Combination Therapies for Smoking Cessation

A Hierarchical Bayesian Meta-Analysis

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Context: Treatment guidelines recommend the use of combination therapies for smoking cessation, particularly behavioral therapy (BT) as an adjunct to pharmacotherapy. However, these guidelines rely on previous reviews with important limitations. This study's objective was to evaluate the efficacy of combination therapies compared with monotherapies, using the most rigorous data available.

Evidence acquisition: A systematic review and meta-analysis of RCTs of pharmacotherapies, BTs, or both were conducted. The Cochrane Library, Embase, PsycINFO, and PubMed databases were systematically searched from inception to July 2015. Inclusion was restricted to RCTs reporting biochemically validated abstinence at 12 months. Direct and indirect comparisons were made in 2015 between therapies using hierarchical Bayesian models.

Evidence synthesis: The search identified 123 RCTs meeting inclusion criteria (60,774 participants), and data from 115 (57,851 participants) were meta-analyzed. Varenicline with BT increased abstinence more than other combinations of a pharmacotherapy with BT (varenicline versus bupropion: OR=1.56, 95% credible interval [CrI]=1.07, 2.34; varenicline versus nicotine patch: OR=1.65, 95% CrI=1.10, 2.51; varenicline versus short-acting nicotine-replacement therapies: OR=1.68, 95% CrI=1.15, 2.53). Adding BT to any pharmacotherapy compared with pharmacotherapy alone was inconclusive, owing to wide CrIs (OR=1.17, CrI=0.60, 2.12). Nicotine patch with short-acting nicotine-replacement therapy appears safe and increases abstinence versus nicotine-replacement monotherapy (OR=1.63, CrI=1.06, 3.03). Data are limited concerning other pharmacotherapy combinations and their safety and tolerability.

Conclusions: Evidence suggests that combination therapy benefits may be less than previously thought. Combined with BT, varenicline increases abstinence more than other pharmacotherapy with BT combinations.

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Context

Treatment guidelines, including those of the American Heart Association/American Stroke Association and the U.S. Public Health Service, recommend the use of behavioral therapy (BT) combined with pharmacotherapy for smoking cessation.[1,2] However, the guidelines are primarily based on a meta-analysis[1] with important limitations. These limitations include breaking the integrity of randomization by not restricting analyses first to within-study comparisons before making indirect

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comparisons between studies (to properly produce ratios of ORs), and not considering whether or not participants also received pharmacotherapy (i.e., data from trials that included pharmacotherapy were pooled with data from trials that did not include pharmacotherapy). Package inserts for first-line smoking-cessation therapies (i.e., nicotine replacement therapies [NRTs], bupropion, and varenicline) likewise recommend adjunctive counseling.[3–6] These recommendations are supported by a Cochrane review, which found a modest increase in abstinence with combined pharmacotherapy and BT versus pharmacotherapy alone.[7] However, this Cochrane review included trials with <12 months of follow-up and those that did not biochemically validate abstinence. A systematic review and meta-analysis of RCTs was therefore conducted to examine the long-term efficacy of combination therapies versus monotherapies, using RCTs with ≥ 12 months of follow-up that biochemically validated smoking abstinence.

Evidence Acquisition

The systematic review and meta-analysis was performed according to a prespecified protocol (PROSPERO #CRD42014007105) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[8]

Search Strategy

Designed by an experienced medical liaison librarian (GG), searches of the Cochrane Library, PubMed, Ovid Embase, and Ovid PsycINFO databases were conducted in July 2015, with no publication date restrictions. Searches were conducted using Medical Subject Headings in PubMed and the Cochrane Library, Emtree terms in Embase, Psychological Index Terms in PsycINFO, and keywords in all databases. Briefly, search terms included *smoking cessation*, *combination therapy*, *pharmacotherapy*, *behavioral therapy*, *bupropion*, *varenicline*, and *nicotine replacement therapy*. Hedges were used in PubMed,[9] Embase,[10] and PsycINFO[11] to filter results to RCTs and systematic reviews (full search strategies in Appendix A, available online).

Study Selection

Titles and abstracts of articles identified by the search were screened; any article deemed potentially relevant was carried forward for full-text review. Full-text screening was conducted independently by two reviewers (JGM and LAW), with disagreements resolved by consensus or a third reviewer (SBW). Eligibility was assessed using prespecified inclusion and exclusion criteria, as described below.

Included studies were restricted to RCTs in which at least one first-line smoking-cessation therapy (NRT, bupropion, varenicline, or BT) was compared with at least one other first-line cessation therapy or placebo (or usual care in trials of BT alone). NRTs included nicotine patch and short-acting NRTs such as nicotine gum, inhaler, nasal spray, lozenge, tablet, and mouth spray. For the purposes of this study, BT was defined as the provision of verbal instructions with the intention of modifying a health-related behavior, which in this case was smoking. This definition encompassed minimal clinical interventions (e.g., brief advice to stop smoking from a healthcare worker), individual counseling, group counseling, and telephone counseling. To be considered for inclusion, RCTs also had to report biochemically validated seven-day point prevalence smoking abstinence at 12 months or continuous smoking abstinence at 12 months. Seven-day point prevalence abstinence describes an individual's smoking status based on the seven days prior to the follow-up visit. If, during the 12-month visit, an individual reports to not have smoked in the past seven days and this self-report is confirmed by a biochemical test conducted during the visit (e.g., exhaled carbon monoxide or cotinine tests), the individual is considered abstinent according to this definition. Continuous abstinence, on the other hand, was defined by biochemically validated self-report of complete abstinence at all follow-ups. Typically, to be considered continuously abstinent, participants must have completed all follow-up visits. RCTs also had to be published in English or French, and report data from a sample of cigarette smokers motivated to quit. Studies without a statement concerning motivation to quit were assumed to meet this criterion. Exclusion criteria included abstract or conference proceedings; cluster randomization; trials conducted exclusively in light smokers (fewer than ten cigarettes/day); and trials of nicotine e-cigarettes, as these are not approved for use in smoking cessation.

Data Abstraction and Quality Assessment

Two individuals (JGM and LAW) independently abstracted data, with disagreements resolved by consensus or a third reviewer (SBW). Data were abstracted concerning study characteristics and outcomes. RCT quality was evaluated in duplicate using the Cochrane Collaboration's Tool for Assessing Risk of Bias.[12]

Statistical Analysis

The meta-analysis used Bayesian hierarchical random-effects meta-analytic models to estimate ORs and credible intervals (CrIs), the Bayesian analogue of CIs. This process involved both direct and indirect comparisons of smoking-cessation treatments. Direct comparisons involved RCTs in which participants were randomized to the treatments being compared. Data were pooled for direct comparisons that were examined in four or more RCTs; having three or fewer studies was considered insufficient to reasonably estimate between-study variance in a random-effects model. To facilitate comparisons, all BTs were grouped together for some analyses. Likewise, some analyses grouped short-acting NRTs (i.e., all NRTs except nicotine patch), all NRTs, or all pharmacotherapies. Placebo used in combination with another therapy was assumed to perform similarly to combinations that used the same therapy without adding placebo.

Indirect comparisons then allowed comparisons of therapies not directly compared in RCTs. In general, if one set of trials compared intervention A to intervention B, and another set of trials compared intervention B to intervention C, then an indirect comparison can be created that compares A to C through common comparator B. These indirect comparisons were created by estimating ORs for A versus B and B versus C using the Bayesian hierarchical meta-analytic models; the first was then divided by the

second, leading to a ratio of ORs (Appendix B, available online, describes additional meta-analytic model details). All statistical analyses were conducted in 2015, following systematic literature searches and data extraction.

Evidence Synthesis

Study and Patient Characteristics

The database search yielded 14,998 records, with two records identified from other sources (Figure 1). After removing duplicates and screening titles and abstracts, 587 articles underwent full-text review, of which 123 met the predefined inclusion criteria (60,774 participants).[13–135] These trials were conducted primarily in the general population (93 trials), and most trials recruited participants from North America, Europe, Australia/New Zealand, or some combination of these regions (117 trials). Included trials were published between 1983 and 2015 (median, 2002) and enrolled 51–3,684 participants (median, 303 participants) (detailed characteristics are provided in Appendix C, available online).

Of the 123 trials, data from 115 (57,851 participants) were included in the meta-analysis. Trials were excluded from the meta-analysis if they examined a combination of therapies for which there was an insufficient number of other studies to pool. Some trials were unable to be included owing to the merging of BTs together (e.g., a treatment arm of nicotine patch with both group and individual counseling would be considered the same as the control arm of nicotine patch with only individual counseling). Risk of bias was largely considered low or uncertain across trials for all categories (86%–98%) except blinding (58%) (Appendix D, available online). This risk of bias in blinding was primarily due to BT use in many trials, where blinding to treatment allocation was impossible. Among trials that did not include BT, the risk of bias in blinding was judged low or uncertain in all trials.

Pharmacotherapy With Behavioral Therapy Combinations

Fourteen direct comparisons were performed of smoking-cessation therapy combinations and monotherapies, including ten of BT combinations (Appendix E, available online). Results showed that any pharmacotherapy (nicotine patch, short-acting NRT, bupropion, or varenicline) combined with BT increased abstinence at 12 months versus BT alone (Figure 2A–D). These direct comparisons were supplemented by indirect comparisons, which found that varenicline with BT was more efficacious than all other combinations of a

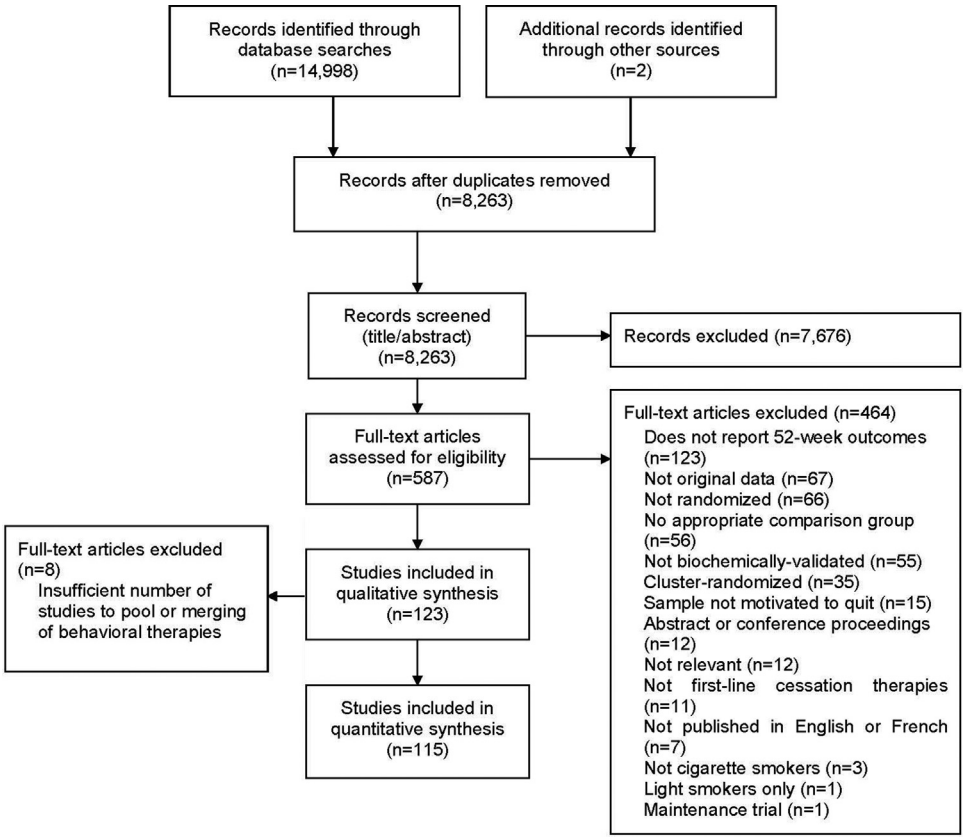

Figure 1. PRISMA flow diagram.

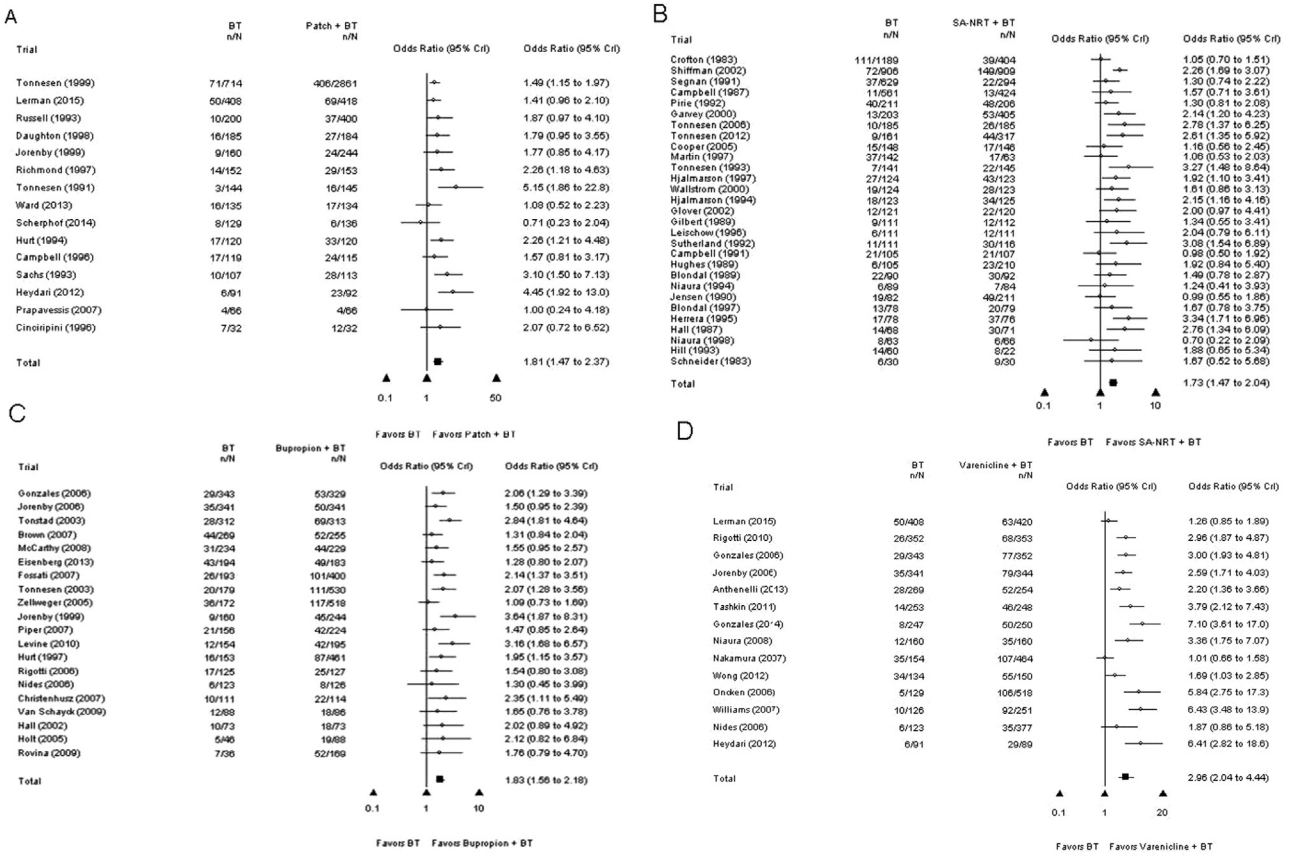

Figure 2. Pharmacotherapy + behavioral therapy versus behavioral therapy for smoking cessation at 12 months. **(A)** Nicotine patch + behavioral therapy versus behavioral therapy. **(B)** Short-acting NRT + behavioral therapy versus behavioral therapy. **(C)** Bupropion + behavioral therapy versus behavioral therapy. **(D)** Varenicline + behavioral therapy versus behavioral therapy.

BT, behavioral therapy; SA-NRT, short-acting nicotine replacement therapy

pharmacotherapy with BT (varenicline versus bupropion, OR=1.56, 95% CrI=1.07, 2.34; varenicline versus nicotine patch: OR=1.65, 95% CrI=1.10, 2.51; varenicline versus short-acting NRTs: OR=1.68, 95% CrI=1.15, 2.53), which performed similarly to each other (Table 1).

When combination pharmacotherapy with BT was compared with pharmacotherapy alone, long-term abstinence was similar between groups (Appendix F, available online). However, the CrIs were wide (e.g., OR=1.17, CrI=0.60, 2.12, for any pharmacotherapy with BT versus pharmacotherapy alone), likely owing to the small number of studies (n=7) included in this comparison. Moreover, results indicated that higher-intensity BT (i.e., individual, group, or telephone counseling) versus minimal clinical intervention did not increase abstinence in individuals prescribed a pharmacotherapy (Appendix G, available online). Likewise, a sensitivity analysis was conducted of any comparison of intensive BT versus minimal clinical intervention, regardless of adjunctive therapies, which also found no difference between groups (data not shown).

Using the most rigorous data available, this meta-analysis did not find strong evidence that BT is a necessary adjunct to pharmacotherapy, although the CrIs were wide. However, when used with BT, varenicline increased abstinence more than all other combinations of a pharmacotherapy with BT.

Pharmacotherapy With Pharmacotherapy Combinations

Data concerning the combination of two or more pharmacotherapies are limited. When all trials of combined NRTs were pooled, there was greater abstinence with combination therapy than with NRT monotherapy (OR=1.63, CrI=1.06, 3.03) (Figure 3A). All of these trials combined the nicotine patch with a short-acting NRT (three trials with gum, two with the inhaler, and one each with the nasal spray or mouth spray), compared with either the nicotine patch or a short-acting NRT alone. When the analysis was restricted to NRT combinations versus nicotine patch alone, the addition of a short-acting

Table 1. Indirect Comparisons of Smoking-Cessation Therapy Efficacy With Respect to Smoking Abstinence

Treatment group	Referent group					
	Usual care	BT	Nicotine patch + BT	Short-Acting NRT + BT	Bupropion + BT	Varenicline + BT
Usual care	**1.00**	*0.47*[a] *(0.29, 0.72)*	0.27 (0.16, 0.43)	0.27 (0.17, 0.43)	0.25 (0.15, 0.40)	0.16 (0.09, 0.28)
BT	*2.12*[a] *(1.38, 3.39)*	**1.00**	*0.55*[b] *(0.42, 0.68)*	*0.58*[c] *(0.49, 0.68)*	*0.55*[d] *(0.46, 0.64)*	*0.34*[e] *(0.23, 0.49)*
Nicotine patch + BT	3.73 (2.30, 6.28)	*1.81*[b] *(1.47, 2.37)*	**1.00**	1.02 (0.78, 1.36)	0.94 (0.72, 1.26)	0.61 (0.40, 0.91)
Short-acting NRT + BT	3.65 (2.31, 6.01)	*1.73*[c] *(1.47, 2.04)*	0.99 (0.74, 1.28)	**1.00**	0.93 (0.73, 1.17)	0.60 (0.40, 0.87)
Bupropion + BT	3.94 (2.48, 6.55)	*1.83*[d] *(1.56, 2.18)*	1.06 (0.79, 1.38)	1.08 (0.85, 1.37)	**1.00**	0.64 (0.43, 0.94)
Varenicline + BT	6.17 (3.54, 11.19)	*2.96*[e] *(2.04, 4.44)*	1.65 (1.10, 2.51)	1.68 (1.15, 2.53)	1.56 (1.07, 2.34)	**1.00**

Note: All data are presented as OR (95% CrI). Results in italics are direct comparisons on which the indirect comparisons are based. The referent group of each comparison is represented by the header of the column the result is listed under. Results to the right of the diagonal are the inverse of the results to the left of the diagonal. For example, in comparing Nicotine Patch + BT versus BT alone, Nicotine Patch + BT seems more effective in achieving smoking abstinence than BT alone, with an OR of 1.81, CrI 1.47, 2.37. The referent group in this comparison is BT alone. This can also be thought of as BT being less effective than the combination Nicotine Patch + BT, with an OR of 0.55, CrI 0.42, 0.68. In this comparison, the referent group is Nicotine Patch + BT.

[a]Estimates are based on the meta-analysis of 17 RCTs.
[b]Estimates are based on the meta-analysis of 15 RCTs.
[c]Estimates are based on the meta-analysis of 29 RCTs.
[d]Estimates are based on the meta-analysis of 20 RCTs.
[e]Estimates are based on the meta-analysis of 14 RCTs.

BT, behavioral therapy; CrI, credible interval; NRT, nicotine replacement therapy; short-acting NRT, any NRT (e.g., gum, inhaler) except nicotine patch.

NRT to the nicotine patch did not increase long-term abstinence (Figure 3B). However, the CrIs were wide, and the possibility of a difference cannot be excluded. Likewise, the combination of bupropion with NRT(s) did not increase abstinence; however, the comparison arms (e.g., bupropion monotherapy, NRT monotherapy) varied (Figure 3C).

In an additional analysis, all 12 trials that examined the efficacy of adding an additional pharmacotherapy to one or more pharmacotherapies were pooled (Figure 3D). Results showed an increase in abstinence with the use of an additional pharmacotherapy. Most trials of combination pharmacotherapies included adjunctive BT in both arms; sensitivity analyses that excluded trials without BT did not substantively alter the findings (data not shown). Overall, data concerning combination pharmacotherapies are limited, with the available evidence suggesting the combination of nicotine patch and a short-acting NRT is more efficacious than NRT monotherapy.

Safety and Tolerability

Data available regarding the safety and tolerability of combination pharmacotherapies are limited. The reporting and occurrence of serious adverse events (SAEs), including death, was rare (Appendices H and I, available online). Only six of the 12 trials examining combination pharmacotherapy versus monotherapy reported SAEs by treatment arm, of which there were 19 total in 2,392 participants (0.8%).[22,30,37,39,70,121] Six studies also specifically reported the number of deaths (or it was inferred from zero reported SAEs), of which there were six in 1,582 participants (0.4%).[21,30,37,39,113,121] SAEs and deaths appear to be similar between pharmacotherapy combination and monotherapy arms; however, the available RCTs were not powered to detect differences in these events. There was one report of attempted suicide in a trial of combination varenicline with bupropion; however, it occurred in the varenicline monotherapy arm, and there were no other reports of serious neuropsychiatric events.[37] No SAEs were considered to be related to any smoking-cessation pharmacotherapy.

The overall incidence of adverse events (AEs) and participant withdrawal due to AEs was rarely reported (Appendices H and I, available online). However, some trials included a summary statement about AEs and/or the incidence of specific AEs. In trials assessing the nicotine patch with short-acting NRT, AEs were considered to be mild, tolerable, and generally similar between groups.[22,24,30,73,95] Among trials that examined

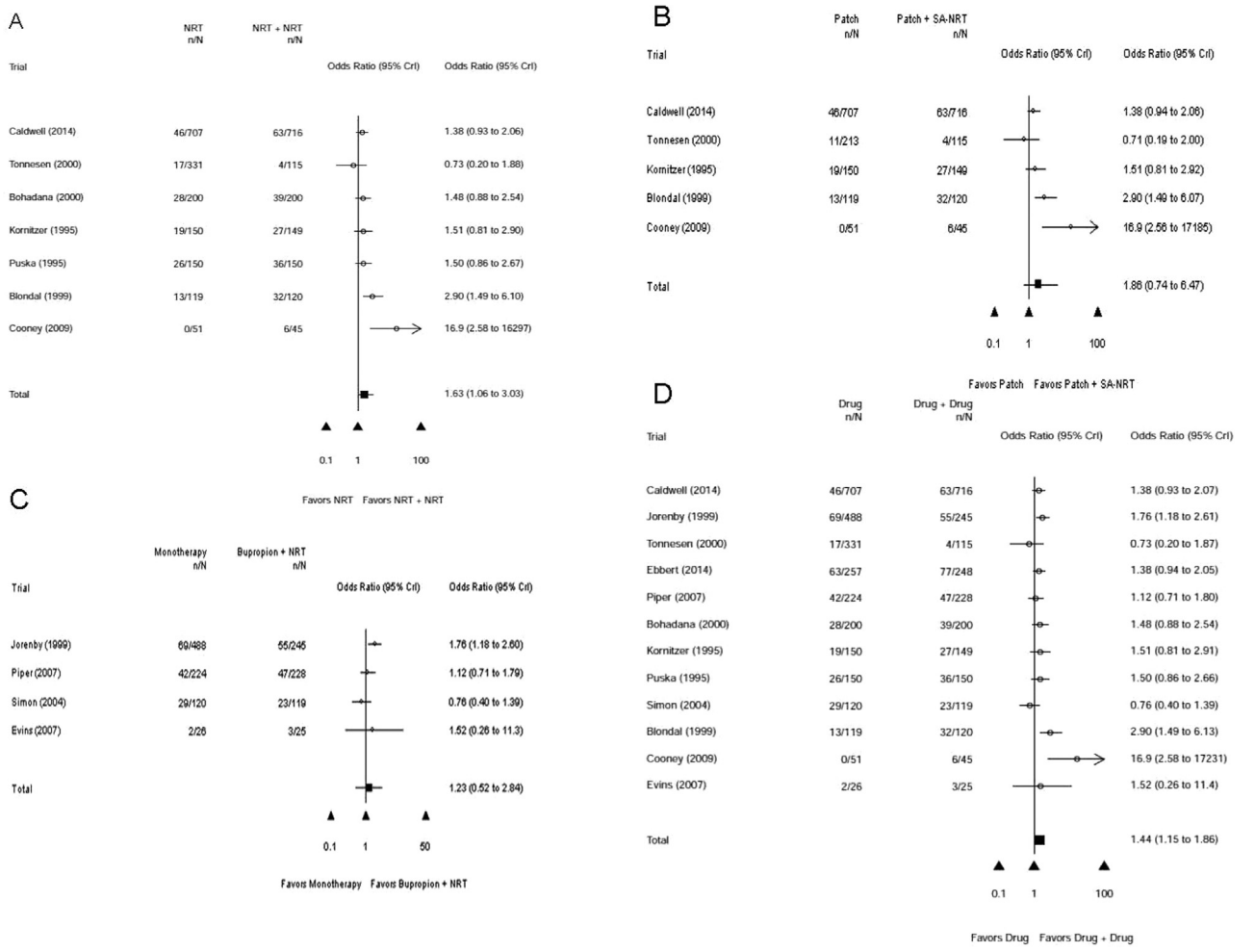

Figure 3. Combined pharmacotherapies versus monotherapies for smoking cessation at 12 months. **(A)** NRT + NRT versus NRT. **(B)** Nicotine patch + NRT versus nicotine patch. **(C)** Bupropion + NRT versus monotherapy. **(D)** Drug + drug versus drug.
Note: One included trial (Evins 2007[39]) compared a three-drug combination to a two-drug combination.
NRT, nicotine replacement therapy; SA-NRT, short-acting nicotine replacement therapy; Drug, any pharmacotherapy.

bupropion with NRTs, reported rates of treatment discontinuation were similar between combination therapy and monotherapy groups, and no AEs were consistently reported more frequently in the combination therapy group across studies.[39,70,113] A single trial (506 participants) had a combined bupropion and varenicline group versus varenicline alone.[37] In this trial, the combination therapy group had a higher rate of anxiety (7.2% versus 3.1%) and depressive symptoms (3.6% versus 0.8%) compared with the varenicline monotherapy group. All other AEs were similar between groups.

Discussion

This study was designed to assess the efficacy of combination therapy versus monotherapy for smoking cessation. Results demonstrated that among pharmacotherapy with BT combinations, varenicline increased long-term abstinence more than either bupropion or NRTs. When examining the most rigorous data available, no strong evidence was found that BT is a necessary adjunct to pharmacotherapy. Among combination pharmacotherapies, nicotine patch with a short-acting NRT appears safe and more efficacious than NRT monotherapy. Other combination pharmacotherapies may be efficacious, but available evidence is insufficient to make specific recommendations for their use at this time.

Combination therapies for smoking cessation have been examined previously. However, these reviews did not restrict inclusion to trials with $\geq$12 months of follow-up nor require biochemical validation of abstinence.[136–141] Consistent findings include the superiority of varenicline over bupropion[136,137] and the similar performance of bupropion and NRTs, when pharmacotherapies are combined with BT.[136,137] Some of the present findings contradict a Cochrane review conducted in 2012,[7] and the review

on which the U.S. Public Health Service clinical practice guideline for treating tobacco use and dependence and the American Heart Association/American Stroke Association stroke prevention guidelines are based.[1]

The Cochrane review found an increase in abstinence with combined pharmacotherapy and BT versus pharmacotherapy alone (relative risk [RR]=1.25, 95% CI=1.08, 1.45). The review also found a small increase in abstinence with higher-intensity versus lower-intensity adjunctive BT (RR=1.16, 95% CI=1.09, 1.24). The discordance between these results and those of the present study is likely attributable to the Cochrane review's inclusion of trials with <12 months of follow-up. The efficacy of smoking-cessation interventions declines over time; therefore, including studies of shorter durations likely resulted in an overestimate of long-term efficacy. Moreover, the Cochrane review included trials not biochemically validating abstinence. In their sensitivity analysis, the review found the point estimate for abstinence with higher-intensity versus lower-intensity adjunctive BT was attenuated when trials not using biochemical validation were excluded (RR=1.09, 95% CI=0.99, 1.21). This is consistent with studies that have shown that smoking prevalence is underestimated when based solely on self-report.[142] The requirement of biochemical validation of abstinence as an inclusion criterion was meant to prevent such bias in the current study.

Several guidelines are based on a meta-analysis[1] conducted for the U.S. Public Health Service, which suggested a strong dose–response for BTs; however, it had important limitations. These limitations include not restricting analyses first to within-study comparisons before making indirect comparisons between studies (to properly produce ratios of ORs), and pooling data from trials that included pharmacotherapy with data from those that did not include pharmacotherapy. These limitations make it difficult to draw conclusions from this review, despite its use in guidelines to support the use of BT with pharmacotherapy. Using the most rigorous evidence available, the current meta-analysis was unable to draw definitive conclusions about the necessity of adjunctive BT in users of pharmacotherapy.

There is a strong underlying rationale to suggest that pharmacotherapy combinations could increase abstinence. Although the mechanism for NRTs is the same across delivery methods, a short-acting NRT can be used to relieve acute cravings in users of the nicotine patch. Indeed, a previous review of NRTs found that the combination of nicotine patch and short-acting NRT increased abstinence versus NRT monotherapy[137]; this meta-analysis suggests that this remains true through ≥1 year in biochemically validated trials.

The unique mechanisms of action of both bupropion and varenicline make these drugs potential candidates for use in combination with NRTs or with each other. A previous review found combination bupropion with NRT to be modestly more efficacious than bupropion alone (RR=1.24, 95% CI=1.06, 1.45)[137]; both this review (OR=1.23, CrI=0.52, 2.88) and a recent review of antidepressants (including bupropion) for smoking cessation (RR=1.19, 95% CI=0.94, 1.51)[137] did not find an increase in abstinence, although the point estimates were similar. This difference likely reflects the use of a fixed-effects model in the NRT review, versus the random-effects models used in the other analyses. This review and a previous review of nicotine receptor partial agonists[137] did not identify any eligible trials of varenicline in combination with NRT, a practice that is not recommended by the manufacturer based on an increase in side effects in a small, unpublished study.[3]

No previous reviews specifically considered the occurrence of AEs with combination pharmacotherapies versus a single drug alone.[136,137] The data from the current review, particularly for combination NRTs, suggest that combinations are safe and tolerable. Safety and tolerability data remain limited for other combination therapies, including bupropion and varenicline, which have the potential for a favorable risk–benefit ratio.

Limitations

This study had several potential limitations. First, when pooling data across trials, there is the potential for heterogeneity in study design, population, and interventions. This is particularly true for BTs, for which varying modes and intensities were grouped in the meta-analysis. However, given the heterogeneity between included trials in the intensity and duration of BTs, the authors chose to group them to facilitate the analysis. Although the inclusion of minimal clinical interventions with more intensive BTs may, in theory, dilute treatment effects, the authors previously showed that all BTs, regardless of their intensity, have similar smoking abstinence effects at 12 months.[143] In addition, random-effects models that accounted for both between- and within-study heterogeneity were employed. Moreover, several subgroup analyses were conducted to explicitly examine sources of this heterogeneity. Second, the grouping of minimal clinical intervention with more intensive modes of BT does not account for the fact that such briefly provided advice and support is now routinely offered to smokers as part of routine care, whether or not they receive some other form of cessation therapy. However, it is for this reason that such interventions were provided as part of the standard of care in many of the more recent trials included in this study. Third, a limitation inherent in indirect comparisons is the assumption that the effects of interest are constant across trials (e.g., when indirectly comparing A versus B and B versus C, the assumption is

that the effect of B is constant). The absolute treatment effects (i.e., the proportion of abstinent participants) were examined for therapies that were treated as constant for the purposes of indirect comparisons, and the assumption was found to be valid (i.e., there were no large differences between comparators). Fourth, many of the treatment comparisons of interest were examined in a limited number of trials, in part because of the use of strict inclusion criteria requiring biochemically validated smoking abstinence at $\geq$12 months. This therefore reduced the number of eligible RCTs and impacted the precision of estimates. However, by decreasing potential misclassification of smoking status, the results have increased validity compared with reviews that did not require biochemical validation. The strict inclusion criteria may have also impacted the availability of data concerning safety and tolerability, which were limited.

Conclusions

This meta-analysis of combination therapies for smoking cessation found several key differences compared with previous reviews. With inclusion restricted to evidence from long-term, biochemically validated trials, this meta-analysis suggests that the benefits of combination behavioral and pharmacotherapy may be less than previously thought. Varenicline with BT increased abstinence more than all other combinations of a pharmacotherapy with BT. If NRT is desired, the combination of nicotine patch and a short-acting NRT should be recommended above a single NRT. There is currently insufficient evidence to recommend combination pharmacotherapies that include bupropion or varenicline.

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Appendix

Supplementary data

Supplementary data associated with this article can be found at http://dx.doi.org/10.1016/j.amepre.2016.07.011.