicotine gum", "transdermal nicotine patch", "nicotine tablet", "inhaler" and "random control trials" were used for this search.

Study Selection

The only placebo-controlled double-blind, randomized control trials, which validated the abstinence from smoking at 6 and 12 months biochemically have been included in this meta-analysis. The trials irrespective of the settings (hospitals, clinics) and adjunctive support therapy (counseling) were also included in this analysis. Some of the factorial designed trials were included as separate trials as long as there counter placebos were appropriately used.

All the unblinded studies were excluded from the analysis. Moreover, the studies that had the subjects suffering from some chronic ailments were also excluded. We made an effort to limit our study to only double-blinded placebo controlled trials which itself suggests that a strict inclusion criteria has been used for this analysis.

Classification of Outcomes

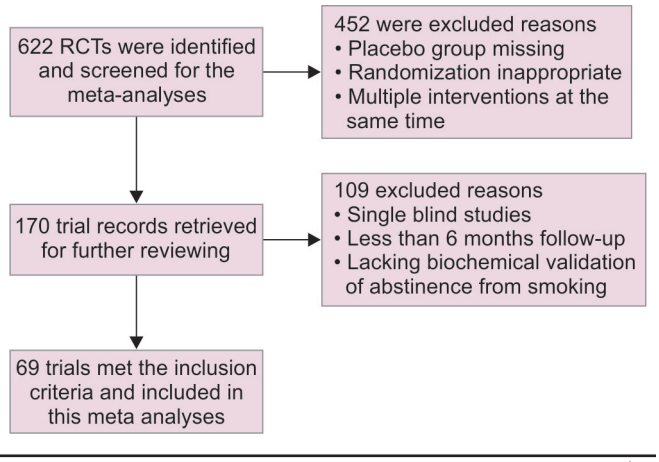
The abstinence for this analysis is defined as either point prevalence or continuous abstinence wherein the later means non-smoking from the baseline quit date until the follow-up period and the point prevalence means abstinence over the given period.

The criterion for the outcome to be included for the analysis was defined on the basis of following grades: 1) Continuous abstinence and point prevalence of one year, 2) Continuous abstinence and point prevalence of six months. The assessment of the outcomes was based on the intent-to-treat principle.

We identified 69 placeboes controlled RCT's through the literature research. All these were meeting the inclusion criteria (Flow chart 1). We found a total of 16 trials of bupropion with a total of 6653 subjects, 13 trials of varenicline with 3395 subjects, 22 trials using nicotine gum with 5200 patients, 4 trial each of inhaler with 976 subject and nasal spray with 887 participants (Figs 1 and 2), 6 studies of nicotine tablet with 2306 subjects (Fig. 3) and 30 trials of transdermal nicotine patch with 14459 participants. The comparison figures of point prevalence of abstinence at 6 and 12 months were 45 and 40, respectively whereas for continuous abstinence at 6 and 12 months were 49 and 55, respectively.

The pooled data and forest plot for each intervention as per the predefined criterion are depicted for bupropion (Fig. 4), nicotine gum in Figures 5 and 6 for transdermal, Figure 7 for varenicline, Figure 8 for comparisons in between the different therapies and Figure 9 is depicting the comparison between varenicline and bupropion. The data for these therapies were adjusted in different ways. For example, the data for bupropion was adjusted for the duration and dosage of the treatment, whereas for

Flow chart 1: Inclusions and exclusions



nicotine gum and tablet, the adjustment was done for dosage only. On the other hand, the data for transdermal nicotine patch was adjusted on the basis of two factors: One, for continuous versus tapered treatment and second, for 16 hours versus 24-hour treatment.

It was found that all therapies used for smoking cessations were efficacious than placebo except nicotine inhalers where, although, the odd ratio 2.17 favored it over placebo but as the 95% confidence interval included unity (95% CI 0.95–5.43), the results remained inconclusive. However when all of these interventions were put together in a meta-analysis, all of these 7 therapies were found to be more effective than placebo (Fig. 5).

Statistical Analysis

To deal with heterogeneity of the variables like metho dologies used in the trials, settings used for the trials, the intensity of the adjunct support therapy used along with these therapies and the differences in the patient's demography, meta-regression analysis was used. There was a likelihood of achieving abstinence from smoking in varied logarithms in both control and treatment groups in not only with-in the study but also in between the studies, but we assumed that the pattern of the odds ratio would follow the normal distribution graph for each outcome within the study, where the mean treatment effect would be considered as the mean and the differences in the odds-ratio between the trials as the variance.

On this prior assumed normal distribution, for each mean treatment effect, a mean of 0 and a variance

Study	*Placebo*	*Treatment*	*Odds ratio (95% CI)*
Holt et al.[24]	5/46	19/88	2.08 (1.41–3.30)
Hall et al.[23]	9/73	15/73	2.05 (1.34–3.06)
Muramoto et al.[43]	6/103	2/103	1.88 (0.91–2.57)
Muramoto et al.[43]	6/103	9/105	2.13 (1.47–3.52)
Nides et al.[53]	6/123	8/126	2.00 (1.21–2.96)
Hurt et al.[9]	19/153	36/156	2.08 (1.49–3.00)
Dalsgareth et al.[9]	8/114	39/221	2.15 (1.57–3.46)
Jorenby et al.[33]	9/160	45/244	2.25 (1.72–3.98)
Gonzales et al.[54]	5/224	27/226	2.31 (1.74–4.57)
Aubin et al.[48]	21/164	85/340	2.11 (1.58–3.03)
Collins et al.[47]	43/270	74/285	2.00 (1.47–2.63)
Fossati et al.[58]	26/193	101/400	2.09 (1.58–2.92)
Ahluwalia et al.[9]	19/300	37/300	2.07 (1.49–2.96)
Gonzales et al.[18]	48/344	75/329	1.99 (1.46–2.58)
Jorenby et al.[32]	59/341	80/342	1.83 (1.26–2.35)
Tonnesen et al.[18]	20/180	111/527	2.08 (1.55–2.93)
Overall	303/2788	763/3865	2.07 (1.73–2.55)

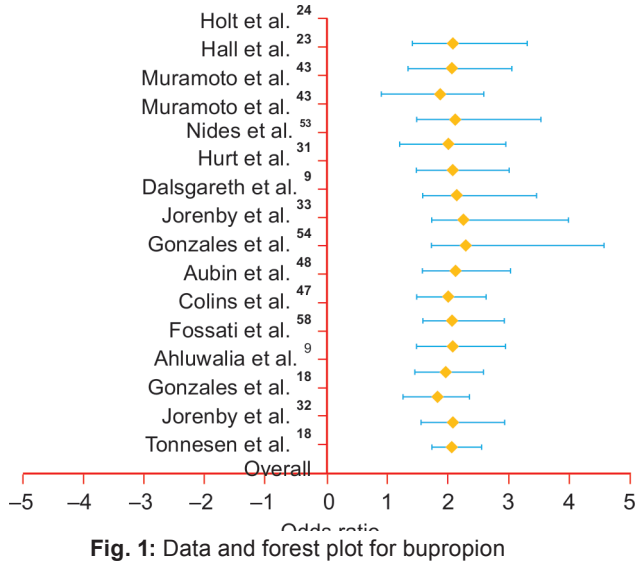


Fig. 1: Data and forest plot for bupropion

Study	*Placebo*	*Treatment*	*Odds ratio (95% CI)*
Schneider et al.[55]	3/23	1/13	1.53 (0.67–3.19)
Jarvik et al.[35]	4/23	7/25	1.73 (0.89–3.59)
Schneider et al.[55]	6/30	9/30	1.70 (0.89–3.40)
Hall et al.[28]	7/34	12/35	1.78 (0.96–3.52)
Hall et al.[28]	7/34	18/36	2.19 (1.24–4.70)
Tonnesen et al.[59]	12/53	23/60	1.86 (1.09–3.43)
Jarvis et al.[37]	8/58	18/58	2.04 (1.18–4.00)
Malcolm et al.[46]	3/63	17/73	2.42 (1.35–5.52)
Herrera et al.[27]	17/78	37/76	2.40 (1.46–4.44)
Blondal et al.[5]	22/90	30/92	1.59 (0.97–2.60)
Areechon et al.[3]	37/101	56/98	2.02 (1.31–3.31)
Jamrozik et al.[36]	8/99	10/101	1.54 (0.81–2.82)
Hall et al.[25]	25/103	21/98	1.19 (0.67–1.93)
Hjalmarson et al.[26]	16/99	29/106	1.82 (1.12–3.08)
Cooper et al.[7]	15/148	17/146	1.43 (0.81–2.39)
Fortmann et al.[14]	44/148	33/152	0.93 (0.56–1.52)
Hughes et al.[22]	6/105	23/210	1.82 (1.04–3.48)
Fee et al.[13]	15/172	23/180	1.62 (0.97–2.71)
Garvey et al.[17]	13/203	27/202	1.91 (1.20–3.25)
Garvey et al.[17]	13/203	26/203	1.85 (1.15–3.14)
Killen et al.[38]	56/309	57/301	1.21 (0.82–1.74)
Campbell et al.[6]	11/424	19/412	1.75 (1.04–3.09)
Overall	335/2397	513/2707	1.71 (1.35–2.21)

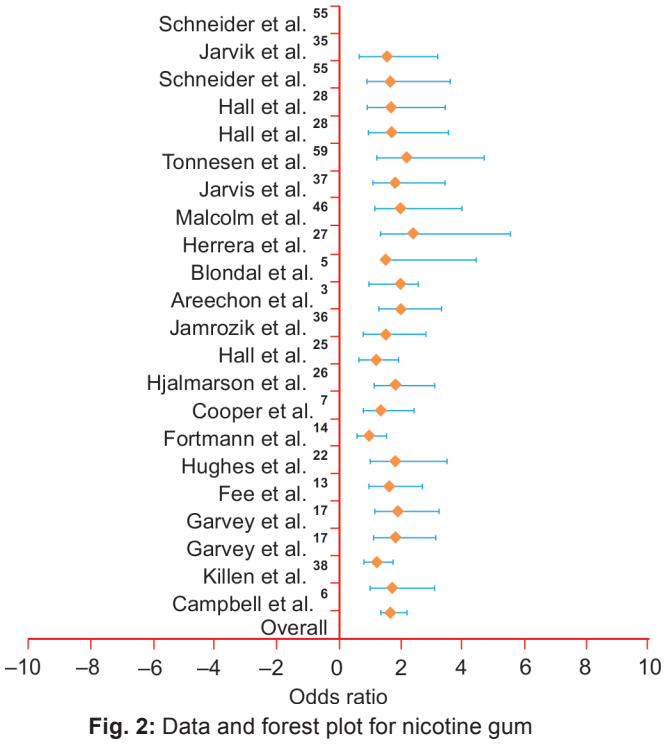


Fig. 2: Data and forest plot for nicotine gum

Study	Placebo	Treatment	Odds ratio (95% CrI)
ICRF GPRG[12,51]	53/844	76/842	1.67 (1.21–2.21)
Daughton et al.[11]	3/25	6/25	1.99 (1.27–3.47)
Daughton et al.[11]	3/25	8/27	2.12 (1.38–3.90)
Fiore et al.[15]	9/43	15/44	1.94 (1.24–3.17)
Glavas et al.[16]	9/56	13/56	1.88 (1.16–2.94)
Fiore et al.[15]	4/55	10/57	2.02 (1.29–3.50)
Paoletti et al.[50]	5/60	17/60	2.20 (1.47–4.00)
Westman et al.[63]	2/80	16/78	2.35 (1.56–4.84)
Abelin et al.[1,2]	12/99	22/100	1.96 (1.31–3.10)
Killen et al.[40]	15/104	21/103	1.83 (1.16–2.75)
Killen et al.[40]	11/108	15/109	1.82 (1.12–2.78)
Sachs et al.[57]	10/107	28/113	2.19 (1.51–3.73)
Kornitzer et al.[39]	10/75	19/150	1.69 (0.96–2.52)
Hurt et al.[31]	17/120	33/120	2.04 (1.41–3.18)
Hughes et al.[30]	6/160	16/119	2.47 (1.66–4.62)
Tonnesen et al.[62]	3/144	16/154	1.70 (1.19–2.33)
Richmond et al.[52]	14/153	29/154	2.03 (1.39–3.18)
Hughes et al.[30]	6/160	4/160	1.52 (0.82–2.26)
Hughes et al.[30]	6/160	12/160	1.97 (1.29–3.15)
Daughton et al.[8]	16/185	27/184	1.91 (1.28–2.86)
Jorenby et al.[33]	9/160	24/244	1.92 (1.25–3.00)
TNSG61	31/253	65/249	1.49 (1.08–1.97)
TNSG61	31/253	46/254	1.71 (1.27–2.19)
Gourlay et al.[19]	4/314	5/315	1.86 (1.09–3.05)
Hays et al.[29]	9/322	18/321	1.97 (1.30–3.15)
Stapleton et al.[56]	19/400	77/800	2.01 (1.45–2.98)
Tonessen et al.[60]	71/714	98/715	1.89 (1.44–2.43)
Tonnesen et al.[60]	71/714	114/715	2.25 (1.51–4.27)
Tonnesen et al.[60]	71/714	110/715	2.27 (1.67–3.30)
Tonnesen et al.[60]	71/714	84/716	1.95 (1.49–2.51)
Overall	342/4581	1044/7850	1.95 (1.65–2.34)

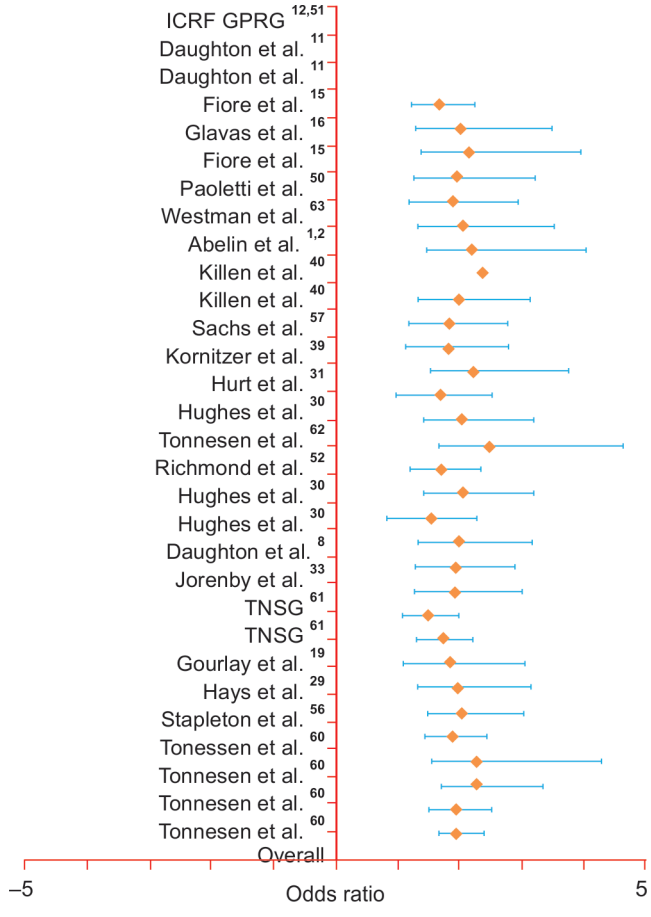


Fig. 3: Data and forest plot for transdermal nicotine

Study	Placebo	Treatment	Odds ratio (95% CrI)
Nides et al.[47]	6/123	18/125	2.61 (1.91–4.64)
Nides et al.[47]	6/123	7/126	2.23 (1.28–3.09)
Nides et al.[47]	6/123	10/126	2.33 (1.49–3.38)
Tsai et al.[44]	27/124	59/126	2.54 (1.90–3.82)
Oncken et al.[42]	5/129	25/129	2.45 (1.77–3.80)
Oncken et al.[42]	5/129	24/129	2.42 (1.74–3.67)
Oncken et al.[42]	5/129	33/130	2.68 (1.99–4.85)
Oncken et al.[42]	5/129	24/130	2.42 (1.73–3.69)
Nakamura et al.[45]	35/154	47/153	2.22 (1.45–2.96)
Nakamura et al.[45]	35/154	56/155	2.40 (1.72–3.28)
Nakamura et al.[45]	35/154	51/155	2.29 (1.56–3.07)
Jorenby et al.[32]	59/341	105/344	2.31 (1.72–2.98)
Gonzales et al.[18]	48/344	99/352	2.41 (1.84–3.19)
Overall	180/1215	558/2180	2.41 (1.91–3.12)

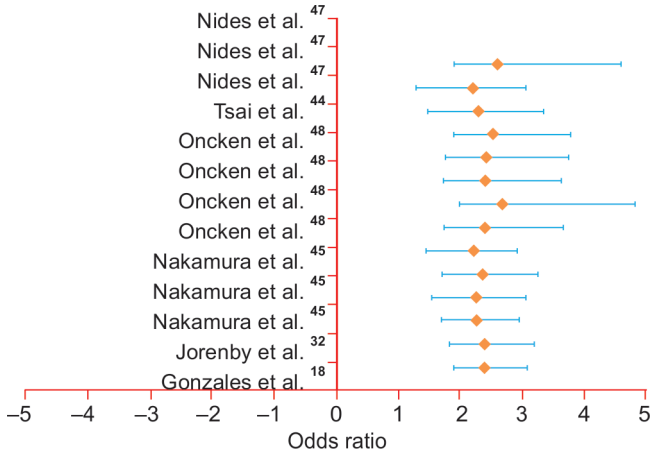


Fig. 4: Data and forest plot for varenicline

Pharmacotherapy	Odds ratio (95% CrI)
Bupropion	2.12 (1.76–2.56)
Nicotine gum	1.65 (1.37–2.01)
Nicotine inhaler	2.18 (1.38–3.45)
Nicotine nasal spray	2.37 (1.57–3.60)
Nicotine patch	1.88 (1.60–2.22)
Nicotine tablet	2.06 (1.47–2.87)
Varenicline	2.55 (1.99–3.24)

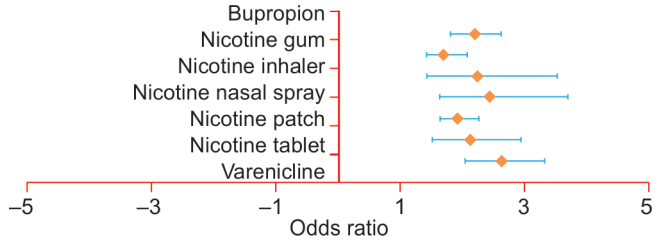


Fig. 5: Data and forest plot for pharmacotherapies

Study	Placebo	Treatment	Odds ratio (95% CrI)
Nides et al.[47]	6/123	18/125	2.73 (1.56–6.46)
Nides et al.[47]	6/123	7/126	1.79 (0.65–3.21)
Nides et al.[47]	6/123	10/126	2.04 (0.91–3.88)
Jorenby et al.[4]	59/341	105/344	2.13 (1.53–2.96)
Gonzales et al.[18]	48/344	99/352	2.33 (1.67–3.33)
Overall	113/808	239/1073	2.18 (1.09–4.08)

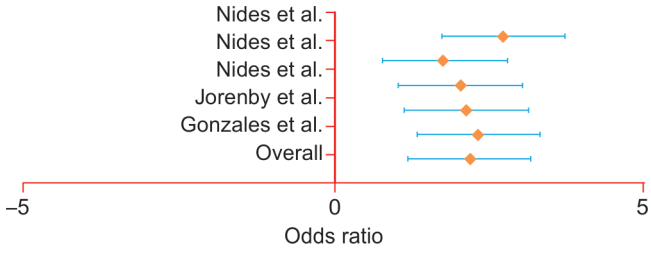


Fig. 6: Data and forest plot for varenicline versus bupropion

Trial	*Placebo*	*Treatment*	*Odds ratio (95% CI)*
Tonnesen et al.[60]	7/141	22/145	2.53 (1.46–6/02)
Hjalmarson et al.[26]	22/124	35/145	2.01 (1.18–3.39)
Schneider et al.[55]	9/111	15/112	2.03 (1.00–3.90)
Leischowet al.[43]	6/110	12/110	2.16 (1.06–4.68)
Overall	44/486	84/490	2.17 (0.95–5.43)

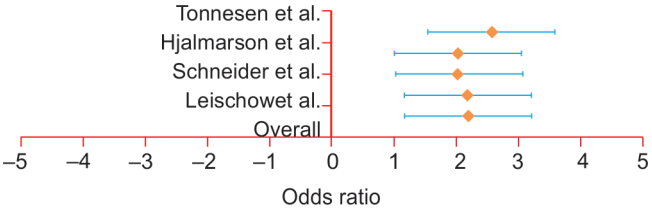


Fig. 8: Data and analysis of spray

Trial	*Placebo*	*Treatment*	*Odds ratio (95% CI)*
Shiffman et al.[22]	44/458	82/459	2.07 (1.48–2.87)
Shiffmanet al.[22]	28/451	67/450	2.30 (1.64–3.56)
Glover et al.[20]	7/80	15/78	2.15 (1.25–3.99)
Wallstorm et al.[20]	11/84	9/58	1.90 (0.86–2.99)
Wallstorm et al [20]	8/40	19/65	2.00 (1.03–3.32)
Total	103/154	199/1152	2.06 (1.27–3.06)

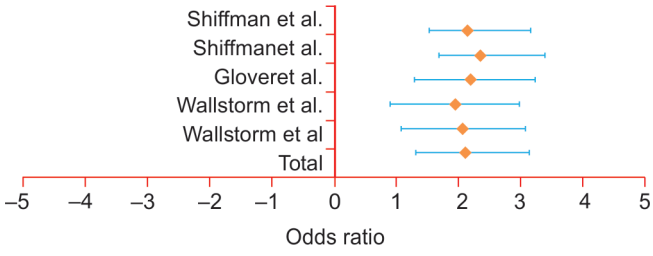


Fig. 7: Data and analysis of tablet

Trial	*Placebo*	*Treatment*	*Odds ratio (95% CI)*
Tonnesen et al.[52]	7/141	22/145	2.53 (1.46–6/02)
Hjalmarson et al.[26]	22/124	35/145	2.01 (1.18–3.39)
Schneider et al.[55]	9/111	15/112	2.03 (1.00–3.90)
Leischow et al.[43]	6/110	12/110	2.16 (1.06– 4.68)
Overall	44/486	84/490	2.17 (0.95 –5.43)

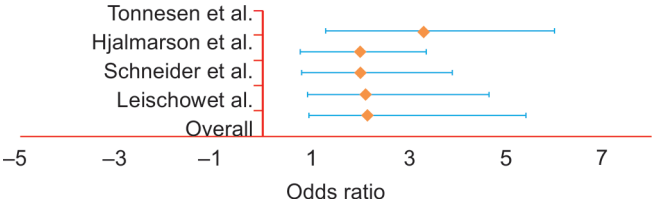


Fig. 9: Data and analysis of inhaler

of 1000000 were used and for placebo group, a mean of 0 and a variance of 10000 were used. Similarly, the same distribution was implied for the regression parameters.

The outcomes at 6 months and at 12 months plus the outcomes of point prevalence and continuous abstinence were pooled separately thereby, resulting in 4 models for each of the seven treatments investigated in this meta-analysis. The efficacy of the included therapies in the analyses was compared by using a single, large meta-analysis modal. A separate model for the odds ratio pertaining to the characteristics like type of therapy used, the age of the participants, sex, and mean a number of cigarettes smoked per day, was used for the analysis.

The ratio of the odds ratio was calculated between the interventions for comparing and creating the indicator variables for each of the therapy used in the analysis. A direct comparison was undertaken in this article for the products like varenicline and bupropion in those trials which used both of them as the treatment arms.

Varenicline versus Bupropion

When varenicline was compared indirectly in the hierarchal meta-analysis, we found that it is more effective than any other therapy but when a direct comparison was done with bupropion as an active arm in three of the trial,[18,32,47] varenicline was also found to be far effective than the bupropion (OR 2.18, 95 CI 1.09–4.08) (Fig. 9). However, in the former case, it was difficult to draw any conclusion because attacks, were reported in the trial using bupropion.

The small number of seizure attacks could be due to excluding all those who were at risk before undertaking randomization. Moreover, the definition used for adversarial effects in the trials also defers. For example, bupropion trial conducted by Jorenby et al.,[33] headache was reported as an adverse event by over 30% in those who were randomized to the placebo group and on the other hand the trial conducted by Ahluwalia et al.,[4] only 4% reported to have observed headache in the placebo randomized group. This heterogeneity in reporting of the adverse effect might be due to assigning them with different definition and assessment procedure.

Although the pharmacotherapies were found to be effective in smoking cessation but the number of subjects who showed abstinence during the follow-up period remained very low, for example, the point prevalence reported to be fewer than 30% by most of the trials and with continuous abstinence, this rate was found to be even lower. Consequently, additional research is required for developing new and improved pharmacotherapies for smoking cessation and future RCTs can focus on multiple ways to incorporate these therapies and agents.

This study has many limitations like, despite strict setting inclusion and exclusion criteria, the heterogeneity between the variables could not be ignored. For example, there were differences in the duration of treatment,

dosages, and assessment of abstinence measures but when these outcomes were analyzed separately, similar results were observed.

Secondly, the trials chosen for the meta-analysis had healthy smoker subjects who can be easily motivated to quit smoking than the subjects who actually are diseased. Thus, it lacks the representativeness and so as the generalizability. Furthermore, the trials included in the meta-analysis have used those settings where dosages, the assessment, and patterns of use of these products can be controlled. Consequently, the effect of these therapies on the smokers remained poorly understood by the users in the actual world.

Thirdly, only trials published in the English language were included in this meta-analyses which could lead to selection biased, and fourthly, a number of statistical comparisons were been undertaken in this analysis for which no adjustment was done.

Finally, the integrity of the randomization process was fragmented as all those patients who died during the trial were excluded from the studies which may result in misinterpreting the results or underestimating the results.

CONCLUSION

With this meta-analysis, it was found that all the 7 pharmacotherapies namely varenicline, bupropion, and the 5 nicotine replacement therapies (nicotine gum, nicotine inhaler, nicotine tablet, nicotine inhaler, and transdermal nicotine patch) have an effective impact on cessation of smoking. Moreover, we also found that varenicline may have a superior and a better effect as compared to bupropion. Despite this result which is favoring these products in the promotion of smoking cessation, their true effect cannot be validated as the absolute count of the participants who showed abstinence at 12 months was quite low. Thus, new and improved agents for smoking cessation needs to be developed and researched along with identifying new strategies to find alternative and different ways of using the currently available agents.

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