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Combination therapy of varenicline and bupropion in smoking cessation: A meta-analysis of the randomized controlled trials

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ABSTRACT

Background: The effects of the combination therapy of varenicline and bupropion in smoking cessation are still controversial.
Methods: Databases including PubMed, EMBASE, Cochrane Library and Web of Science were scanned without time and language limitation. Subgroup analysis was performed to assess the effect of combination therapy in smokers with different level of nicotine dependence and cigarette consumption.
Results: Four randomized controlled trials involving a total of 1230 smokers were included. Compared with varenicline monotherapy, combination treatment with varenicline and bupropion could significantly improve the abstinence rate at the end of treatment (RR 1.153, 95% CI 1.019 to 1.305, P = 0.024). The benefit existed at 6 months follow-up (RR 1.231, 95% CI 1.017 to 1.490, P = 0.033), disappeared at 12 months follow-up (RR 1.130, 95% CI 0.894 to 1.428, P = 0.305), and mainly concentrated in highly dependent smokers (RR 1.631, 95% CI 1.290 to 2.061, P < 0.001) and heavy smokers (RR 1.515, 95% CI 1.226 to 1.873, P < 0.001) rather than individuals with low nicotine dependence (RR 0.989, 95% CI 0.815 to 1.199, P = 0.907) or low cigarette consumption (RR 0.985, 95% CI 0.800 to 1.212, P = 0.252). For safety outcomes, the combination treatment was associated with more anxiety (RR 1.717, 95% CI 1.176 to 2.505, P = 0.005) and insomnia (RR 1.268, 95% CI 1.076 to 1.494, P = 0.005) symptoms compared with varenicline monotherapy.
Conclusion: Compared with varenicline monotherapy, combination treatment with varenicline and bupropion can significantly improve the abstinence rate at the end of treatment and 6 months follow-up, mainly in highly dependent smokers and heavy smokers.

1. Introduction

Smoking is a leading cause of premature death and preventable disease in the world [1]. Though several smoking cessation drugs have been developed, most of these medications could only lead to an abstinence rate lower than 25% at 1-year follow-up [2]. Given the continually increasing number of smokers worldwide [3], more effective pharmacotherapy strategies need to be explored.

As a high-affinity partial agonist for the α4β2 nicotinic acetylcholine receptor (nACHR), varenicline can reduce the binding of nicotine through competitive inhibition and has been widely used in nicotine dependence treatment [4,5]. A couple of studies have demonstrated that varenicline is more effective than all other monotherapies in smoking cessation [6,7]. However, while taking varenicline, some patients may be troubled with nicotine withdrawal symptoms, which could increase the rate of treatment failure [8]. Bupropion is an atypical antidepressant, which also acts as a nicotinic receptor antagonist, with similar efficacy to nicotine replacement therapy (NRT) [6]. Considering the different action mechanisms, the hypothesis that these two medications could be co-administered is reasonable. Ebbert et al. reported that compared to the control group (combined use of varenicline and placebo), combination therapy of varenicline and bupropion increased the prolonged abstinence rate at 12 and 26 weeks [9]. However, some other studies have drawn inconsistent conclusions that varenicline plus bupropion did not increase smoking abstinence rates compared with monotherapy (varenicline plus placebo) [10,11]. To clarify the efficacy and safety of combined pharmacotherapy with varenicline and bupropion in cigarette smokers, we performed this meta-analysis of randomized controlled trials (RCTs).

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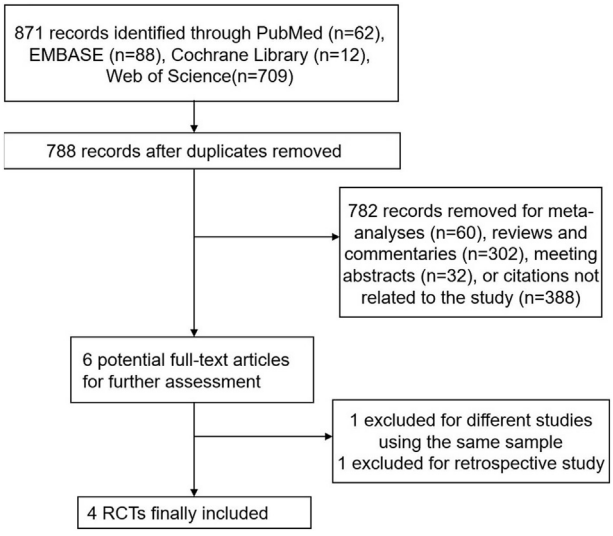

Fig. 1. Flow chart of study selection.

2. Methods

2.1. Search strategy

All published RCTs that investigated the efficacy and safety of varenicline and bupropion combined therapy compared with varenicline monotherapy were sought out by searching the electronic databases, including PubMed, EMBASE, Cochrane Library and ISI Web of Science from the establishment to Mar 2019. Search terms were performed as: ((varenicline) AND (bupropion) AND (randomized) AND ((combination) OR (combined) OR (combining) OR (coadministration) OR (plus))). No language restrictions were used. Two authors (Z.-S.Z. and S.-J.Z.) performed the study selection independently, and if the authors could not reach an agreement, a decision was made referring to the third author (S.-Y.X.).

2.2. Inclusion and exclusion criteria

Trials were included for the meta-analysis if they met the following criteria: (1) RCT; (2) varenicline and bupropion combination therapy was administered and compared with the control group (varenicline plus placebo), and (3) reported information on efficacy (abstinence rate at the end of treatment, 6 months follow-up and 12 months follow-up) and safety outcomes (dry mouth, anxiety, insomnia, depressive symptoms, etc.). Reviews, meta-analyses, meeting abstracts, non-clinical studies, case observations, and duplicated literature were excluded from the present study.

2.3. Data extraction and quality assessment

Two independent authors (Z.-S.Z. and S.-J.Z.) assessed the eligibility and methodological quality of each study according to the Modified Jadad scale [12], and extracted the following data: (1) basic information of the trial such as the name of the author, the year of publication, sample size, intervention regimens, and patient characteristics including smoking history, current smoking rate (individuals with ≥20 cigarettes/day were regarded as heavy smokers), baseline carbon monoxide and Fagerstrom Test for Nicotine Dependence score (FTND score, individuals with FTND ≥6 were regarded as highly dependent smokers); (2) follow-up information; (3) efficacy and safety outcomes of each trial as mentioned above. In cases of conflicting evaluations between the two authors, the disagreements would be resolved by the third author (S.-Y.X.).

Table 1
Characteristics of included studies.

Study	Year	Study period	Follow-up*	Combo/Var	Sample size, n	Lost at follow-up, n	Age, y	Males, n (%)	Cigarettes/day	Baseline carbon monoxide (p.p.m.)	FTND score	Number of years smoked
Cinciripini et al. [10]	2018	2010–2013#	12 months	Combo	163	38	49.36 ± 9.38	95(58.28)	19.64 ± 9.49	25.93 ± 12.58	4.74 ± 2.01	NR
				Var	166	48	48.75 ± 10.89	98(58.04)	19.02 ± 9.49	27.89 ± 15.11	4.65 ± 2.04	NR
Rose et al. [11]	2017	NR	8–11 weeks	Combo	84	NR	43.1 ± 10.6	84 (100)	20.2 ± 7.7	28.2 ± 12.0	5.6 ± 1.8	23.1 ± 10.6
				Var	90	NR	44.8 ± 11.4	90 (100)	19.8 ± 7.1	27.3 ± 10.8	5.4 ± 1.9	24.4 ± 11.1
Ebbert et al. [9]	2014	2009–2013	12 months	Combo	249	40	42.2 ± 12.2	136 (55)	19.5 ± 7.3	NR	5.2 ± 2.0	23.5 ± 12.1
				Var	257	42	41.9 ± 12.7	131 (51)	19.7 ± 7.9	NR	5.3 ± 2.0	23.3 ± 12.0
Rose et al. [17]	2014	NR	6 months	Combo	113	41	43.7 ± 10.5	55(48.7)	20.7 ± 8.5	24.6 ± 9.6	6.2 ± 2.0	25.2 ± 10.3
				Var	108	38	44.5 ± 12.6	46(42.6)	20.6 ± 8.8	24.8 ± 10.8	6.0 ± 1.8	26.9 ± 11.5

Combo: varenicline (0.5 mg/day for days 1–3; 0.5 mg bid for days 4–7; and 1 mg bid through 12 weeks) plus bupropion (150 mg/day for days 1–3; 150 mg bid through 12 weeks); Var: varenicline (0.5 mg/day for days 1–3; 0.5 mg bid for days 4–7; and 1 mg bid through 12 weeks) plus placebo (escalated dosing in the same fashion with bupropion in Combo group); FTND: Fagerström Test for Nicotine Dependence; p.p.m.: parts per million; NR: not reported;
*After the target quit date; #Time for enrollment.

Table 2
Assessment of methodological quality of included studies [12].

Author	Randomization	Double blinding	Allocation concealment	Withdrawals/dropouts	Scores
Cinciripini et al. [10]	Yes (method unclear)	Yes	Yes	Yes	6
Rose et al. [11]	Yes (method unclear)	Yes	Unclear	Yes	5
Ebbert et al. [9]	Yes	Yes	Yes	Yes	7
Rose et al. [17]	Yes (method unclear)	Yes	Unclear	Yes	5

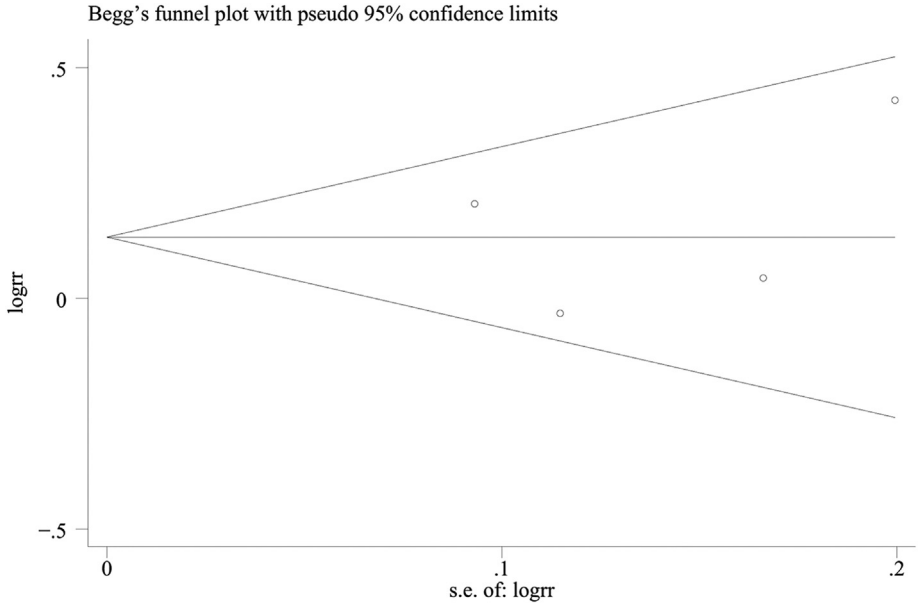

Fig. 2. Funnel Plot for the abstinence rate at the end of treatment. No publication bias was found (Begg's test, P = 0.734).

2.4. Statistical analysis

This meta-analysis was conducted according to the PRISMA statement [13]. Data were entered and analyzed using the Stata v12.0 (Stata Corp, College Station, TX, USA) with metan function. The treatment effect for dichotomous outcomes would be expressed as pooled risk ratios (RRs) and the significance of the pooled estimate was determined by the Z test. The heterogeneity across the studies was measured by the I^2 test. The fixed-effects (FE) model (Mantel-Haenszel method) would be applied when $I^2 \leq 50\%$. In the case of $50\% < I^2 \leq 75\%$, further sensitivity or subgroup analysis would be conducted, or a random-effects (RE) model would be used. If the heterogeneity was considerable ($I^2 > 75\%$), the data would be regarded as not suitable for pooling [14]. The publication bias was investigated through the use of a funnel plot with Begg's test [15]. Results with a two-sided P value <0.05 were considered reaching statistical significance.

3. Results

3.1. Search results and study characteristics

Our search strategy yielded 871 records that were potentially eligible, in which 83 were removed as duplicate citations. After screening the titles and abstracts, 782 records were further excluded according to the inclusion and exclusion criteria, and 6 studies were retrieved for a full-text review. Among the 6 studies, 2 studies were finally excluded because of the retrospective design [8] and using the same sample of another RCT [16]. Eventually, Four RCTs [9–11,17] involving a total of 1230 smokers were included in the present meta-analysis. The literature selection process is illustrated in Fig. 1, and the baseline characteristics of the enrolled studies are presented in Table 1.

3.2. Quality assessment and publication bias

The quality of the studies was assessed according to the Modified Jadad scale, involving randomization, double-blinding, withdrawals and dropouts, and allocation concealment [12]. The Modified Jadad scores are summarized in Table 2, which ranged from 5 to 7, suggesting that the overall quality of the literature was high. The publication bias risk was assessed by symmetrical funnel plot, based on the outcome of the abstinence rate at the end of treatment (Fig. 2). No publication bias was found (Begg's test, P = 0.734).

3.3. Efficacy outcomes

3.3.1. Abstinence rate at the end of treatment

All of the 4 RCTs reported the abstinence rate at the end of treatment. Compared with varenicline monotherapy (Var group), combination treatment with varenicline and bupropion (Combo group) could significantly improve the abstinence rate at the end of treatment ($I^2 = 42.2\%$, P = 0.158; RR 1.153, 95% CI 1.019 to 1.305, P = 0.024). No significant heterogeneity was observed across the studies, and the FE model was applied (Fig. 3).

3.3.2. Abstinence rate at 6 months and 12 months

Three enrolled trials [9,10,17] involving 1056 smokers reported the abstinence rate at 6 months follow-up, and only 2 of them [9,10] including 835 smokers further provided the information on abstinence rate at 12 months follow-up. Since no significant heterogeneity was found among the studies for the 2 outcome indicators, the FE model was used and no sensitivity analysis was performed. The present meta-analysis demonstrated that compared with Var group, the improvement of Combo treatment on the abstinence rate at the end of treatment was still observed at 6 months follow-

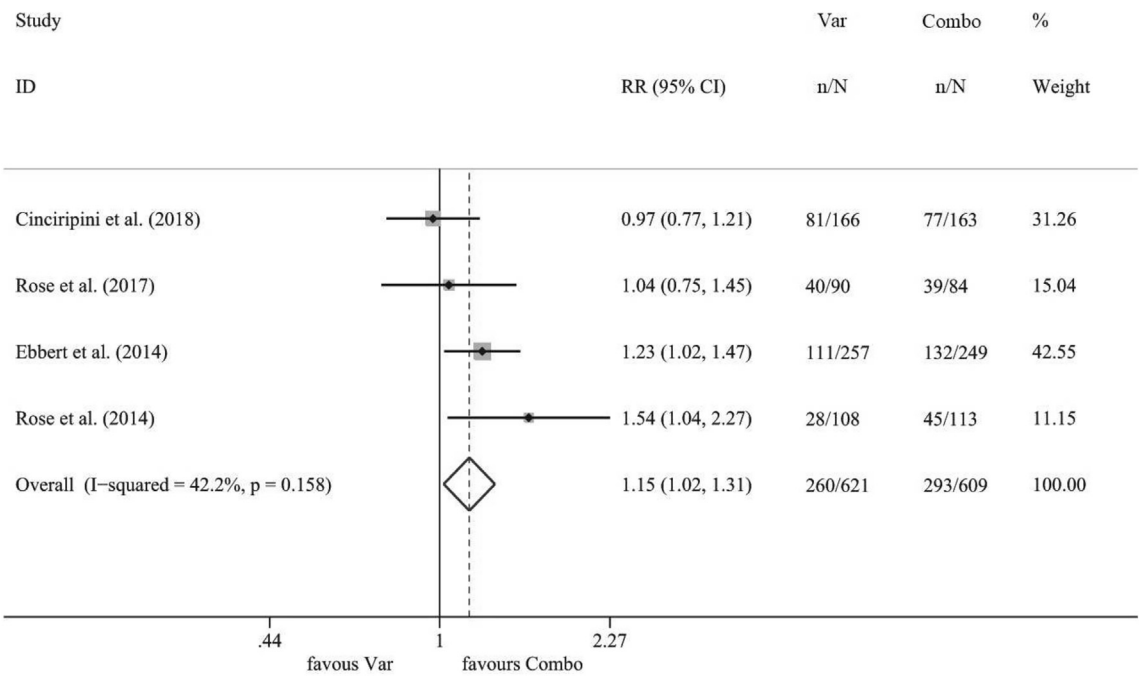

Fig. 3. Forest plot for the abstinence rate at the end of treatment. Compared with Var group, Combo therapy significantly improves the abstinence rate at the end of treatment. Combo = varenicline plus bupropion; Var = varenicline plus placebo; RR = relative risk; n = number of subjects with events; N = number of total subjects.

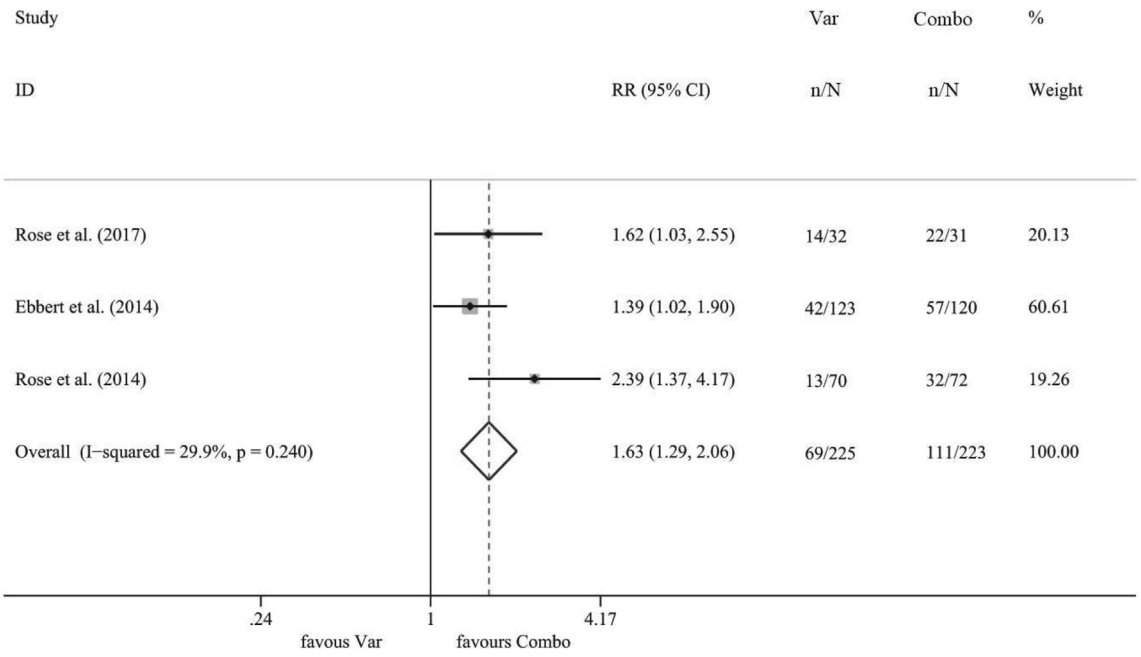

Fig. 4. Forest plot for the abstinence rate at the end of treatment in highly dependent smokers. Compared with Var group, Combo therapy significantly increased the abstinence rate at the end of treatment in highly dependent smokers. Combo = varenicline plus bupropion; Var = varenicline plus placebo; RR = relative risk; n = number of subjects with events; N = number of total subjects.

up (I^2 = 27.8%, P = 0.250; RR 1.231, 95% CI 1.017 to 1.490, P = 0.033), but disappeared at 12 months (I^2 = 38.8%, P = 0.201; RR 1.130, 95% CI 0.894 to 1.428, P = 0.305).

3.3.3. *Abstinence rate in smokers with different dependence level*

All of the 4 RCTs investigated the abstinence rate at the end of treatment according to different baseline nicotine dependence level, and 3 of them [9,11,17] involving a total of 901 smokers reported data in detail. Compared with Var treatment, Combo treatment significantly increased the abstinence rate at the end of treatment in highly dependent smokers (FTND ≥6) (I^2 = 29.9%, P = 0.240; RR 1.631, 95% CI 1.290 to 2.061, P < 0.001) (Fig. 4), but not in smokers with lower level of dependence (FTND <6) (I^2 = 49.3%, P = 0.139; RR 0.989, 95% CI 0.815 to 1.199, P = 0.907) (Fig. 5). No significant heterogeneity was observed among the studies, so the FE model was applied.

3.3.4. *Abstinence rate in smokers with different cigarette consumption*

Three RCTs [9,11,17] involving 901 smokers reported the abstinence rate at the end of treatment according to different baseline cigarette consumption. Compared with Var treatment, Combo

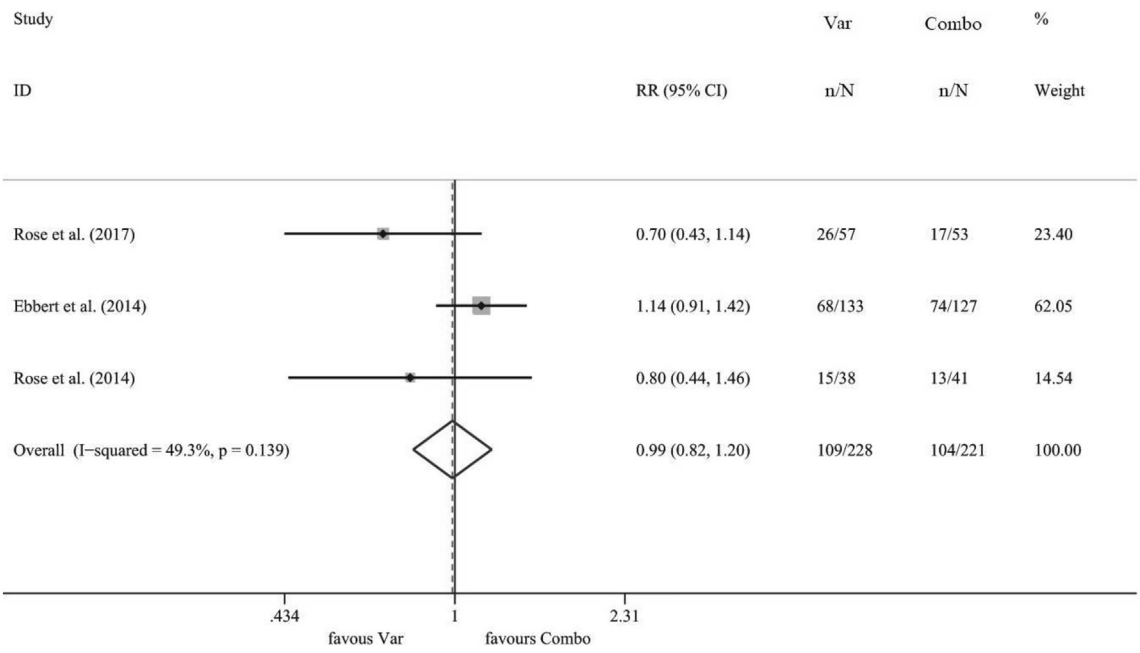

Fig. 5. Forest plot for the abstinence rate at the end of treatment in low dependent smokers. Compared with Var group, Combo therapy did not improve the abstinence rate at the end of treatment in smokers with a lower level of dependence. Combo = varenicline plus bupropion; Var = varenicline plus placebo; RR = relative risk; n = number of subjects with events; N = number of total subjects.

Table 3
Results of safety outcomes.

Outcome	Trials, n	Events of Combo, n (%)	Events of Var, n (%)	I^2, %	P value for heterogeneity	Statistical Model	RR (95% CI)	P value
Dry mouth [9–11]	3	46 (9.3)	24 (4.7)	71.3	0.031	RE	1.727(0.673–4.432)	0.256
Irritability [9–11]	3	64 (12.9)	62 (12.2)	60.5	0.079	RE	1.180(0.659–2.113)	0.577
Anxiety [9–11]	3	62 (12.5)	37 (7.3)	0.0	0.607	FE	1.717(1.176–2.505)	0.005
Headache [9–11]	3	59 (11.9)	63 (12.4)	0.0	0.983	FE	0.961(0.693–1.333)	0.810
Insomnia [9–11]	3	195 (39.4)	158 (31.0)	17.2	0.299	FE	1.268(1.076–1.494)	0.005
Abnormal dreams [9–11]	3	70 (14.1)	89 (17.5)	64.7	0.059	RE	0.837(0.482–1.452)	0.526
Depressive symptoms [9,10]	2	48 (9.7)	42 (8.2)	73.9	0.050	RE	1.799(0.403–8.037)	0.442
Nausea [9,10]	2	102 (24.8)	118 (27.9)	54.1	0.140	RE	0.881(0.631–1.231)	0.459

Combo: varenicline plus bupropion treatment; Var: varenicline plus placebo treatment; RR: relative risk; FE: fixed model; RE: random model.

treatment significantly increased the abstinence rate at the end of treatment in heavy smokers (≥20 cigarettes/day) (I^2 = 0.0%, P = 0.729; RR 1.515, 95% CI 1.226 to 1.873, P < 0.001), but not in light smokers (<20 cigarettes/day) (I^2 = 27.4%, P = 0.884; RR 0.985, 95% CI 0.800 to 1.212, P = 0.252). No significant heterogeneity was observed across the studies, and the FE model was applied.

3.4. Safety outcomes

In the present study, the incidence rate of most adverse events was comparable between the Combo group and Var group, including dry mouth, irritability, headache, abnormal dreams, and depressive symptoms. However, compared with Var treatment, Combo group was associated with higher rate of anxiety (I^2 = 0.0%, P = 0.607; RR 1.717, 95% CI 1.176 to 2.505, P = 0.005) and insomnia (I^2 = 17.2%, P = 0.299; RR 1.268, 95% CI 1.076 to 1.494, P = 0.005). The detail information for each indicator is presented in Table 3.

4. Discussion

The main finding of this study was that compared with varenicline monotherapy, combination treatment with varenicline and bupropion could significantly improve the abstinence rate at the end of treatment. The benefits existed at 6 months follow-up but disappeared at 12 months follow-up. In the sub-analyses, the higher success rate of combination therapy at the end of treatment was found to be mainly driven by the subgroups of highly dependent smokers (FTND ≥6) and heavy smokers (≥20 cigarettes/day), rather than individuals with lower nicotine dependence (FTND <6) or lower cigarette consumption (<20 cigarettes/day). These findings were consistent with most previous studies [9,17]. Although no detail data were available, Cinciripini et al. also reported that "Combo treatment was superior to Var only among smokers with FTCD ≥6" [10]. The exact mechanisms underlying the beneficial effects of combination therapy on highly dependent and heavy smokers were still unclear, but there's a hypothesis that varenicline could not provide enough dopamine through enhancing dopamine release [5] and upregulating dopamine D2/D3 receptors [18] in these individuals, which might be partly resolved by bupropion, through blocking dopamine reuptake [19]. Since no trials reported the information on highly dependent smokers and heavy smokers at 6 months or 12 months follow-up, whether the benefit could continue remains unclear.

Gender was also once considered as an important factor that may influence the abstinence rate, and male smokers might benefit more from the combination therapy [20]. The potential mechanisms may involve more nicotinic receptor upregulation in male smokers' striatum [21] and different striatal dopamine D2/D3 receptor availability than female [22]. In the present study, we did not perform the meta-analysis for the subgroup of gender since only

1 RCT provided relevant data [17]. However, another RCT included in our study, which involved only male smokers, demonstrated that the overall abstinence rate was comparable between combination therapy and varenicline monotherapy at the end of treatment (39 of 84 in Combo group vs. 40 of 90 in VAR group) [11], and the main benefit was also driven by the level of nicotine dependence and cigarette consumption [11]. Similarly, Cinciripini et al. reported they did not find evidence of any treatment interactions with gender as well [10].

As to safety outcomes, the combination therapy was generally safe and well tolerated, though may be associated with more anxiety and insomnia symptoms compared with varenicline monotherapy. Anxiety is known to be associated with bupropion in smoking cessation treatment [23], which needs more regular monitoring. Previously, Ebbert et al. reported that the depressive symptom was more common in combination therapy [9]. However, in the following study, Hong et al. found that after 4 weeks treatment, the combination treatment was not associated with a higher incidence rate of depressive symptom, and a history of depression did not influence the efficacy of combination therapy for smoking abstinence [16]. In the present study, we also did not find an increased rate of depressive symptom in the combination therapy group.

There are several limitations in the present study, mainly including the lack of long-term follow-up data for high nicotine dependence and heavy smokers subgroup, and the limited study number and population size, which might restrict the power of the analysis (especially for the abstinence rate at 12 months and the depressive symptom). Therefore, the results of the study should be interpreted with caution. However, to the authors' knowledge, this is the first meta-analysis focused on the combination therapy of varenicline and bupropion, and no published evidence was found when the study was proposed. Overall, given that the combination therapy showed no significant benefits at 12 months follow-up, as well as higher anxiety and insomnia incidence rate, it seems that the combination treatment of varenicline and bupropion should not be recommended as a first line therapy to all smokers currently. By contrast, combination therapy may be more promising in highly dependent and heavy smokers. For further investigation, more RCTs should be designed with a long-term follow-up, especially for heavy smokers or those with a higher level of nicotine dependence.

5. Conclusions

Compared with varenicline monotherapy, combination therapy of varenicline and bupropion can significantly improve the abstinence rate at the end of treatment and 6 months follow-up, mainly in highly dependent smokers and heavy smokers. Considering the limitations of the study, the results should be interpreted with caution. More RCTs with a long-term follow-up, especially for highly dependent smokers and heavy smokers, are warranted for further investigation.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Author contributions

Z.-S.Z. and S.-Y.X. conceived and designed the study. Z.-S.Z. and S.-J.Z. performed the study and wrote the main manuscript text. Y.Z. contributed analysis tools and prepared figures. All authors reviewed the manuscript.

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