JAMA Psychiatry | Original Investigation

Combining Antidepressants vs Antidepressant Monotherapy for Treatment of Patients With Acute Depression
A Systematic Review and Meta-analysis

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IMPORTANCE Combining antidepressants is frequently done in the treatment of acute depression, but studies have yielded conflicting results.

OBJECTIVE To conduct a systematic review and meta-analysis assessing efficacy and tolerability of combination therapy. Combinations using presynaptic α2-autoreceptor antagonists or bupropion were investigated separately.

DATA SOURCES MEDLINE, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials were systematically searched from each database inception through January 2020.

STUDY SELECTION Randomized clinical trials (RCTs) comparing combinations of antidepressants with antidepressant monotherapy in adult patients with acute depression were included.

DATA EXTRACTION AND SYNTHESIS Following guidelines from Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and recommendations from the Cochrane Handbook, 2 reviewers independently performed a literature search, study selection, data extraction, and evaluation of risk of bias. Data were pooled in random-effects analyses.

MAIN OUTCOMES AND MEASURES Primary outcome was efficacy measured as standardized mean difference (SMD); secondary outcomes were response, remission, change from baseline in rating scale scores, number of dropouts, and number of dropouts due to adverse events.

RESULTS Thirty-nine RCTs including 6751 patients were eligible. Combination treatment was statistically significantly associated with superior treatment outcomes relative to monotherapy (SMD = 0.31; 95% CI, 0.19-0.44). Combining a reuptake inhibitor with an antagonist of presynaptic α2-autoreceptors was superior to other combinations (SMD = 0.37; 95% CI, 0.19-0.55). Bupropion combinations were not superior to monotherapy (SMD = 0.10; 95% CI, −0.07 to 0.27). Numbers of dropouts and dropouts due to adverse events did not differ between treatments. Studies were heterogeneous, and there was indication of publication bias (Egger test result was positive; $P = .007$, $df = 36$), but results remained robust across prespecified secondary outcomes and sensitivity and subgroup analyses, including analyses restricted to studies with low risk of bias.

CONCLUSIONS AND RELEVANCE In this meta-analysis of RCTs comparing combinations of antidepressants with antidepressant monotherapy, combining antidepressants was associated with superior treatment outcomes but not with more patients dropping out of treatment. Combinations using an antagonist of presynaptic α2-autoreceptors may be preferable and may be applied as a first-line treatment in severe cases of depression and for patients considered nonresponders.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2021.4313
Published online February 16, 2022.

Supplemental content

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Guidelines by the National Institute for Health and Care Excellence,[1] American Psychological Association,[2] and American Psychiatric Association,[3] as well as the German National Clinical Practice Guideline[4] recommend use of a single, non-monoamine oxidase inhibitor antidepressant as initial treatment in severe depression. Despite a host of antidepressant agents, response rates to initial antidepressant monotherapy hover at 60%, and remissions occur in only up to 40% of patients, even after 12 to 24 weeks of treatment.[5]

Guidelines advocate a number of second-step treatments for patients considered nonresponders, most prominently switching to a different monotherapy, dose escalation, augmentation (eg, with lithium or second-generation antipsychotics), or combining 2 antidepressants.[1,2,6] Combining 2 antidepressants is a common next step, particularly in primary care settings,[7,8] based on the assumption that combining 2 antidepressants with different modes of action increases clinical efficacy.

In a previous meta-analysis,[9] we showed that, compared with monotherapy, combination therapy is more effective and comparably tolerable as a treatment for acute depression, most notably when applied as a first-line treatment. We also found that this was particularly the case for combinations that include monoamine reuptake inhibitors (selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant) and antagonists of presynaptic α2-autoreceptors (mianserin, mirtazapine, trazodone). In the meantime, several important studies have been published, presenting partly contradictory results.[10-13] Based on complementary mechanisms of action, combining mirtazapine or bupropion with reuptake inhibitors has been viewed as particularly promising, with regard to both efficacy and tolerability.[9,14] In light of these recent developments, an updated synopsis of the evidence is warranted.

This systematic review and meta-analysis of randomized clinical trials (RCTs) comparing combinations of 2 antidepressants with antidepressant monotherapy in adults with acute depression addresses a number of questions. What is the efficacy of combination therapy, relative to monotherapy, both as first-line treatment and as treatment for nonresponders? Are combination treatments that include mirtazapine or bupropion particularly effective? What is the comparative tolerability of combination therapies?

Key Points

Question What is the treatment efficacy and tolerability of antidepressant combination therapy compared with monotherapy in the treatment of acute depression, and are specific combinations preferable to others?

Findings This meta-analysis of 39 trials comprising 6751 patients found that combination treatment using a reuptake inhibitor with an antagonist of presynaptic α2-autoreceptors (mianserin, mirtazapine, trazodone) was associated with significantly superior treatment outcomes compared with monotherapy, both as first-line treatment and for nonresponder populations. The dropout numbers did not differ between treatments.

Meaning Combination therapy using an antagonist of presynaptic α2-autoreceptors may be an effective and safe antidepressant treatment option for patients who are nonresponders to monotherapy and as a potential first-line treatment in severe cases of depression.

Methods

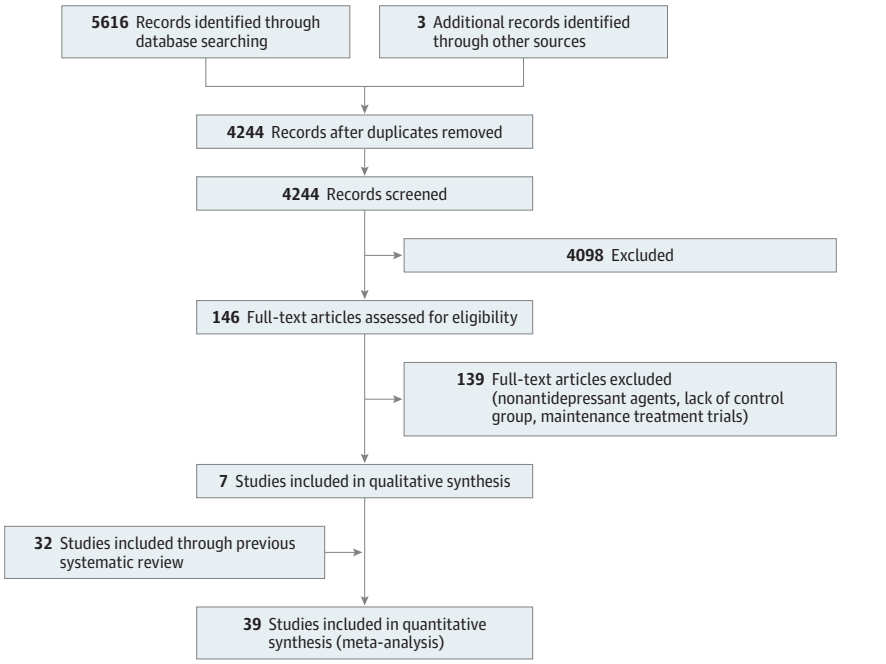
The protocol of this study has been published on PROSPERO (CRD42020167739). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guidelines for systematic reviews[15] and closely adhered to recommendations from the Cochrane Collaboration.[16] The methods are described in detail in the eMethods and eAppendix in the Supplement. In brief, we searched MEDLINE, PsycINFO, Embase, and the Cochrane Central Register of Controlled Trials and selected RCTs meeting the following criteria: an intervention using a combination of 2 antidepressants, irrespective of dosage; a control group of patients taking antidepressant monotherapy; inclusion of participants 18 years or older; and depressive disorder diagnosed according to standard operationalized criteria. Comorbid medical conditions and concomitant diagnoses of other psychiatric disorders were not exclusion criteria. Studies solely focusing on bipolar depression were excluded. We also excluded trials of maintenance therapy. Trials of first-line treatment and trials with patients who had resistance to previous antidepressive treatments were eligible, including both initial combination therapy and adjunctive administration of a second antidepressant. In first-line studies, after randomization, monotherapy control groups received antidepressant monotherapy. In studies including patients resistant to previous antidepressive treatment, monotherapy control-group patients received either ongoing monotherapy with the same antidepressant (the same dose or an increased dose) or monotherapy with a different (switched) antidepressant.

Literature search, study selection, data extraction, and evaluation of risk of bias all were carried out independently by 2 reviewers (J.H. and D.A.) and followed the Cochrane Collaboration Handbook.[16] The included studies were added to the trials retrieved by our previous systematic search,[9] and all analyses were based on the combined set of studies, thus covering all available evidence from the inception of each database to January 1, 2020.

The primary outcome criterion was treatment efficacy measured as the standardized mean difference (SMD) between combination and monotherapy, on an intention-to-treat basis, if possible. Secondary outcome criteria were remission (score below predetermined thresholds, eg, ≤7 on the 17-item Hamilton Depression Rating Scale [HDRS]) and response (eg, ≥50% decrease on the 17-item HDRS or the Montgomery-Asberg Depression Rating Scale [MADRS]) as defined by the study authors, change from baseline on a rating scale score, and numbers of dropouts and dropouts due to adverse events.

Prespecified subgroup analyses included studies with nonresponders to previous treatment trials and with patients new

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flowchart



to treatment, combinations including antagonists of presynaptic α2-autoreceptors and combinations including bupropion, and RCTs with low risk of bias. Following the Cochrane Handbook,[16] RCTs were evaluated according to the Cochrane risk-of-bias tool, taking into account random sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective reporting; sponsorship; and other potential sources of bias. An overall assessment of risk of bias (low or unknown/high) was added. Summary SMDs and odds ratios (with 95% CI) were calculated in random-effects meta-analyses because included studies differed methodologically, eg, in regard to blinding or diagnostic criteria and the assessment scales used. Meta-regression analyses carried out post hoc investigated a possible association of baseline depression severity with effect size. Statistical significance was set at $\alpha = .05$ (2-sided) for the primary, hypothesis-testing outcome. For all secondary outcomes and for all subgroup analyses, *P* values are presented, but not as a marker of statistical significance. Data analyses were carried out with Comprehensive Meta-analysis software (Version 3, Professional version; Biostat).

During screening of titles and abstracts, most articles were excluded because they did not report on combination treatment, RCTs, or clinical depression.

Results

Our database search retrieved 4244 different articles. During screening of titles and abstracts, most articles were excluded because they did not report on combination treatment, RCTs, or clinical depression. The full texts of 146 articles were read and 7 new studies included. In addition to the previously retrieved set of trials, this amounted to a final set of 39 studies as a basis for the analyses (**Figure 1**).

In total, trials included 6751 patients. Publication dates ranged from 1977 to 2020. Articles were published in English, Chinese (1 article), and Korean (1 article). Twenty-three studies (59%) were double-blind, 5 studies single-blind, and 11 studies open-label. Twenty-one trials (54%) recruited nonresponders to initial antidepressant treatment. (**Table 1** lists study groups, trial size, and initial antidepressant pharmacotherapy in nonresponder studies.) According to the published reports, only 1 of the studies[17] included patients previously exposed to antidepressant combination treatment.

Primary Outcome

Of 39 studies included, 38 trial reports provided data on the primary outcome. The SMD was 0.31 (95% CI, 0.19-0.44) in favor of combination treatment ($P < .001$). Thirty-one of 38 studies (82%) suggested superior efficacy of combination treatments. Between-study heterogeneity was $I^2 = 77.5\%$ and τ was 0.296 (**Figure 2**).

Combination therapy was associated with superior outcomes when analyses were restricted to studies of low risk of bias (SMD = 0.29; 95% CI, 0.15-0.42), among nonresponder populations (SMD = 0.18; 95% CI, 0.04-0.33), and when applied as a first-line treatment (SMD = 0.52; 95% CI, 0.24-0.79) (eFigure 1 and eFigure 2 in the Supplement).

Table 1. Characteristics of Trials

Source	Diagnosis	No.	Follow-up, wk	ITT population, No.		Blinding	Nonresponder only	Risk of bias	Depression severity at baseline[a]
				Combination	Monotherapy				
Bares et al,[17] 2013	MDD, *DSM-IV*, at least stage 1 criteria for resistant depression (≥1 adequate antidepressant treatment in current episode), including prior combination treatment	61	6	Variable, n = 31	Variable, n = 29	Open	Y	Unknown/high	MADRS, C: 28.6 (3.2), M: 28.4 (3.2)[b]
Blier et al,[18] 2009	MD, *DSM-IV*	61	6	Mirtazapine (15-45 mg/d) + paroxetine (10-30 mg/d), n = 21	Paroxetine (10-30 mg), n = 19; or mirtazapine (15-45 mg), n = 21	Double	N (first-line)	Low	MADRS, C: 34.4 (7.2), M: 32.2 (5.9); 32.0 (6.4)[c]
Blier et al,[19] 2010	MDD, *DSM-IV*	105	6	Mirtazapine (30 mg/d) + fluoxetine (20 mg/d), n = 25; mirtazapine (30 mg/d) + venlafaxine (75 mg increased to 225 mg/d), n = 26; mirtazapine + bupropion (150 mg/d), n = 26	Fluoxetine (20 mg/d), n = 28	Double	N (first-line)	Low	MADRS, C: 32.4 (5); 31.7 (4.1); 31.0 (4.1); M: 31.8 (4.8). HAMD-17, C: 22.4 (3.5); 22.6 (3.1); 21.7 (2.6); M: 22.6 (3.0)
Carpenter et al,[20] 2002	MD episode, *DSM-IV*; significant persistent depressive symptoms despite ≥4 wk of standard antidepressant monotherapy at maximum recommended or tolerated doses	26	4	Mirtazapine (15-30 mg/d) + primary antidepressant, n = 11	Primary antidepressant agents continued at prestudy daily doses throughout augmentation trial (bupropion 450 mg, citalopram 30-60 mg, fluoxetine 40-50 mg, fluvoxamine 300 mg, paroxetine 30-40 mg, sertraline 100-200 mg, venlafaxine 200-300 mg), n = 15	Double	Y	Low	HDRS-17, C: 21.9 (3.8), M: 22.5 (5.8)
Cha et al,[21] 1997	*DSM-IV*	36	6	Dothiepin (75 mg/d, dose increase due to clinical state) + sertraline (75 mg/d, dose increase due to clinical state), n = 20	Dothiepin (150 mg/d, dose increase due to clinical state), n = 16	Open	N (first-line)	Unknown/high	HAMD-17, C: 22.9 (6.0), M: 21.0 (4.8)[b]
Dam et al,[22] 1998	Depression, *ICD-10*, moderate to severe degree (corresponding to a *DSM-III-R* diagnosis of MD)	34	6	Mianserin (30 mg/d) + fluoxetine (20 mg/d), n = 16	Fluoxetine (20 mg/d), n = 18	Double	N (first-line)	Unknown/high	HAMD, median (range), C: 25.0 (20-34), M: 21.5 (17-30)
Fang et al,[23,24] 2010/2011	MDD *DSM-IV*, stage 2 TRD, failed response to 2 or more adequate treatments from different classes of antidepressants in current depressive episode	197	8	Paroxetine (20 mg/d) + trazodone (100 mg/d), n = 47	Venlafaxine XR (225 mg/d), n = 50; mirtazapine (45 mg/d), n = 55; paroxetine (20 mg/d), n = 45	Double	Y	Unknown/high	HDRS-17, 24.6 (5.8) (only whole-sample data)
Fava et al,[25] 1994	MDD, *DSM-III-R-Patient Edition*, refractoriness to initial fluoxetine 20 mg/d for 8 wk	27	4	Fluoxetine (20 mg/d) + desipramine (25-50 mg/d), n = 12	Fluoxetine (40-60 mg/d), n = 15	Double	Y	Unknown/high	HAMD-17, C: 17.5 (4.7), M: 16.2 (3.9)
Fava et al,[26] 2002	MDD, *DSM-III-R-Patient Edition*, refractoriness to initial fluoxetine 20 mg/d for 8 wk	67	4	Fluoxetine (20 mg/d) + desipramine (25-50 mg/d), n = 34	Fluoxetine (40-60 mg/d), n = 33	Double	Y (+ partial)	Unknown/high	HAMD-17, C: 19.6 (3.1), M: 17.7 (3.4)
Ferreri et al,[27] 2001	MDD, *DSM III-R*, nonresponders to 6 wk of fluoxetine 20 mg/d	103	6	Fluoxetine (20 mg/d) + mianserin (60 mg/d), n = 32	Mianserin (60 mg/d), n = 33; fluoxetine (20 mg/d), n = 38	Double	Y	Low	HAMD-17, C: 27.7 (1.9), M: 27.1 (2.52); 26.9 (1.9)

(continued)

Table 1. Characteristics of Trials (continued)

Source	Diagnosis	No.	Follow-up, wk	ITT population, No.		Blinding	Nonresponder only	Risk of bias	Depression severity at baseline[a]
				Combination	Monotherapy				
Fornaro et al,[28] 2014	MD episode with atypical features, *DSM-IV*, SCID-I/P, and a HAMD-21 baseline score ≥14, documented TRD history concerning ≥1 previous "adequate" SSRI trial	48	6	Duloxetine (60-120 mg/d, mean dose: 86.09 mg/d) + bupropion (150-300 mg/d, mean dose: 215.22 mg/d), n = 23	Duloxetine (60-120 mg/d, mean dose: 91.30 mg/d), n = 23	Double	Y	Low	HAMD-21, C: 26.82 (6.15), M: 27.30 (7.71)
Gulrez et al,[29] 2012	MDD, *DSM-IV-TR*, partial responders to SSRI treatment, ie, HDRS score ≥16 after 4 wk of SSRI	60	4	SSRI (escitalopram 10-30 mg/d, citalopram 20-60 mg/d, paroxetine 25-75 mg/d, sertraline 50-200 mg/d) + bupropion SR (300 mg/d), n = 30	SSRI (dosing see left) + placebo, n = 30	Single	Y	Unknown/high	HDRS, C: 17.80 (0.60), M: 17.57 (0.48)[d]
Jie et al,[30] 2019	Depression, *CCMD-3* diagnostic criteria for depression, ie, HAMD-17 score >18	104	12	Fluoxetine (20 mg increased to 60 mg/d) + amitriptyline (≥150 mg/d), n = 52	Fluoxetine (20 mg increased to 60 mg/d), n = 52	Open	N (first-line)	Unknown/high	HAMD-17, C: 25.97 (3.75), M: 25.03 (3.35)
Kato et al,[31] 2017	MDD *DSM-IV*, HAMD-17 > 14/17, inadequate response to 4 wk of SSRI or mirtazapine	47	4	SSRI (paroxetine or sertraline) + mirtazapine, n = 21	SSRI (paroxetine 20-40 mg/d, mean dose[e]: 38.9 ± 5.8 mg/d, or sertraline 50-100 mg/d, mean dose[e]: 91.7 ± 22.9 mg/d), n = 13; mirtazapine 30-45 mg/d, mean dose[e]: 38.4 ± 10.1 mg/d, n = 13	Open	Y	Unknown/high	HAMD-17, C: 19.3 (4.6), M: 14.4 (5.2); 13.7 (3.8)
				Dosage of antidepressant added: SSRI (paroxetine 10-40 mg/d, mean dose[e]: 33.5 ± 4.8 mg/d, or sertraline 25-100 mg/d, mean dose[e]: 65.0 ± 33.5 mg/d) + mirtazapine 15-45 mg/d, mean dose[e]: 27.5 ± 10.8 mg/d					
				Dosage of antidepressant continuously prescribed from step 1: SSRI (paroxetine 20-40 mg/d, mean dose[e]: 38.9 ± 5.8 mg/d, or sertraline 50-100 mg/d, mean dose[e]: 91.7 ± 22.9 mg/d) + mirtazapine 30-45 mg/d, mean dose[e]: 38.4 ± 10.1 mg/d					
Kato et al,[10] 2018 (SUN☺D) 6 wk	Primary diagnosis of a nonpsychotic unipolar MD episode within the past month, *DSM-IV*, PRIME-MD, nonremission (ie, PHQ-9 score >4) with 3 wk of sertraline	1647	6	Sertraline (25-100 mg/d) + mirtazapine (7.5-45 mg/d), n = 527	Sertraline (25-100 mg/d), n = 537; mirtazapine (7.5-45 mg/d), n = 550	Single (raters)	Y	Low	PHQ, C: 12.6 (5.1), M: 12.8 (5.2); 12.8 (5.2). BDI-II, C: 24.1 (10.7), M: 24.5 (10.7); 24.4 (10.9)
Kessler et al,[12] 2018 (MIR) 12 wk	Depression, *ICD-10*. TRD, BDI-II score ≥14, current treatment with an SSRI or SNRI at an adequate dose for ≥6 wk	480	12	SSRI/SNRI + mirtazapine (15 mg increased to 30 mg/d from week 3), n = 241	SSRI/SNRI + placebo, n = 239	Double	Y	Low	BDI-II score, C: 31.5 (10.2), M: 30.6 (9.6)
Lauritzen et al,[32] 1992	HDRS >16 and or a Melancholia Scale score >15. Inclusion: depressed patients aged 18-67 y who were either too ill to go through a washout period of 7 days, or who had a depressive episode of more than 1 year (prolonged depression), and depressed patients aged >67 y	40	6	Imipramine (50-100 mg/d according to target plasma level 200 nmol/L) + mianserin (30 mg/d), n = 22	Imipramine (50-100 mg/d according to target plasma level 200 nmol/L), n = 18	Double	N (first-line)	Low	HAMD-17, median (IQR), C: 25.2 (21.0-27.0), M: 22.4 (19.0-29.0)

(continued)

Table 1. Characteristics of Trials (continued)

Source	Diagnosis	No.	Follow-up, wk	ITT population, No.		Blinding	Nonresponder only	Risk of bias	Depression severity at baseline[a]
				Combination	Monotherapy				
Leuchter et al,[33,34] 2009	MDD, *DSM-IV*	220	6	Escitalopram (10 mg/d) + bupropion XL (300 mg/d), n = 74 (PP; ITT not indicated)	Escitalopram (10 mg/d), n = 73 (PP; ITT not indicated); bupropion XL (300 mg/d), n = 73 (PP; ITT not indicated)	Open	N (first-line)	Unknown/high	HAMD-17, C: 20.4 (4.3), M: 20.6 (4.4); 21.7 (4.0)[b]
Licht et al,[35] 2002	MDD, *DSM-IV*, nonresponse to 4 wk of 50 mg/d and additional 2 wk of 100 mg/d sertraline	293	5	Sertraline (100 mg/d) + mianserin (30 mg/d), n = 98	Sertraline (100 mg/d), n = 98; sertraline (200 mg/d), n = 97	Double	Y	Low	HDRS-17 median (quartiles), C: 23 (21-26), M: 23 (21-26); 23 (22-26)
Maes et al,[36] 1996	MD, *DSM-III-R*, nonresponse to ≥2 adequate trials with antidepressive agents from different classes, no prior antidepressant combination treatment	22	4	Fluoxetine (20 mg/d) + trazodone (100 mg/d), n = 12	Trazodone (100 mg/d), n = 10	Double	Both	Unknown/high	HAMD-17, no baseline data specified
Maes et al,[37] 1999	MDD, *DSM-III-R*, TRD defined as nonresponse to prior treatment with a single adequate trial with antidepressants	23	5	Fluoxetine (20 mg/d) + mianserin (30 mg/d), n = 11	Fluoxetine (20 mg/d), n = 12	Double	Both	Low	HAMD-17, C: 23.7 (4.2), M: 21.0 (4.6)
Matreja et al,[38] 2012	MDD, *ICD-10* and *DSM-IV*; newly diagnosed patients, nonresponders, or partial responders to the earlier prescribed antidepressants	60	6	SSRI (daily escitalopram 10-30 mg, citalopram 20-60 mg, sertraline 50-150 mg, fluoxetine 20-40 mg, paroxetine 10-50 mg) + low-dose mirtazapine (7.5 mg/d), n = 30	SSRI (daily dose of escitalopram 10-30 mg, citalopram 20-60 mg, sertraline 50-150 mg, fluoxetine 20-40 mg, paroxetine 10-50 mg), n = 30	Open	Both	Unknown/high	HDRS-17, C: 20.53 (0.47), M: 20.76 (0.32)[d]
Medhus et al,[39] 1994	Major depressive episode, *DSM-III*, nonresponse after treatment with adequate doses of a TCA for ≥4 wk	37	3	TCA (≥150 mg/d or maximum tolerable dose/range: 100-200 mg/d) + mianserin (60 mg/d), n = 18	TCA (≥150 mg/d or maximum tolerable dose/range: 75-225 mg/d) + placebo, n = 19	Double	Y	Unknown/high	MADRS, C: 32.6 (4.3), M: 31.7 (5.6)
Mohamed et al,[40] 2017 (VAST-D)	MDD *DSM-IV-TR*; PHQ-9; suboptimal response to SSRI, SNRI, or mirtazapin, ie, QIDS-C16 score ≥16 after ≥6 wk or a score ≥11 after ≥8 wk or treatment	1017	12	Augmentation of current antidepressive agent with bupropion SR (150 mg increased to 400 mg/d by 6 wk and kept at that level through 12 wk) + current antidepressive agent, n = 506	Switch from current antidepressive agent to bupropion SR (150 mg increased to 400 mg/d by 6 wk and kept at that level through 12 wk), n = 511	Single (raters)	Y	Unknown/high	QIDS-C16, C: 16.6 (3.2), M: 16.6 (3.3)
Murphy et al,[41] 1977	Depressive illness of sufficient severity to justify treatment with TCA	173	4	Clomipramine (10 mg/d) + desipramine (25 mg/d), n = 58	Clomipramine (10 mg/d), n = 57; desipramine (25 mg/d), n = 58	Double	N (first-line)	Low	CDR scale-17 item, mean scores, C: 22.98; M: 24.06; 23.71
Navarro et al,[11] 2019	Moderate to severe MDD episode, *DSM-IV*, after nonresponse to 10 wk of venlafaxine ER (225-300 mg/d), pretreatment HDRS-17 score ≥21	112	10	Add-on group: venlafaxine (225-300 mg/d) + mirtazapine (15 mg increased to 30 mg/d), n = 56	Switching group (from venlafaxine): imipramine (50 mg increased to 150 mg/d), n = 56	Open	Y	Unknown/high	HDRS-17, C: 28.55 (5.95), M: 27.89 (5.40)
Nelson et al,[42] 2004	Yale Depression Inventory, unipolar nonpsychotic MD	39	6	Desipramine (target plasma level 160 ng/mL) + fluoxetine (20 mg/d), n = 13	Fluoxetine (20 mg/d), n = 14; desipramine (target plasma level 160 ng/mL), n = 12	Double	N (first-line)	Low	MADRS, C: 32 (6.3), M: 37.2 (7.1); 38.3 (7.5)
O'Brien et al,[43] 1993	Research diagnostic criteria for MD	79	6	Amitriptyline (150 mg/d) + tranylcypromine (30 mg/d), n = 25	Amitriptyline (150 mg/d), n = 28; tranylcypromine (30 mg/d), n = 26	Double	N (first-line)	Unknown/high	HDRS-17: C: 22.0 (4.9), M: 24.1 (6.0); 20.8 (4.9)
Raisi et al,[44] 2007	MDD, *DSM-IV*	45	8	Nortriptyline (50 mg/d) + citalopram (40 mg/d), n = 23	Citalopram (40 mg/d), n = 22	Double	N (first-line)	Unknown/high	HAMD-17, C: 30.80 (4.16); M: 31.2 (5.07)

(continued)

Table 1. Characteristics of Trials (continued)

Source	Diagnosis	No.	Follow-up, wk	ITT population, No. Combination	Monotherapy	Blinding	Nonresponder only	Risk of bias	Depression severity at baseline[a]
Rush et al,[45] 2011	*DSM-IV-TR*, recurrent MD or chronic MD (current episode lasting ≥2 y)	665	12	Bupropion SR (150-400 mg/d) + escitalopram (10-20 mg/d), n = 221; venlafaxine ER (150-300 mg/d) + mirtazapine (15-45 mg/d), n = 220	Escitalopram (10-20 mg/d), n = 224	Single	N (first-line)	Low	HAMD-17, C: 23.8 (4.6); 24.3 (5.0); M: 23.4 (4.9)
Stewart et al,[46] 2014	MDD, *DSM-IV-TR*, MADRS ≥22	245	12	Escitalopram (10 mg/d increased to 40 mg/d) + bupropion (150 mg/d increased to 450 mg/d), n = 78	Escitalopram (10 mg/d increased to 40 mg/d), n = 84; bupropion (150 mg/d increased to 450 mg/d), n = 83	Double	N (first-line)	Low	HAMD-17, C: 21 (5), M: 20 (5); 20 (5). MADRS, C: 30 (5), M: 29 (5); 29 (5). QIDS-SR-16, C: 22 (5), M: 21 (6); 21 (5)
Tanghe et al,[47] 1997	*DSM-III-R*, MD episode, resistant to treatment with ≥2 separate antidepressants	39	4	Moclobemide (200-600 mg/d) + amitriptyline (increased to 280 mg/d), n = 20	Moclobemide (200-600 mg/d), n = 19; amitriptyline (increased to 280 mg/d), n = 19	Double	Y	Unknown/high	MADRS, C: 41.8 (6.08), M: 41.26 (8.22); 39.16 (5.1)
Vezmar et al,[48] 2009	MD, *DSM-IV*	22	2-6[f]	Amitriptyline (75 mg/d) + fluvoxamine (100 mg/d), n = 7	Amitriptyline (75 mg/d), n = 9; fluvoxamine (100 mg/d), n = 6	Open	N (first-line)	Unknown/high	HAM-D, C: 28.0 (5.5), M: 29.3 (5.8); 29.2 (8.1)
White et al,[49] 1980	Major or minor depressive disorder	30	4	Amitriptyline (50-150 mg/d) + tranylcypromine (10-15 mg/d), n = 10	Amitriptyline (75-300 mg/d), n = 9; tranylcypromine (10-20 mg/d), n = 11	Open	N (first-line)	Unknown/high	HAMD, no baseline data specified
Xiao et al,[13] 2020	MD episode, *DSM-IV*, HAMD-17 score ≥20, and ≥2 on item 1 (depressed mood), non-early response to paroxetine (≥20% decrease of HAMD-17 total score at wk 2)	204	6	Mirtazapine (30 mg/d) + paroxetine (20 mg/d), n = 68	Mirtazapine (30 mg/d), n = 68; paroxetine (20 mg/d), n = 68	Double	Y	Low	HAMD-17, C: 23.60 (3.24), M: 25.34 (4.31); 23.94 (3.47)
Xu et al,[50] 2002	Depressive neurosis according to *CCMD-2-R*	69	8	Fluoxetine (20 mg/d) + amitriptyline (37.5 mg/d), n = 21	Fluoxetine (20 mg/d), n = 21; amitriptyline (50 mg/d), n = 20	Open	N (first-line)	Unknown/high	SDS, data not available
Yang et al,[51] 2005	Refractory depression	36	6	Citalopram (20 mg increased to 40 mg/d) + amitriptylin (50 mg/d), n = 20	Citalopram (20 mg/d increased to 40 mg/d), n = 16	Single	Y	Unknown/high	HAMD, C: 28.9 (6.3), M: 28.5 (6.8)
Yazicioglu et al,[52] 2006	MDD, *DSM-IV*	43	10	Reboxetine (4 mg/d increased to 8 mg/d) + sertraline (50 mg/d), n = 21	Venlafaxine XR (75 mg/d increased to 150 mg/d), n = 22	Open	N (first-line)	Unknown/high	HDRS-17, C: 18.1 (1.7), M: 18.3 (1.6)
Young et al,[53] 1979	Mild or moderate depression not requiring ECT or inpatient admission	135	6	Trimipramine (mean: 102 mg/d) + phenelzine (mean: 44 mg/d); trimipramine (mean: 96 mg/d) + isocarboxazide (mean: 30 mg/d), n = 51	Trimipramine (mean: 106 mg/d) + placebo; phenelzine (mean: 45 mg/d) + placebo; isocarboxazide (mean: 32 mg/d) + placebo, n = 84	Double	N (first-line)	Unknown/high	HDRS, mean score, C: 22.9; 26.6, M: 22.5; 24.8; 24.8

Abbreviations: BDI, Beck Depression Inventory; C, combination therapy; CDR, Clinical Depression Rating scale; *CCMD*, Chinese Classification of Mental Disorders; ECT, electroconvulsive therapy; HDRS, Hamilton Depression Rating Scale (aka HAMD); *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; ITT, intent to treat; M, monotherapy; MADRS, Montgomery-Asberg Depression Rating Scale; MD, major depression; MDD, major depressive disorder; N, no; PHQ, Patient Health Questionnaire; PP, per protocol; PRIME-MD, Primary Care Evaluation of Mental Disorders; QIDS-C16, Quick Inventory of Depressive Symptomatology; SCID, Structured Clinical Interview for *DSM-III-R*; SDS, Self-Rating Depression Scale; SNRI, serotonin-norepinephrine reuptake inhibitor; SR, sustained release; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TRD, treatment-resistant depression; XL, extended release (aka XR); Y, yes.

[a] Values are mean (SD) unless noted otherwise.

[b] Not specified.

[c] Mean (SEM).

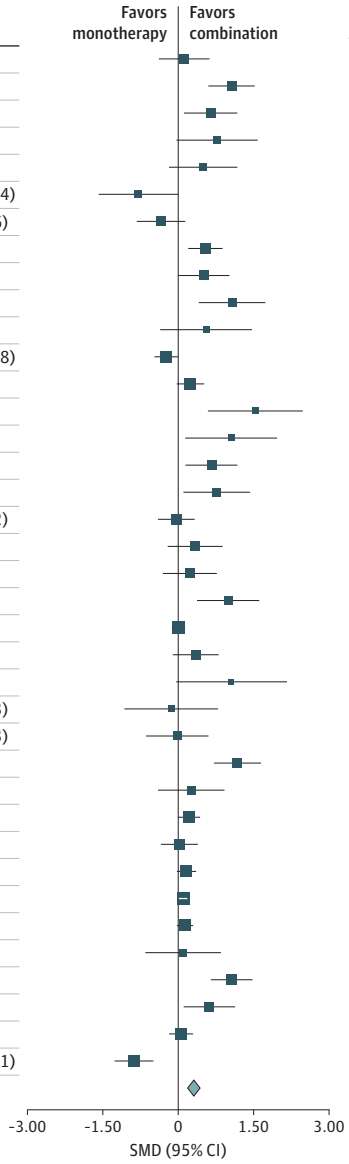
[d] Mean (SE).

[e] In week 8.

[f] Follow-up at 2 wk for response and at 4 wk and 6 wk for remission.

Figure 2. Primary Outcome: Efficacy Measured as Standardized Mean Difference (SMD)

Source	SMD (95% CI)	z Score	P value
Bares et al,[17] 2013	0.120 (-0.386 to 0.627)	0.466	.64
Blier et al,[18] 2009	1.064 (0.601 to 1.527)	4.508	<.001
Blier et al,[19] 2010	0.649 (0.117 to 1.181)	2.389	.02
Carpenter et al,[20] 2002	0.777 (-0.029 to 1.583)	1.889	.06
Dam et al,[22] 1998	0.501 (-0.183 to 1.185)	1.435	.15
Fava et al,[25] 1994	-0.792 (-1.580 to -0.004)	-1.971	.049
Fava et al,[26] 2002	-0.337 (-0.819 to 0.146)	-1.369	.17
Ferreri et al,[27] 2001	0.544 (0.200 to 0.889)	3.096	.002
Gulrez et al,[29] 2012	0.508 (-0.006 to 1.022)	1.938	.05
Lauritzen et al,[32] 1992	1.075 (0.409 to 1.741)	3.165	.002
Cha et al,[21] 1997	0.558 (-0.357 to 1.472)	1.196	.23
Leuchter et al,[33] 2009, and Leuchter et al,[34] 2009	-0.240 (-0.472 to -0.008)	-2.028	.04
Licht and Qvitzau,[35] 2002	0.246 (-0.028 to 0.521)	1.760	.08
Maes et al,[36] 1996	1.548 (0.592 to 2.504)	3.174	.002
Maes et al,[37] 1999	1.053 (0.139 to 1.967)	2.259	.02
Matreja et al,[38] 2012	0.666 (0.146 to 1.186)	2.510	.01
Medhus et al,[39] 1994	0.772 (0.103 to 1.440)	2.263	.02
Murphy,[41] 1977	-0.035 (-0.403 to 0.332)	-0.189	.85
Nelson et al,[42] 2004	0.340 (-0.208 to 0.888)	1.216	.22
O'Brien et al,[43] 1993	0.235 (-0.303 to 0.774)	0.857	.39
Raisi et al,[44] 2007	0.996 (0.376 to 1.616)	3.150	.002
Rush et al,[45] 2011	0.009 (-0.123 to 0.140)	0.131	.90
Tanghe et al,[47] 1997	0.351 (-0.104 to 0.806)	1.511	.13
Vezmar et al,[48] 2009	1.063 (-0.040 to 2.165)	1.890	.06
White et al,[49] 1980	-0.139 (-1.070 to 0.793)	-0.292	.77
Yazicioglu et al,[52] 2006	-0.017 (-0.636 to 0.603)	-0.053	.96
Xu et al,[50] 2002	1.180 (0.714 to 1.646)	4.959	<.001
Yang et al,[51] 2005	0.262 (-0.399 to 0.922)	0.777	.44
Stewart et al,[46] 2014	0.214 (-0.006 to 0.434)	1.911	.06
Fang et al,[24] 2010, and Fang et al,[23] 2011	0.028 (-0.338 to 0.393)	0.148	.88
Kessler et al,[12] 2018	0.165 (-0.024 to 0.355)	1.714	.09
Kato et al,[10] 2018	0.102 (0.018 to 0.186)	2.372	.02
Mohamed et al,[40] 2017	0.136 (-0.022 to 0.294)	1.690	.09
Fornaro et al,[28] 2014	0.101 (-0.651 to 0.853)	0.262	.79
Jie et al,[30] 2019	1.066 (0.655 to 1.477)	5.086	<.001
Kato et al,[31] 2017	0.622 (0.110 to 1.134)	2.383	.02
Xiao et al,[13] 2020	0.058 (-0.179 to 0.295)	0.479	.63
Navarro et al,[11] 2019	-0.878 (-1.266 to -0.491)	-4.439	<.001
Total	0.313 (0.190 to 0.437)	4.969	<.001



Weighted according to random-effects analysis.

Sensitivity and Subgroup Analyses

Results for sensitivity and subgroup analyses are presented in **Table 2**.

Combination of a monoamine reuptake inhibitor with an antagonist of presynaptic α2-autoreceptors (RI+α2) was associated with superior outcomes relative to monotherapy: among all 18 RCTs (SMD = 0.37; 95% CI, 0.19-0.55) (**Figure 3**), among nonresponder populations (SMD = 0.24; 95% CI, 0.03-0.45), and in particular when applied as a first-line treatment (SMD = 0.64; 95% CI, 0.12-1.15).

Combination therapy that included bupropion was not associated with superior outcomes compared with monotherapy. This applied to analyses among all 7 RCTs (SMD = 0.10; 95% CI, −0.07 to 0.27) (eFigure 3 in the Supplement), and to its application as first-line treatment (SMD = 0.04; 95% CI, −0.20 to 0.29). Among nonresponder populations, bupropion combinations were superior to monotherapy, with an SMD of 0.17 (95% CI, 0.02 to 0.31).

To avoid undue reliance on single studies, we removed each of the 38 studies in our primary outcome analysis 1 at a time from the calculation of the summary effect. None of the 38 rounds resulted in a substantial change of point estimate or significance for the primary outcome analysis of all RCTs. Effect sizes varied between 0.2 (after elimination of Xu et al[50]) and 0.34 (when Navarro et al[11] was removed).

For RI+α2 analyses of RCTs, effect sizes varied between 0.32 (after elimination of Blier et al[18]) and 0.43 (when Kato et al[10] was removed).

Table 2. Results: Outcomes Across Subgroup Analyses

	Primary outcome[b]		Secondary outcomes				
			OR (95% CI)[c]		Continuous change from baseline, SMD (95% CI)	OR (95% CI)[d]	
Results[a]	SMD (95% CI)	τ	Remission	Response		Dropouts	Dropouts due to AE
Whole sample	0.31 (0.19 to 0.44) [38 studies]	0.296	1.52 (1.20 to 1.92) [25 studies]	1.40 (1.15 to 1.69) [30 studies]	0.38 (0.22 to 0.54) [28 studies]	0.99 (0.86 to 1.14) [30 studies]	1.17 (0.79 to 1.75) [17 studies]
I^2, %	77.52		63.38	44.11	84.21	3.66	20.87
Whole sample; low risk of bias	0.29 (0.15 to 0.42) [15 studies]	0.188	1.44 (1.12 to 1.85) [11 studies]	1.46 (1.14 to 1.87) [14 studies]	0.34 (0.17 to 0.50) [11 studies]	1.09 (0.94 to 1.28) [12 studies]	1.43 (0.87 to 2.34) [9 studies]
I^2, %	69.18		51.61	48.07	77.95	0	15.34
α2 + RI	0.37 (0.19 to 0.55) [18 studies]	0.305	1.42 (1.01 to 2.01) [12 studies]	1.49 (1.18 to 1.87) [15 studies]	0.44 (0.22 to 0.66) [15 studies]	1.02 (0.86 to 1.21) [14 studies]	1.06 (0.49 to 2.31) [10 studies]
I^2, %	80.58		74.27	47.77	85.10	0	34.82
α2 + RI; low risk of bias	0.36 (0.19 to 0.53) [11 studies]	0.221	1.39 (1.11 to 1.75) [9 studies]	1.52 (1.15 to 2.00) [11 studies]	0.36 (0.16 to 0.56) [9 studies]	1.04 (0.88 to 1.24) [9 studies]	1.17 (0.43 to 3.19) [6 studies]
I^2, %	75.28		37.42	53.44	78.26	0	49.63
α2 + RI; nonresponder/TRD	0.24 (0.03 to 0.45) [12 studies]	0.283	1.17 (0.82 to 1.67) [8 studies]	1.35 (1.08 to 1.69) [10 studies]	0.23 (−0.01 to 0.48) [9 studies]	1.00 (0.83 to 1.20) [8 studies]	0.75 (0.31 to 1.82) [6 studies]
I^2, %	79.52		68.26	34.11	82.55	0	0
α2 + RI; first-line	0.64 (0.12 to 1.15) [5 studies]	0.523	1.80 (0.74 to 4.37) [3 studies]	1.54 (0.77 to 3.09) [3 studies]	0.84 (0.30 to 1.38) [2 studies]	0.81 (0.38 to 1.72) [3 studies]	0.62 (0.15 to 2.62) [2 studies]
I^2, %	84.21		72.19	58.54	44.05	0	0
Combination with bupropion	0.10 (−0.07 to 0.27) [7 studies]	0.161	1.29 (0.95 to 1.74) [6 studies]	1.06 (0.88 to 1.29) [5 studies]	0.06 (−0.19 to 0.31) [4 studies]	1.45 (0.95 to 2.23) [2 studies]	1.79 (0.50 to 6.35) [2 studies]
I^2, %	59.48		45.52	0	74.07	0	29.45
Combination with bupropion; low risk of bias	0.12 (−0.07 to 0.31) [4 studies]	0.106	1.13 (0.80 to 1.59) [3 studies]	1.05 (0.75 to 1.48) [3 studies]	0.09 (−0.14 to 0.32) [2 studies]	1.45 (0.95 to 2.23) [2 studies]	1.79 (0.50 to 6.35) [2 studies]
I^2, %	30.22		13.78	0	60.35	0	29.45
Combination with bupropion; nonresponder/TRD	0.17 (0.02 to 0.31) [3 studies]	0.000	2.24 (0.61 to 8.26) [2 studies]	1.15 (0.89 to 1.48) [2 studies]	0.51 (−0.01 to 1.02) [1 study only]	No data	No data
I^2, %	0		80.93	0	NA		
Combination with bupropion; first-line	0.04 (−0.20 to 0.29) [4 studies]	0.200	1.09 (0.83 to 1.43) [4 studies]	0.95 (0.70 to 1.28) [3 studies]	−0.01 (−0.26 to 0.23) [3 studies]	1.45 (0.95 to 2.23) [2 studies]	1.79 (0.50 to 6.35) [2 studies]
I^2, %	71.05		0	0	74.60	0	29.45

Abbreviations: α2, antagonists of presynaptic α2-autoreceptors; AE, adverse events; NA, not applicable; OR, odds ratio; RI, (monoamine) reuptake inhibitor; SMD, standardized mean difference; TRD, treatment-resistant depression.

[a] Of note, depending on design specifics, not all studies may be included in all outcome analyses (eg, only 17 randomized double-blind studies reported data on the number of dropouts due to AE).

[b] For the primary outcome, SMD >0 in favor of combination.

[c] For the secondary outcomes remission, response, and continuous change from baseline, OR >1 designates superiority of combination treatment; SMD >0 designates superiority of combination treatment.

[d] For the secondary outcomes dropouts and dropouts due to AE, OR >1 designates superiority of monotherapy, ie, fewer dropouts in monotherapy groups.

For bupropion combination analyses of RCTs, effect sizes varied between 0.06 (after elimination of Gulrez et al[29]) and 0.15 (when Leuchter et al[33,34] was removed).

Post Hoc Analyses

In meta-regression, baseline HDRS scores were not associated with the SMD between combination treatment and mono-therapy (coefficient: 1.1; 95% CI, −1.3 to 3.5; P = .37; n = 26 studies). In a sensitivity analysis of 18 studies reporting outcome data that were based on follow-up examinations, such as remission rates, meta-regression returned similar results (coefficient: −2.6; 95% CI, −8.3 to 3.1; P = .37). Meta-regression based on MADRS baseline scores was not calculated as planned because the number of studies providing data was too small.

Secondary Outcomes

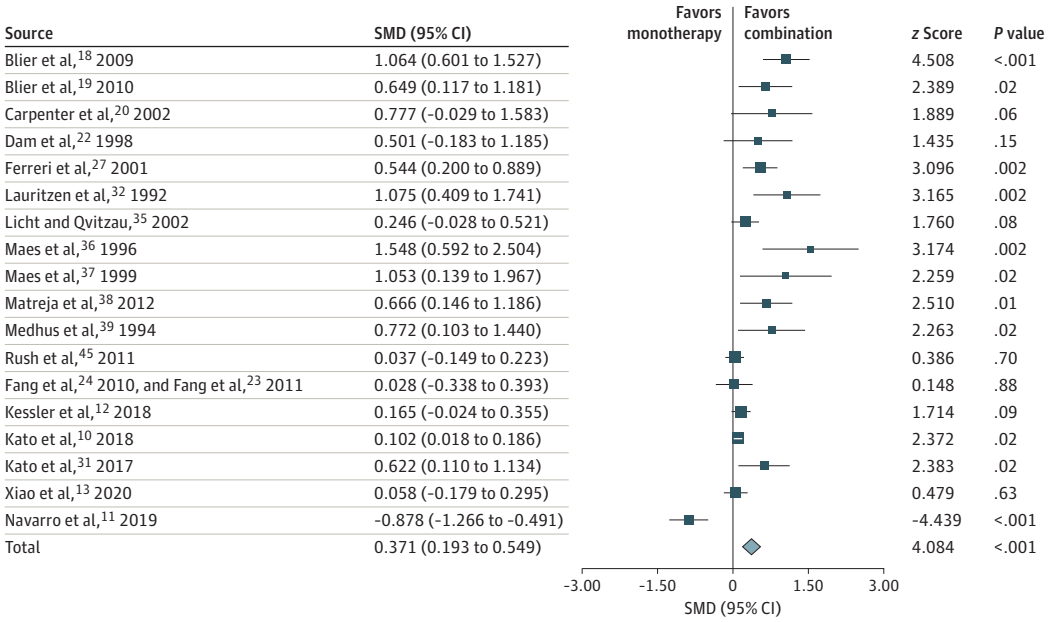
Primary and secondary outcomes as well as subgroup analyses are presented in Table 2.

Secondary outcome analyses of efficacy, based on remission and response rates as well as continuous data (change from baseline in rating scale scores), produced results that were generally in line with our primary outcome results (Table 2).

Tolerability

With respect both to patients dropping out of treatment for any reason and to dropouts due to adverse events, data for combination and monotherapy were similar (odds ratio = 0.99; 95% CI, 0.86-1.14; and odds ratio = 1.17; 95% CI, 0.79-1.75, respectively).

Figure 3. Primary Outcome: Subgroup Analysis of Treatment With a Monoamine Reuptake Inhibitor Plus an Antagonist of Presynaptic α2-Autoreceptors



Source	SMD (95% CI)	z Score	P value
Blier et al,[18] 2009	1.064 (0.601 to 1.527)	4.508	<.001
Blier et al,[19] 2010	0.649 (0.117 to 1.181)	2.389	.02
Carpenter et al,[20] 2002	0.777 (-0.029 to 1.583)	1.889	.06
Dam et al,[22] 1998	0.501 (-0.183 to 1.185)	1.435	.15
Ferreri et al,[27] 2001	0.544 (0.200 to 0.889)	3.096	.002
Lauritzen et al,[32] 1992	1.075 (0.409 to 1.741)	3.165	.002
Licht and Qvitzau,[35] 2002	0.246 (-0.028 to 0.521)	1.760	.08
Maes et al,[36] 1996	1.548 (0.592 to 2.504)	3.174	.002
Maes et al,[37] 1999	1.053 (0.139 to 1.967)	2.259	.02
Matreja et al,[38] 2012	0.666 (0.146 to 1.186)	2.510	.01
Medhus et al,[39] 1994	0.772 (0.103 to 1.440)	2.263	.02
Rush et al,[45] 2011	0.037 (-0.149 to 0.223)	0.386	.70
Fang et al,[24] 2010, and Fang et al,[23] 2011	0.028 (-0.338 to 0.393)	0.148	.88
Kessler et al,[12] 2018	0.165 (-0.024 to 0.355)	1.714	.09
Kato et al,[10] 2018	0.102 (0.018 to 0.186)	2.372	.02
Kato et al,[31] 2017	0.622 (0.110 to 1.134)	2.383	.02
Xiao et al,[13] 2020	0.058 (-0.179 to 0.295)	0.479	.63
Navarro et al,[11] 2019	-0.878 (-1.266 to -0.491)	-4.439	<.001
Total	0.371 (0.193 to 0.549)	4.084	<.001

Efficacy was measured as standardized mean difference (SMD) and weighted according to random-effects analysis.

Heterogeneity in these analyses was low (I^2 = 3.66% and I^2 = 20.87%, respectively).

Risk of Bias

Fifteen of the 39 included studies (38%) were considered to be of higher methodological rigor ("low" risk of bias). Summary ratings confirmed our primary outcome analysis and are displayed in Table 1 (also Figure 2 and Figure 3).

Heterogeneity

I^2 statistics indicated substantial between-study heterogeneity in most of the primary outcome analyses, but significantly less so in most of the subgroup analyses, especially in analyses of response and dropouts (Table 2). Heterogeneity as measured by τ was substantially lower in sensitivity analyses (restricted to studies with low risk of bias), and τ indicated that the standard deviation of the weighted SMD estimate was approximately equal to or lower than the effect size.

Publication Bias

The funnel plot of studies included in the primary outcome analysis indicated small study effects (eFigure 4 in the Supplement). An Egger test result was positive (P = .007, df = 36). A trim-and-fill procedure (Duval and Tweedie) with 10 studies trimmed to the left of the mean resulted in a reduced effect size that was still statistically significant (0.13; 95% CI, 0.001-0.26). Twenty-two studies with an effect size of 0 would be necessary to reduce the overall effect to 0.1 (Orwin fail-safe N).

For RI+α2 analyses, an Egger test result was positive (P = .02, df = 16). A trim-and-fill procedure (Duval and Tweedie) with 6 studies trimmed to the left of the mean resulted in a reduced effect size that was still statistically significant (0.19; 95% CI, 0.01-0.36).

Discussion

This study yielded 2 main results. First, combination treatment as a general principle seems to be more effective than monotherapy without being associated with higher numbers of patients dropping out. Second, the combination of monoamine reuptake inhibitors (selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant) and α2-adrenergic receptor antagonists (RI+α2) seems to be the most effective and preferable antidepressant combination.

Combination therapy may primarily be applied as a second-step treatment after insufficient response to initial monotherapy. Our findings suggest that using an RI+α2 combination is more effective in these cases compared with monotherapy. On the other hand, in a recent meta-analysis, switching antidepressant monotherapy for patients considered nonresponders was not more effective than sticking to the initial antidepressant.[54] In the same vein, after nonresponse to a standard dose of selective serotonin reuptake inhibitor, a dose increase did not result in superior efficacy compared with continuation of the initial dose.[55]

Combination therapy was not associated with more dropouts or adverse events leading to discontinuation. It may thus be a safe treatment alternative when compared with other second-step strategies in treatment-resistant depression, such as augmenting monotherapy with lithium or atypical

antipsychotics.[56,57] Our analysis of the RI+α2 combination in nonresponders resulted in statistically significant but small effect sizes (SMD = 0.2). Still, patients who are resistant to treatment present a particular challenge, and effect sizes resulted from comparisons with active treatment (ongoing monotherapy, increasing the dose, or switching antidepressants). Such comparisons are likely to result in lower estimates of efficacy than contrasting combination and monotherapy in first-line treatment trials. Here, the RI+α2 combination seems to be particularly effective, with an effect size of SMD = 0.64. Antidepressant monotherapy itself has effect sizes of no more than about 0.3 compared with placebo.[58,59] Of note, trials in our analysis also included populations with difficult-to-treat chronic depression.[32,45]

We have previously shown that the favorable treatment outcomes of combination therapy in comparison with monotherapy are not a dosage effect only.[9] Also, some of the included trials found superior effects with subtherapeutic doses of a second antidepressant in RI+α2 combinations.[32,36-38] Therefore, pharmacodynamic and clinical synergisms seem likely. For example, sedating α2-adrenergic receptor antagonists may counteract the restlessness, agitation, and sexual dysfunction associated with monoamine reuptake inhibitors. Reuptake inhibitors in monotherapy are likely to stimulate presynaptic α2-receptors by enhancing the intrasynaptic concentrations of serotonin and norepinephrine. However, combinations with blockers of presynaptic α2-receptors are supposed to prevent the negative feedback effect on neurotransmission induced by a stimulation of α2-receptors.

The relative tolerability of combination therapy and the modest response rates with initial antidepressant monotherapy also suggest considering RI+α2 combination therapy as a first-line treatment, at least in severe cases of depression.

On the whole, in our analysis, treatment effects of antidepressant combinations were not associated with baseline severity. According to these results, combination treatment is effective regardless of initial illness severity. Nevertheless, this finding must be viewed as preliminary because it rests on a subset of studies and only on outcomes ascertained by HDRS.

While the addition of bupropion has previously been shown to alleviate antidepressant-induced sexual dysfunction,[14] and its addition to antidepressant monotherapy can be clinically sensible, our findings indicate that bupropion combinations in general are not associated with substantial enhancement of antidepressive efficacy compared with monotherapy. This result is counterintuitive because bupropion, with its dopaminergic properties, has a mechanism of action that may complement classical antidepressant pathways. Note that in nonresponder populations, the summary results for bupropion combinations remain inconclusive rather than negative, mainly because of the small number of methodologically sound studies existing to date: the CI spans a negative as well as a sizable positive effect.

Limitations

First, I^2 values indicated substantial heterogeneity of effects. However, heterogeneity is known to increase with accumulating numbers. Additional τ statistics were calculated, indicating a spread of data not unfamiliar in medical studies: the standard deviation was lower than or had the same order of magnitude as the effect size. Nevertheless, as in most meta-analyses, included studies were not homogenous in their design, eg, with differences in blinding status or in the definition of nonresponse to previous antidepressant treatment. As a consequence, we applied random-effects models and showed that results remained robust after each study was left out. Further, dichotomizing criteria of treatment success in subgroup analyses, as in remission and response, supported the main results and explained large parts of the between-study heterogeneity. In the same vein, sensitivity analyses among studies of high methodological rigor (low risk of bias) and among double-blind studies (data not shown) also backed our main findings.

Second, funnel plot asymmetry indicated possible reporting bias. However, in combination treatment studies, reporting bias might not be as important as it is in placebo trials of antidepressant monotherapies because there is no negative result in the strict sense, and thus no disincentive to publish. Nevertheless, even when fully adjusting for possible publication bias, a reduced but still positive and statistically significant effect remained (for RI+α2 combination: SMD = 0.19; 95% CI, 0.01-0.36). Also, the observed funnel plot asymmetry may be caused by plot distortion associated with transforming a variety of outcomes into SMD, as has recently been emphasized.[60] Reassuringly, therefore, sensitivity analyses using raw mean differences resulted in a substantially reduced funnel plot asymmetry (data not shown).

There also is considerable indication that the funnel plot asymmetry may represent a true asymmetry of observable effects. For example, many of the studies on bupropion combinations were recent and had large sample sizes but yielded only small effects. Low effect size and small-variance studies may distort funnel plots to the upper left quadrant. Besides, we observed funnel plot asymmetry only among studies of treatment-resistant depression and not among studies using a combination as a first-line treatment.

Third, true between-study heterogeneity may result not only from different study populations and combination treatments but also from different control groups. This particularly applies to studies of treatment-resistant depression, where active comparators were continuation, increased dose, or switching antidepressant. And yet, regardless of the kind of comparator, combination treatment was associated with higher efficacy (data not shown).

It is conceivable that antidepressant discontinuation syndromes may have interacted with outcomes. However, it has been shown that when the switch is between antidepressants, discontinuation syndromes rarely pose clinical problems.[61]

Conclusions

For clinical practice, physicians should be aware that combinations of reuptake inhibitors (selective serotonin reuptake in-

hibitor, serotonin-norepinephrine reuptake inhibitor, or tricyclic antidepressant) with α2-autoreceptor antagonists are a potent treatment option, associated with superior outcomes relative to monotherapy. Clinicians can inform patients that on average this advantage does not come at the cost of lower tolerability and that there is reason to believe in a synergistic therapeutic effect. While we did not find an association of outcome and severity of depression, we believe combination treatment particularly suggests itself in severe cases of depression and for patients resistant to standard treatment. Research should focus on the dearth of methodologically rigorous data on bupropion combinations for nonresponder populations.

ARTICLE INFORMATION

Accepted for Publication: December 8, 2021.

Published Online: February 16, 2022. doi:10.1001/jamapsychiatry.2021.4313

Author Contributions: Dr Henssler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Henssler, Bschor, Baethge.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Henssler, Alexander, Baethge.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Henssler, Schwarzer, Bschor, Baethge.
Administrative, technical, or material support: Henssler, Alexander, Bschor.
Supervision: Henssler, Bschor, Baethge.

Conflict of Interest Disclosures: Outside of this work, Dr Henssler received a research grant from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF) (grant No. 01KG1808). Dr Schwarzer reported personal fees from Roche Pharma as an external statistical consultant outside the submitted work. No other disclosures were reported.

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