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REVIEW

Combination bupropion SR and varenicline for smoking cessation: a systematic review

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ABSTRACT

Background: Tobacco is the leading cause of preventable death in the world. Current cessation medications include nicotine replacement therapy (NRT), varenicline, and bupropion, while combination therapy primarily entails NRT with either varenicline or bupropion. However, recent studies have examined varenicline and bupropion in combination. *Objectives*: A systematic review assessing the efficacy and safety of combination varenicline and bupropion was conducted. *Methods*: PubMed and Clinicaltrials.gov were searched using terms: "varenicline combination", "bupropion combination", "bupropion AND varenicline", and "bupropion AND varenicline combination smoking cessation", yielding four studies including 1193 total patients. *Results*: Combination therapy yielded greater efficacy than varenicline monotherapy in two randomized controlled trials and one retrospective outcomes study. One single-arm Phase II trial provided additional efficacy and safety data. Of the prospective trials, one displayed a greater 4-week smoking abstinence for weeks 8–11 with combination (39.8%) versus monotherapy (25.9%) (OR = 1.89; 95% CI = 1.07–3.35). The other demonstrated greater prolonged abstinence (continuous abstinence from week 2) at 12 weeks (OR = 1.49; 95% CI = 1.05–2.12) and 26 weeks (OR = 1.52; 95% CI = 1.04–2.22), though results were not significant at 52 weeks in this study. The retrospective study displayed higher success rates (continuous abstinence rates at 52 weeks) with combination varenicline and bupropion (55.0%; compared to varenicline monotherapy (32.1%), *p* < 0.001). Subgroup analyses suggest that this combination may be more beneficial in males and patients with higher baseline nicotine dependence. *Conclusion*: To the authors' knowledge, this is the first review conducted to compile current literature on this novel pharmacotherapy combination for smoking cessation. Combination bupropion SR and varenicline displayed greater efficacy in smoking cessation than varenicline monotherapy, though further safety analysis is warranted to rule out additive psychiatric adverse effects.

Introduction

Tobacco continues to be the leading cause of preventable death in the United States and in the world, as its use is a major contributor in four out of the five leading causes of death: heart disease, cancer, chronic lower respiratory disease, and cerebrovascular diseases (1). Smoking cessation confers tremendous immediate and long-term health benefits (2). Current pharmacologic treatments available to aid in smoking cessation include: nicotine replacement therapy (NRT), varenicline and bupropion sustained release (SR) (3). Unfortunately, with current pharmacotherapy, success rates remain low, with less than 25% of smokers remaining abstinent one year after treatment (4).

Varenicline (Chantix®) and bupropion SR (Zyban®) are non-nicotine pharmacologic treatment options approved by the Food and Drug Administration (FDA) for smoking cessation (5,6). Varenicline acts as a partial agonist at the α4β2 nicotinic receptor. Its efficacy in smoking cessation is thought to be due to its high affinity and selective binding to these receptors, simultaneously preventing nicotine from binding (5). Bupropion SR inhibits neuronal reuptake of dopamine and norepinephrine in the reward center of the brain, which may stimulate rewards similar to those achieved when smoking, thus reducing the craving for nicotine (6). Bupropion SR is also believed to function as a noncompetitive nicotine antagonist at the α4β2 receptors (7). Due to these mechanisms, varenicline and bupropion SR may produce additive or synergistic effects. However, as both drugs act on the central nervous system and each feature black box warnings for suicidal ideation, concern of additive side-effects could limit their use in combination. Recently, several clinical trials have been conducted to assess the safety and efficacy of

combination varenicline and bupropion SR for smoking cessation. This narrative review provides the evidence from each study individually, specifically focusing on efficacy in terms of point-prevalence and prolonged smoking abstinence as well as safety and tolerability of bupropion and varenicline in combination. Additionally, efficacy in specific subpopulations and strengths and limitations of the identified trials are discussed. This systematic review is the first to evaluate the total body of evidence available relating to the use of this combination for smoking cessation.

Methods

Search strategy

PubMed and ClinicalTrials.gov were searched up to 5 August 2015 with the following terms specified *a priori*: "varenicline combination", "bupropion combination", "bupropion AND varenicline", and "bupropion AND varenicline combination smoking cessation". Human studies featuring a treatment arm in which patients received both bupropion and varenicline concurrently were included without language restrictions. Abstracts of studies identified were screened for eligibility, initially by two reviewers, with 100% agreement. A third reviewer assessed the included studies post-agreement by the initial reviewers. Details of the trials (timeframe, inclusion criteria, demographics, sample size, study design, outcomes, trial length and follow-up, recruitment methods, adverse effects, overall results and subgroup analyses) were extracted and imported into a spreadsheet (Table 1). Any discrepancies identified between the studies were discussed and reviewers reached a consensus before proceeding.

Results

Search results

The literature search yielded 1295 results. Those that were not conducted in humans (245) were excluded. Of the remaining 1050 results, only four published studies included a combined varenicline and bupropion SR arm. The four remaining, three prospective clinical trials and one retrospective outcome research study enrolling a total of 1193 patients, are included in this review (4,8–10). A flow diagram for trial exclusion is depicted in Figure 1.

Outcome measures

Three studies (4,8,9) incorporated comparable definitions of abstinence, defining success as either 7-day point-prevalence or prolonged abstinence up to a specified time-point. However time-points at which 7-day point-prevalence and prolonged abstinence were assessed varied between studies. Abstinence was determined based on patient self-reporting and confirmed through measured exhaled CO levels in all studies, but method of self-reporting and acceptable CO levels varied slightly. The fourth study assessed complete abstinence rates at 52 weeks (CAR 52 weeks), measured by CO concentrations (10). Table 1 describes the primary endpoints of each trial.

Two of the studies (8,9) featured a uniform definition of adherence (pill counts and self-reported missed doses during each visit), while a third (4) assessed adherence, but based on daily diary entry of missed doses. The fourth study (10) did not report adherence assessment.

Description of included studies

Two phase III trials, both published in 2014, were included, one comparing combination varenicline and bupropion SR versus varenicline plus placebo for 12 weeks in nicotine patch non-responders via an adaptive treatment paradigm (4) and the other assessing combination varenicline and bupropion SR versus varenicline plus placebo for 12 weeks with subsequent follow-up through week 52 (9). Additionally, one phase II clinical trial, published in 2009, assessing the efficacy and safety of combination varenicline and bupropion SR, was included (8). The fourth study featured retrospective outcome research, assessing 52-week abstinence in patients treated with varenicline monotherapy versus patients with either bupropion, a serotonin reuptake inhibitor (SSRI), or both added to varenicline (10).

Summary of evidence

Ebbert et al. conducted a phase II, open-label, one-arm trial to obtain preliminary data on the potential effectiveness and safety of combination therapy with varenicline and bupropion SR for the treatment of tobacco dependence (8). Patients were included if they met the following criteria: 18 years of age or older, currently smoking ≥ 10 cigarettes per day for ≥ 6 months, and motivated to stop smoking. A total of 38 smokers were enrolled in this study, with five subsequently withdrawing. Patients underwent an initial telephone screen and were required to attend 10 clinic visits, including: an informational meeting, baseline visit, seven biweekly medication phase appointments, and an end-of-study visit at 6 months. Patients were assessed for nicotine dependence, depression, and readiness to quit at

Table 1. Trial summaries.

Study	Years conducted	Inclusion criteria	Baseline patient characteristics	Sample size	Study design	Length and follow-up	Methods of recruitment	Primary endpoint	Adverse effects of combination therapy	Results	Results in specific patient populations
(8)	10 Sept 2007 to 25 Oct 2007; published 2009	≥ 18 years old; smoking at least 10 cigarettes/day for ≥ 6 months; motivated to stop smoking	Mean age: 49.1 (SD 12.4); 55% male; mean cigarettes/day: 19.9 (SD7.8); mean FTND: 5.2 (SD 2.2)	38	Phase II, open-label	12 weeks of treatment with 6 month follow-up	Press releases, local adverts in Rochester, MN, USA	7-day point-prevalent and a prolonged smoking abstinence rate at the end of 12 weeks of treatment (secondary outcome at 6 months)	Sleep disturbance (26%), nausea (24%), insomnia (16%)	Results showed a 71% 7-day point-prevalent smoking abstinence rate and a 63% prolonged smoking abstinence rate at the end of treatment (12 weeks). At 6 months, the 7-day point prevalent smoking abstinence rate was 58% and the prolonged smoking abstinence rate was 53%.	None reported
(4)	Not reported; published 2014	Age 18–65 years old; smoking an average of ≥ 10 cigarettes/day for 3 cumulative years; expired-air CO level ≥ 10 ppm; no exclusionary features on history, physical exam, or laboratory evaluation	Mean age 44.1 (SD 10.5); 45.7% male; 62.4% white; mean cigarettes/day: 20.7 (SD 8.5); mean FTND: 6.1 (SD 2.0)	349	Randomized, adaptive treatment, double-blind phase III clinical trial	12 week treatment with follow-up during treatment and at 6 months	Newspaper, radio, and television adverts	Continuous smoking abstinence at weeks 8–11 after the target quit date (secondary outcome at 6 months)	Headache (9.3%), diaphoresis (8.8%), nasal/sinus irritation (5.9%), change in taste perception (17.2%), dry mouth (10.8%), thirst (15.7%), cough (8.8%), irritability (11.3%), vivid dreams (18.1%), insomnia (13.7%), anxiety (8.8%)	Results showed a significant difference in the primary endpoint of 4-week smoking abstinence for weeks 8–11 with combination treatment (39.8%) versus varenicline plus placebo (25.9%) (odds ratio = 1.89; 95% CI 1.07–3.35; p value 0.029)	The results show 50.9% 4-week smoking abstinence rate in males in the combination treatment group versus 19.6% of males in the varenicline plus placebo group (odds ratio = 4.26; 95% CI = 1.73–10.49; p value 0.002). Female smokers did not show a statistically significant difference between combination and placebo groups (odds ratio = 0.94; 95% CI = 0.43–2.05; p value 0.87). This variable effect was also seen in those with a high level of nicotine dependence (odds ratio = 3.51, 95% CI = 1.64–7.51; p value 0.001) compared to a low level of dependence (odds ratio = 0.71, 95% CI = 0.28–1.80; p value 0.47)

(Continued)

Table 1. Continued.

Study	Years conducted	Inclusion criteria	Baseline patient characteristics	Sample size	Study design	Length and follow-up	Methods of recruitment	Primary endpoint	Adverse effects of combination therapy	Results	Results in specific patient populations
(9)	October 2009 to April 2013; published 2014	Age ≥ 18 years old; smoking at least 10 cigarettes/day for ≥ 6 months; motivated to stop smoking; completed written informed consent; good health	Mean age: 42.2 (SD 12.2); 55% male; mean cigarettes/day: 19.5 (SD 7.3); mean FTND: 5.2 (SD 2.0)	506	Randomized, blinded, placebo-controlled phase III clinical trial	12 week treatment with 52 week follow-up	Not reported	Prolonged abstinence and 7-day point prevalence; abstinence rates at week 12 (secondary outcomes at weeks 26 and 52)	Sleep disturbances (40.2%), nausea (22.1%), constipation (10.4%), anxiety (7.2%), depressive symptoms (3.6%)	Results displayed significantly higher prolonged abstinence rate at 12 weeks (OR = 1.49; 95% CI = 1.05–2.12; p value 0.03) and 26 weeks (OR = 1.52; 95% CI = 1.04–2.22; p value 0.03).	Statistically significant difference in heavier smokers with 7-day point prevalence at 26 and 52 weeks (p value 0.02 and 0.03, respectively) and prolonged smoking abstinence at 12, 26 and 52 weeks (p values 0.01, 0.003 and 0.004, respectively). In participants with higher nicotine dependence with prolonged smoking abstinence at 12, 26 and 52 weeks (p value 0.04, 0.002, and 0.002, respectively)
(10)	1 Sept 2007 to 31 Dec 2009; published 2013	Consecutive patients who received a prescription for varenicline from a cardiovascular smoking cessation service at the study site	Mean age 49.9 (SD 10.5); 54.3% female; 85.8% white; mean FTND: 7.3 (SD 2.6)	427	Retrospective outcome research study	Followed for 52 weeks	None	Continuous abstinence rate (CAR) at 52 weeks	Nausea and abnormal dreams (adverse effects not specifically reported; these adverse effects only noted to be especially bothersome and primary reasons 15.2% of treatment failure group patients failed)	Results showed a significantly higher amount of combination treatment patients in the success group. Success (CAR in 52 weeks) rates: varenicline monotherapy (32.1%); varenicline + bupropion [(55.0%), OR 3.21 (1.68–6.14)]; varenicline + bupropion + SSRI [(57.7%), OR 5.05 (1.99–12.80)]. Lower success rates and higher failure rate observed in varenicline monotherapy group (32.1% and 32.8%) compared to varenicline + bupropion combination group (55.0% and 18.3%), p value not reported	Success group patients displayed greater weight gain (5.7 ± 5.8 kg) vs. failure group (0.7 ± 2.4 kg) (p < 0.01). Success group patients also had a higher number of clinical visits (p < 0.01).

FTND, Fagerström test for nicotine dependence.
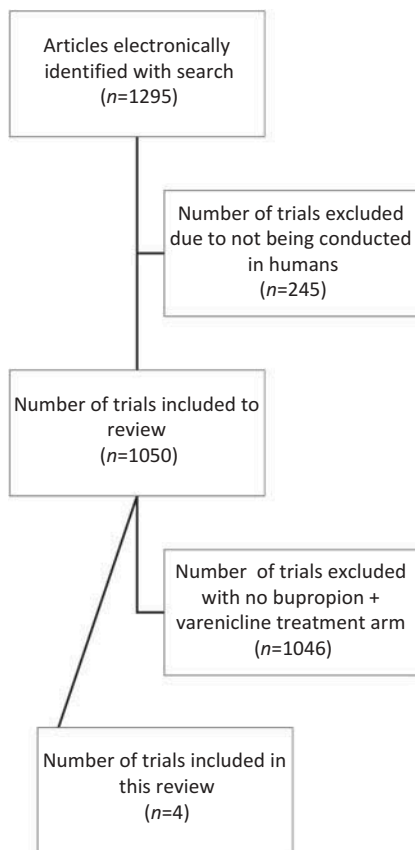
Figure 1. Reasons for trial exclusion.

baseline. Subjects received varenicline and bupropion SR simultaneously. Varenicline was titrated as follows: once daily (0.5 mg tablet) for 3 days, 0.5 mg twice daily for days 4–7, 1 mg twice daily maintenance dose for a total of 12 weeks, while bupropion SR was titrated: one tablet by mouth (150 mg) once daily on days 1–3, followed by one tablet by mouth twice daily, for a total of 12 weeks. The target quit date (TQD) was day 8 of therapy. Patients received brief behavioral counseling by a trained study assistant during each visit and maintained a daily diary to record tobacco craving and nicotine withdrawal, utilizing a 5-point scale to rate their cravings over the past 24 h. Adherence was assessed through pill counts at each visit and by self-reporting of missed doses. Expired CO measured in parts per million (ppm) was obtained at every visit.

Primary endpoints included 7-day point-prevalence and prolonged smoking abstinence rate at the end of treatment (12 weeks) (8). Secondary endpoints included 7-day point-prevalence and prolonged smoking abstinence rate at 6 months. Point-prevalence smoking abstinence was defined as self-reported abstinence for the last 7 days as well as an expired CO ≤ 8 ppm. Prolonged smoking abstinence was defined as criteria for 7-day point-prevalence smoking abstinence being satisfied and a negative response to tobacco use at each visit. Results displayed a 71% 7-day point-prevalence smoking abstinence rate and a 63% prolonged smoking abstinence rate at the end of treatment. At 6 months, the 7-day point-prevalence smoking abstinence rate was 58% and the prolonged smoking abstinence rate was 53%. It was reported that 74% of patients took at least 90% of prescribed doses.

Rose et al. conducted a phase III, double-blind, parallel-arm, adaptive treatment trial to assess the efficacy and safety of combination varenicline and bupropion SR compared with varenicline monotherapy for smokers who, based on an assessment of initial smoking reduction with the use of nicotine patch prior to the quit date, were deemed unlikely to achieve abstinence using nicotine patch treatment (4). In the trial's pre-quit phase, early response to nicotine patch treatment was assessed. Participants failing to show a decrease of > 50% of their baseline cigarette smoking (assessed using expired-air CO) after the first week were randomized to receive either varenicline and bupropion SR or varenicline and placebo. Eligible patients met the following criteria: were aged 18–65 years, reported smoking ≥ 10 cigarettes per day for 3 cumulative years, produced an expired-air CO level of ≥ 10 ppm, completed written consent, and had no exclusionary features on history, physical examination, or laboratory evaluation. The study consisted of clinic visits 2 weeks prior to the quit date and four additional visits at weeks 1, 3, 7, and 11 after. Participants were provided brief support, clinical trial materials were dispensed, smoking diaries were collected, and measured expired-air CO was collected at each visit.

The primary endpoint was continuous (no smoking within 4 weeks) smoking abstinence for 8–11 weeks after the target quit date (4). Initial nicotine patch dose was based on baseline expired-air CO reading: those with CO levels above 30 ppm at baseline received 42 mg/day (two 21 mg/day patches), while the remaining received one 21 mg/day patch. Each patient failing nicotine patch therapy received varenicline in addition to randomly assigned bupropion SR or identical-appearing placebo tablets administered in a blinded fashion. Both varenicline and bupropion SR were titrated in an identical manner to the Ebbert study (8) previously discussed. Using an intent-to-treat analysis, those lost to follow-up were classified as non-abstinent. The study initially included 349 participants in the pre-quit phase, and 222 participants were nicotine patch non-responders at one week and thus randomly assigned to one of the two rescue treatment phases

described. Those originally deemed responsive to nicotine patch therapy continued with NRT treatment, with their results presented in a separate study; 35.6% of participants dropped out after randomization. Results demonstrated a significant difference in the primary endpoint of 4-week smoking abstinence for weeks 8–11 with combination treatment (39.8%) versus varenicline plus placebo (25.9%) (odds ratio [OR] = 1.89; 95% confidence interval [CI] = 1.07–3.35; p value 0.029).

However, after subpopulation analyses, a beneficial effect was demonstrated only in males (50.9% 4-week abstinence rate in males in the combination treatment group versus 19.6% of males in the monotherapy group [OR = 4.26; 95% CI = 1.73–10.49; p value 0.002]) (4). Female smokers did not show a statistically significant difference between combination and monotherapy groups (29.3% versus 30.6%, respectively: OR = 0.94; 95% CI = 0.43–2.05; p value 0.87). This variable effect was also seen in those with high levels of nicotine dependence (44.4% vs. 18.6% for combination and monotherapy respectively: OR = 3.51; 95% CI = 1.64–7.51; p value 0.001) compared to low levels (31.7% for combination vs. 39.5% for monotherapy; OR = 0.71; 95% CI = 0.28–1.80; p value 0.47). At 6-month follow-up, findings similar to the primary endpoint were found, with significant differences in males (29.1% in combination group compared with 10.9% in monotherapy [OR = 3.36; 95% CI = 1.12–10.06; p value 0.03]) and those with greater nicotine dependence (29.2% in combination group compared with 10.0% with monotherapy; [OR=3.71; 95% CI = 1.46–9.41; p = 0.006]).

Ebbert and colleagues also conducted a phase III, randomized, double-blind, placebo-controlled trial to determine efficacy and safety of varenicline and bupropion SR compared with varenicline and placebo for smoking cessation (9). Participants were eligible if they met the following criteria: were aged 18 years or older, smoked ≥ 10 cigarettes/day for ≥ 6 months, were motivated to quit smoking, completed informed consent, and were in good health (defined as not having any exclusionary health issues). From a total of 506 patients enrolled and randomized, 191 patients dropped out by the end of 52 weeks (63% completion in combination group vs. 61% completion in monotherapy group). Patients lost to follow-up were assumed to have continued smoking and identified as non-abstinent. The study consisted of an initial telephone screening call, 11 clinic visits (two before, six during, and three after the medication phase), and three follow-up telephone calls (one during the medication phase at the time of the target quit date and two after the medication phase). Smoking dependence, depressive

symptoms, and suicidal ideation were collected at baseline and at 2, 4, 8, 14, 26, and 52 weeks. Patients received 12 weeks of varenicline and bupropion SR or 12 weeks of varenicline and placebo. Varenicline was administered open-label and titrated in an identical manner to that previously discussed. Medication was started the day after baseline visit and the TQD was set as day 8 of therapy for all patients. During each clinic visit, participants received brief behavioral counseling. Tobacco use status, vital signs, exhaled-air CO measurements, and weight were obtained at each visit. A level of ≤ 8 ppm CO was considered to verify self-reported smoking abstinence. Additionally, participants completed tobacco craving and nicotine withdrawal assessment using a daily diary. Adherence was assessed through pill counts at each visit and self-reports of missed doses.

Primary endpoints included: 12-week abstinence rates, defined as prolonged (no smoking from 2 weeks after target quit date) abstinence and 7-day point-prevalence (no smoking in the past 7 days) abstinence (9). Secondary endpoints included: prolonged and point-prevalence smoking abstinence rates at weeks 26 and 52, tobacco craving and nicotine withdrawal symptoms, and weight changes. Preplanned exploratory analysis of age, sex, baseline smoking rate, and level of nicotine dependence were also conducted.

Results displayed significantly higher prolonged abstinence rate at 12 weeks (OR = 1.49; 95% CI = 1.05–2.12; p value 0.03) and 26 weeks (OR = 1.52; 95% CI = 1.04–2.22; p value 0.03) with combination therapy (9). There were no significant differences observed between groups for prolonged abstinence at 52 weeks (OR = 1.39; 95% CI = 0.93–2.07; p value 0.11) or 7-day point-prevalence at any time-point. However, heavier smokers (≥ 20 cigarettes/day) showed a statistically significant difference in abstinence rates between combination and monotherapy in 7-day point-prevalence at weeks 26 (OR = 1.79; 95% CI = 1.09–2.96; p value 0.02) and 52 (OR = 1.76; 95% CI = 1.06–2.93; p value 0.03). Prolonged smoking abstinence was also significantly different in the heavier smokers group at weeks 12 (OR = 1.84; 95% CI = 1.16–2.93; p value 0.01), 26 (OR = 2.24; 95% CI = 1.32–3.81; p value 0.003) and 52 (OR = 2.26; 95% CI = 1.31–3.92; p value 0.004). Light smokers in the combination group did not show a significant difference versus monotherapy at any time-point. Highly addicted smokers (Fagerström Test for Nicotine Dependence [FTND] ≥ 6) showed a significant difference versus monotherapy at all prolonged smoking abstinence time-points (week 12: [OR = 1.74; 95% CI = 1.04–2.93; p value 0.04], week 26: [OR = 2.76; 95% CI = 1.47–5.21; p value 0.002], and week 52: [OR =

2.77; 95% CI 1.44–5.30; *p* value 0.002]), and in 7-day point-prevalence at week 52 (OR = 2.04; 95% CI = 1.14–3.66; *p* value 0.02). However, those participants with low/moderate dependence did not show a significant difference at any time point for 7-day point-prevalence or prolonged smoking cessation. Despite the increased efficacy in terms of smoking abstinence, no difference in nicotine withdrawal or craving symptoms were noted between the two groups (mean treatment difference for withdrawal: +0.4; 95% CI = −0.02 to + 0.10; mean treatment difference for craving +0.05; 95% CI = −0.2 to +0.3), though these results were not stratified based on heavy versus light smoker status. Exploratory analyses showed no treatment difference based on age or gender (*p* > 0.25 for both).

Issa et al. conducted a retrospective outcome study to assess the efficacy of varenicline monotherapy compared to varenicline and bupropion, varenicline and SSRI, or varenicline, bupropion, and SSRI (10). Primary outcome was CAR at 52 weeks; 476 consecutive patients who received a prescription for varenicline from a single institution in Brazil were included. Varenicline was prescribed as part of a cardiovascular smoking cessation service in patients who had failed previous attempts with NRT or bupropion, or were currently smoking ≥ one pack of cigarettes per day. Of these 476 patients, 49 never started taking varenicline and therefore, data was collected in 427. Treatment consisted of an initial medical visit and an average of five or more follow up visits in-person or by phone over 52 weeks. Presence and intensity of abstinence symptoms were monitored and adverse events (AEs) collected at each visit utilizing a previously non-validated psychometric questionnaire (Programa de Assistencia ao Fumante, or PAF) developed by the smoking cessation program to evaluate comfort according to presence and degree of craving, irritability, anxiety, impatience, depression/mood, attention disturbance, appetite changes, insomnia, restlessness and headache. Additionally, weight and CO concentration were collected at each visit. Patients also received drug treatment and behavioral counseling from physicians specialized in smoking cessation.

If patients were taking bupropion or an SSRI prior to receiving varenicline, these drugs were continued (10). All patients included were prescribed varenicline 2 mg daily until week 12 and whether to add bupropion and/or SSRI was determined after initiation of therapy. Bupropion 150 mg daily (half the dose of other studies) was added if patients did not achieve complete abstinence after 2 or 3 weeks of starting varenicline, or if they achieved complete abstinence, but presented moderate/intense abstinence symptoms according to the PAF. Patients were coadministered a SSRI (most commonly sertraline), regardless of receipt of bupropion or current smoking status, if the patients showed depression symptoms or mood changes after varenicline initiation. Analysis was performed on four treatment groups: varenicline alone (*n* = 262), varenicline + bupropion (*n* = 60), varenicline + SSRI (*n* = 79), and varenicline + bupropion + SSRI (*n* = 26). Outcomes were classified into success group (CAR at 52 weeks confirmed by CO concentration), relapse group (did not complete 52 weeks of CAR) and failure group (never achieved CAR after starting varenicline).

Of the 427 patients evaluated, 112 (26.2%) failed treatment, 143 (33.5%) relapsed, and 172 (40.3%) achieved 52-week CAR (10). Within the success group, a higher prevalence of adjuvant therapy was seen (bupropion 19.2%, SSRI 23.3%, and bupropion + SSRI 8.7%) compared to the relapse group (bupropion 11.2%, SSRI 19.6% and bupropion + SSRI 4.9%) and the failure group (bupropion 9.8%, SSRI 9.8% and bupropion + SSRI 3.6%) (*p* < 0.001). Specifically assessing varenicline and bupropion combination, failure rates were higher in the varenicline monotherapy group compared to the varenicline + bupropion group (32.8% and 18.3%, respectively; *p* = 0.003). Success rates (52-week CAR) were also lower in the varenicline monotherapy group (32.1%) compared to the varenicline + bupropion treatment group (55.0%) (*p* < 0.001). SSRI use was associated with significantly higher abstinence rates than varenicline monotherapy in a multivariate analysis, both in the varenicline + SSRI (OR 3.58, 95% CI 1.98–6.48) and varenicline + bupropion + SSRI (OR 5.05, 95% CI 1.99–12.80) arms. Bupropion and SSRI groups were not directly compared but displayed similar results compared with monotherapy.

Adverse events

Each of the three prospective studies evaluated AEs, showing combination treatment to be well-tolerated, with adverse effects similar to that of the control group (4,8,9). In each of these studies, very few serious AEs were reported, and none determined to be related to the study drugs. The most common AEs that occurred were also common AEs of either drug as monotherapy. While bupropion monotherapy was not included as a treatment arm in the three studies, common AEs of bupropion monotherapy include headache, agitation, dizziness, and insomnia (6). The most common AEs with varenicline monotherapy include: headache, insomnia, abnormal dreams, and suicidal ideation (5). Both medications have a black box warning for suicidal ideation. None of the trials reported any cases

of suicidal ideation as an adverse effect. However, the percentage of patients experiencing such effects, nor discussion of a complete absence of such effects among participants, was not specifically addressed in the published results. Additionally, patients were excluded from each of the prospective trials if they had a past medical history significant for psychiatric illness or untreated depression. Therefore, based on the studies included in this review, insufficient evidence exists to predict the potential harm if the combination were to be administered in this high risk patient population. In the retrospective trial, AEs were not specifically reported.

The Phase III trial conducted by Ebbert et al. identified anxiety (18% with combotherapy vs. 8% with monotherapy; p value 0.04) and depressive symptoms (9% with combotherapy vs. 2% with monotherapy; p value 0.03) as the only AEs occurring more commonly with combination therapy (9). Flatulence was more common in the varenicline + placebo group (9% with monotherapy vs. 1% with combination; p value 0.02). Rose et al. stated that no significant difference in the incidence of adverse effects existed between the two treatment groups (4). Specific frequencies of each side-effect per treatment group were not published, though AEs that were rated more than moderate in severity and occurred with a frequency > 5% for the entire study population were listed. Those AEs included: headache (9.3%), diaphoresis (8.8%), nasal/sinus irritation (5.9%), change in taste perception (17.2%), dry mouth (10.8%), thirst (15.7%), cough (8.8%), muscle/joint pain/aches (7.4%), heartburn (5.8%), nausea (5.8%), constipation (6.8%), irritability (11.3%), vivid dreams (18.1%), insomnia (13.7%), and anxiety (8.8%). While Issa et al. did not specifically report AEs, the authors did note that 15.2% of the patients that were classified as treatment failures, failed due to intense AEs, specifically nausea and abnormal dreams (10).

Weight gain was also addressed in all four studies, displaying inconsistent findings. In the phase II study, the authors noted that the participants gained more weight than varenicline monotherapy but not more than bupropion monotherapy as compared to previous studies, though as an open-label, single-arm trial there was no monotherapy group in this study to directly compare the participants' weight gain (8). Rose et al. observed that abstinent smokers gained more weight on average than non-abstainers (2.84 kg compared with 1.02 kg; p value 0.001), with no significant sex or treatment differences (4). Mean weight gain among successful quitters was 3.05 kg for those in the combination group and 2.5 kg for those receiving varenicline plus placebo. Similarly, Issa et al. reported that successful patients gained more weight than those in the failure group, regardless of treatment arm (5.7 ± 5.8 kg vs. 0.7 ± 2.4 kg, p < 0.01, respectively) (10). However, the Phase III trial from Ebbert et al. displayed dissimilar results, as a significant difference in weight gain was observed between the two treatment groups at 12 weeks, with those receiving monotherapy gaining more weight compared to the combination group (2.5 kg [95% CI, 2.0–3.0] vs. 1.1 kg [95% CI, 0.5–1.7]; p value < 0.001, respectively) (9).

Discussion

Based on this review, recent literature demonstrates that combination bupropion SR and varenicline displays potential benefit as a treatment for smoking cessation versus varenicline alone, especially in certain subpopulations, with significant increases in adverse effects from combination therapy not shown in the current trials. However, further research is needed before conclusive statements can be made regarding the role in therapy of this treatment modality or the increased risk of utilizing these drugs in combination.

Populations studied

One difference between the trials that should be noted is the difference in patient populations studied with regard to smoking status and previous cessation treatment prior to enrollment. In both trials conducted by Ebbert, patients were only required to have been smoking 10 or more cigarettes; patients' previous smoking cessation treatments were not elucidated nor a specific determinant of inclusion or exclusion (8,9). In the trial by Rose, patients were similarly required to have been smoking 10 or more cigarettes per day, but all entered into the trial immediately after failing nicotine patch therapy (4). Finally, Issa included only patients that were currently smoking one or more packs per day or who had failed previous attempts with NRT or bupropion, though the timing of these previous attempts were not specified (10).

Subpopulation findings

Ebbert et al. demonstrated no difference in results based on sex or age (9). However, this study did demonstrate that those with a higher average cigarette consumption at baseline (≥ 20 cigarettes per day) experienced a significantly greater rate of abstinence when receiving combination therapy versus varenicline monotherapy at weeks 26 and 52, based on 7-day

point-prevalence check, as well as all prolonged abstinence time-points. Additionally, participants with a higher level of nicotine dependence (FTND ≥ 6) at baseline displayed significantly greater abstinence rates with combination therapy at the 52-week 7-day point-prevalence check and all prolonged smoking abstinence time-points. Conversely, combination therapy did not yield significantly greater results in lighter smokers (< 20 cigarettes per day) or those with FTND < 6.

Rose et al. provided additional evidence for the greater impact of combination therapy in patients with increased nicotine dependence, but contradictory to the Ebbert trial, this study also displayed a significantly greater response to combination therapy in males versus females (4). Males and those with a higher level of nicotine dependence at baseline experienced statistically significantly improved abstinence rates with combination therapy versus varenicline monotherapy at weeks 8–11 and at 6 months, whereas females and those less nicotine dependent experienced similar results regardless of treatment arm. This study also included a logistic regression model confirming significant sex-by-treatment ($p = 0.013$) and dependence-by-treatment ($p = 0.009$) interactions. However, in participants with a higher baseline-smoking rate, combination treatment trended toward greater efficacy but was not statistically significant in this trial.

While not fully elucidated, Rose and colleagues point to animal and neurological imaging studies portraying greater up-regulation of nicotine receptors in response to nicotine dependence (counteracted by bupropion's nicotinic receptor antagonism), as well as greater dopaminergic release (influenced by both bupropion and varenicline) in response to drugs of abuse in males than females as a potential mechanism for this greater efficacy displayed in men (4,8,11–18). The reason behind the greater efficacy in patients with higher levels of nicotine dependence is less clear.

The Issa et al. study included only heavy or highly dependent smokers (10). An assessment of variable efficacy based on number of cigarettes smoked was not conducted, but the authors did assess the impact of level of dependence on efficacy, showing no difference among treatment arms based on initial FTND score ($p = 0.21$). However, as dependence likely varies along a continuum, identifying a significant difference based on level of dependence may be difficult when assessing only heavy smokers. Similarly, there was no significant difference in treatment success versus failure among sexes ($p = 0.5$).

Thus, it appears as though combination bupropion SR and varenicline therapy may potentially be more beneficial in males, those with higher levels of nicotine

dependence, and heavier smokers, but further studies are needed to confirm these results as these findings were not consistently displayed.

Finally, as the combined psychiatric effects of bupropion and varenicline represent a potential area of concern, it is important to note that the trials demonstrated no cases of suicide or suicidal ideation, but that additional study, specifically in more vulnerable populations, must be conducted to fully understand the safety of this combination (4,8–10). Patients were excluded from each of the prospective trials if they had a past medical history significant for psychiatric illness or untreated depression (4,8,9). It was noted that 22 patients with depression or mood imbalance were included in the retrospective study; however, without clarification of whether or not they were well-controlled (10). Patients in this trial were allowed to continue their current depression medication during the study and those exhibiting new depression symptoms during the trial were prescribed an SSRI, providing limited insight into the safety of the combination in patients with new or worsening depression. Furthermore, a subsequent analysis of the Phase III trial conducted by Ebbert was recently published assessing the impact of the combination therapy on depression symptoms (19). This study indicated greater depressive symptoms at week 2 in the combination therapy arm, but at weeks 2–4 patients with a history of depression displayed less depressive symptoms with combination therapy. However, beyond 4 weeks, there was no difference in depressive symptoms based on treatment arm. Based on this lack of a prolonged difference on depression symptoms and the fact that overall efficacy was not affected by a history of depression, the authors concluded that in patients not currently experiencing moderate or severe symptoms, depression history should not factor into treatment choice.

Strengths and limitations

Some limitations to this systematic review exist. First, only four studies were identified that met the criteria for inclusion, one of which was a small, non-controlled, open-label Phase II study and another was a retrospective outcomes study (i.e. patients were not randomized to a specific treatment arm, but instead treated open-label at the providers' discretion with outcomes collected and evaluated retrospectively, thus increasing the potential for inconsistency in treatment decisions and added bias compared with a randomized trial). Additionally, analysis of the combined data was not performed.

Furthermore, though the studies were fairly homogeneous, some results were incongruent at different timepoints and means of assessment (i.e. differing effects at 12, 26, and 52 weeks and in point-prevalence vs. prolonged abstinence), leading to some uncertainty as to the increased efficacy of the combination. Finally, each study displayed high patient dropout rates, though such rates are consistent with previous smoking cessation trials.

In contrast, there were several strengths to this review. Both evaluators were in agreement with which studies to include, and an additional independent reviewer confirmed relevance of the included studies. The two phase III trials summarized in this review were high quality, randomized, controlled trials recently completed and similarly designed. Both studies monitored efficacy by patient-reported cessation and confirmed with CO measurements, increasing the validity of the results. Additionally, combination treatment with bupropion and varenicline was studied both in NRT non-responders (4) and as first-line therapy (8–10). Three studies compared combination treatment to an active comparator, which is a strength in the trials. However, the active comparator was varenicline in each, not providing specific head-to-head data of this combination versus other treatment modalities. Lastly, all trials identified featuring a combination varenicline and bupropion SR arm were included in this review.

Suggestions for future research

There is a need for further investigation with combination bupropion SR and varenicline treatment to increase the body of evidence assessing the safety and efficacy of this combination and determine its ideal role in therapy, particularly to solidify its safety in terms of additive CNS effects. As previously mentioned, both Phase III trials and the retrospective analysis compared combination therapy to varenicline monotherapy. Direct comparison versus other treatment modalities, such as bupropion monotherapy or combination of NRT plus bupropion or varenicline, would provide additional insight. Further investigation behind mechanisms that account for subpopulation differences would be beneficial with the conflicting data in the current studies. Based on a search of ClinicalTrials.gov, three trials evaluating combination varenicline and bupropion SR are underway with results yet unpublished (21–23). These trials will provide additional insight into the combination versus placebo and NRT and in males only (20–23). Additionally, one trial will assess the effects of varenicline, NRT, and varenicline plus bupropion through brain imaging (23).

Conclusion

In summary, the combination of bupropion SR and varenicline has been shown safe and effective in the treatment of smoking cessation in four clinical studies, with additional trials underway to provide further insight into this novel treatment modality. Early data suggest this effect may be more pronounced in males and those smoking greater numbers of cigarettes. However, further data needs to be collected to confirm these findings. This combination treatment will likely not be a first line option due to potential risks of additive CNS adverse effects. It is important to note that patients at greatest risk of such effects were excluded from each of the prospective trials and this combination should be avoided in patients with psychiatric conditions predisposing them to suicidal ideation until additional research has proven its safety in this population. However, based on the limited data available, the use of this combination may be warranted in treatment-refractory patients, as the risks of continued smoking are likely greater than the risk of the combination of these medications.

Declaration of interest

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