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Combining Antidepressants in Acute Treatment of Depression: A Meta-Analysis of 38 Studies Including 4511 Patients

Combiner les antidépresseurs dans le traitement aigu de la dépression: une méta-analyse de 38 études comportant 4511 patients

Jonathan Henssler, MD[1,2,*], Tom Bschor, MD[3,4,*], and Christopher Baethge, MD[1]

Abstract

Objective: Combining antidepressants (ADs) for therapy of acute depression is frequently employed, but randomized studies have yielded conflicting results. We conducted a systematic review and meta-analysis aimed at determining efficacy and tolerability of combination therapy.

Methods: MEDLINE, Embase, PsycINFO, and CENTRAL databases were systematically searched through March 2014 for controlled studies comparing combinations of ADs with AD monotherapy in adult patients suffering from acute depression. The prespecified primary outcome was standardized mean difference (SMD), secondary outcomes were response, remission, and dropouts.

Results: Among 8688 articles screened, 38 studies were eligible, including 4511 patients. Combination treatment was statistically, significantly superior to monotherapy (SMD 0.29; 95% CI 0.16 to 0.42). During monotherapy, slightly fewer patients dropped out due to adverse events (OR 0.90; 95% CI 0.53 to 1.53). Studies were heterogeneous ($I^2 = 63\%$), and there was indication of moderate publication bias (fail-safe *N* for an effect of 0.1:44), but results remained robust across prespecified secondary outcomes and subgroups, including analyses restricted to randomized controlled trials and low risk of bias studies. Meta-regression revealed an association of SMD with difference in imipramine-equivalent dose. Combining a reuptake inhibitor with an antagonist of presynaptic α2-autoreceptors was superior to other combinations.

Conclusion: Combining ADs seems to be superior to monotherapy with only slightly more patients dropping out. Combining a reuptake inhibitor with an antagonist of presynaptic α2-autoreceptors seems to be significantly more effective than other combinations. Overall, our search revealed a dearth of well-designed studies.

Abrégé

Objectif : Combiner les antidépresseurs pour traiter la dépression aiguë est une méthode fréquemment utilisée, mais les études randomisées ont offert des résultats conflictuels. Nous avons mené une revue systématique et une méta-analyse visant à déterminer l'efficacité et la tolérabilité du traitement combiné ou polythérapie.

Méthodes : Une recherche des bases de données MEDLINE, Embase, PsycINFO, et CENTRAL a été systématiquement menée jusqu'en mars 2014 pour repérer les études contrôlées comparant les polythérapies d'antidépresseurs avec la monothérapie d'antidépresseur chez des patients adultes souffrant de dépression aiguë. Le résultat principal prédéterminé était la différence des

[1] Department of Psychiatry and Psychotherapy, University of Cologne Medical School, Cologne, Germany
[2] Charité University Medicine, St Hedwig-Krankenhaus, Clinic for Psychiatry and Psychotherapy, Berlin, Germany
[3] Department of Psychiatry, Schlosspark-Hospital, Berlin, Germany
[4] Department of Psychiatry and Psychotherapy, University Hospital of Dresden, Dresden, Germany
[*] These authors contributed equally

Corresponding Author:
Christopher Baethge, MD, Klinik für Psychiatrie und Psychotherapie, Universität zu Köln; Kerpener Straße 62, 50937 Köln, Germany.
Email: cbaethge@uni-koeln.de

moyennes standardisées (DMS), et les résultats secondaires étaient la réponse, la rémission, et les abandons.

Résultats : Sur 8688 articles examinés, 38 études étaient admissibles, portant sur 4511 patients. La polythérapie était statistiquement significativement supérieure à la monothérapie (DMS 0,29; IC à 95% 0,16 à 0,42). Durant la monothérapie, un nombre légèrement moindre de patients ont abandonné en raison d'effets indésirables (RC 0,90; 0,53 à 1,53). Les études étaient hétérogènes ($I^2 = 63\%$), et il y avait une indication d'un biais de publication modéré (N à sécurité intégrée pour un effet de 0,1: 44), mais les résultats demeuraient solides dans les résultats secondaires prédéterminés et les sous-groupes, y compris les analyses restreintes aux essais randomisés et aux études à faible risque de biais. La méta-régression a révélé une association de la DMS avec une différence d'imipramine pour une dose équivalente. Combiner un inhibiteur du recaptage avec un antagoniste des autorécepteurs $\alpha 2$ présynaptiques était supérieur aux autres combinaisons.

Conclusion : Combiner des antidépresseurs semble être supérieur à la monothérapie, et un nombre légèrement plus élevé de patients seulement abandonnent le traitement. Combiner un inhibiteur du recaptage avec un antagoniste des autorécepteurs $\alpha 2$ présynaptiques semble être significativement plus efficace que les autres combinaisons. En général, notre recherche a révélé une pénurie d'études bien conçues.

Keywords
antidepressants, combination therapy, monotherapy, depression

Depressive disorders are major challenges. Twelve-month prevalence estimates differ depending on diagnostic methods but are consistently high ranging between 1% and 10% for major depressive episodes.[1] The global burden of disease study ranks major depressive disorder (MDD) as fourth and fifth of the most burdensome disorders in Western Europe and North America, respectively, and globally ranked eleventh, with an increase of illness burden of 37% over the last 2 decades.[2]

International guidelines by the American Psychiatric Association[3] and the Canadian Network for Mood and Anxiety Treatments,[4] as well as the German National Clinical Practice Guideline[5] recommend use of a single, non-monoamine oxidase inhibitor antidepressant (AD) as initial treatment in severe depression. However, despite the quantity of ADs and despite continuing development of new antidepressive agents, responder rates to initial AD monotherapy remain unsatisfactory, ranging from 40% to 60%,[6-8] and remissions occur in only 20% to 30%.[9,10]

In nonresponders, several second-step treatments are advocated in guidelines,[11] especially switching to a different monotherapy, high-dose treatment, augmentation (for example, with lithium), or combining 2 ADs.[12] As a consequence, combination treatment is frequent. In a recent naturalistic study[13] of nonresponders to initial monotherapy, 19% of patients received combined AD pharmacotherapy. Also, in Veterans Health Administration settings, 11% of all patients with depression were treated with the combination of 2 ADs.[14] However, studies have yielded conflicting results regarding the efficacy of combination treatment. For example, Blier et al[15] and Maes et al[16,17] published results in favour of combining ADs, but studies by Fava et al[18] and Leuchter et al[19] were negative. Despite a considerable number of trials comparing combination treatment to AD monotherapy, to our knowledge, no comprehensive systematic review and meta-analysis of available controlled trials exists. The authors of 1 earlier meta-analysis of 5 combination studies in treatment-naive patients concluded that there were too few studies to draw definitive conclusions.[20] In another systematic review of 5 studies, combination treatment, compared with monotherapy among incomplete responders, was summarized but not quantified, and a lack of evidence was emphasized.[21] Both studies applied restrictive selection criteria resulting in the exclusion of many studies carried out on the subject. Moreover, both studies did not contain a meta-analysis of dropouts, a critical aspect of combination treatment. In this vein, Thase,[22] in a recent qualitative review, emphasized the lack of adequate research on AD combinations. Accordingly, we carried out a systematic review and meta-analysis of controlled studies comparing combinations of 2 ADs and AD monotherapy in adult patients with acute depression. As data from randomized controlled trials (RCTs) were expected to be sparse, we intended to evaluate all accessible evidence by including controlled trials of different methodological rigour and to present studies both in subgroups according to methodological similarity, as well as in a global assessment across all studies. We hypothesized that combination therapy is superior to monotherapy regarding efficacy but at the price of higher dropout rates.

Methods

This is a systematic literature review and meta-analysis. The protocol has been published on Prospero (Prospero record registration no: CRD42013004407). Methods followed the PRISMA guidelines for systematic reviews and are described in detail in an online supplement (available at cpa.sagepub.com/supplemental). In brief, employing the Cochrane Highly Sensitive Search Strategy we searched PubMed, PsycINFO, Embase, and CENTRAL databases. Trials were included when they met the following criteria: existence of a control group of AD monotherapy (including open label and nonrandomized trials), inclusion of participants aged 18 years or older, of both sexes with depressive disorder, and diagnosis according to standard operationalized criteria. Diagnoses of other psychiatric disorders, as well as comorbid medical conditions, were no exclusion

criteria. Studies specifically on bipolar disorder (BD) were excluded. Irrespective of dosage, we included all pharmacological interventions using a combination of 2 ADs, that is, initial combination therapy, as well as adjunctive administration of a second to a first AD. Both trials on first-line treatment and trials among patients with resistance to previous AD treatment(s) were included. We excluded trials on maintenance therapy.

All full texts included were screened independently by 2 reviewers. Study evaluation, data extraction, meta-analyses, tests for heterogeneity, and publication bias, followed the Cochrane Collaboration Handbook.[23] Primary outcome criterion was standardized mean difference (SMD) between treatments on an intention-to-treat basis. Secondary outcome criteria were rates of remission, response, and dropouts. Prespecified subgroup analyses included double-blind RCTs, studies in nonresponders to previous treatment trials, and studies with a low risk of bias. Trials were evaluated according to Cochrane's risk of bias tool[23]: 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 or high) was added. Post hoc analyses referred to samples restricted to continuation of monotherapy, compared with switch to another monotherapy, to combining monoamine reuptake inhibitors (selective serotonin reuptake inhibitor [SSRI], serotonin-norepinephrine reuptake inhibitor [SNRI], and tricyclic antidepressant [TCA]) with antagonists of presynaptic α2-autoreceptors (mianserin, mirtazapine, and trazodone), to MDD and to unipolar depressive disorder.

Results

Our literature search retrieved 8688 different articles. After screening titles and abstracts full texts of 172 articles were read, and 38 studies included (Figure 1).

In total, trials included 4511 patients, with 1857 receiving combinations and 2654 receiving monotherapy. Publication dates ranged from 1977 to 2013. Articles were published in English, Chinese (4 articles), and Korean (1 article). Thirty-two studies (84%) were randomized, 27 (71%) used blinding measures, and 20 (53%) were double-blind. Seventeen trials (45%) recruited nonresponders to initial AD treatment only (Table 1).

Efficacy

Primary Outcome. The analysis sample regarding our primary outcome criterion—efficacy as measured in SMD—consisted of 36 studies with 4342 patients. The SMD was 0.29 (95% CI 0.16 to 0.42) in favour of combination treatment ($P < 0.001$; random effects model) (Figure 2). Between-study heterogeneity was substantial ($I^2 = 63\%$, $\tau^2 = 0.08$).

To avoid undue reliance on single studies, we removed studies one by one from the analysis. None of the 36 rounds resulted in a substantial change of point estimate or significance. Effect sizes varied between 0.26 (after elimination of Xu et al[24]) and 0.31 (when Fava et al[18,25] were removed).

Sensitivity and Subgroup Analyses. The effect remained robust across subgroup analyses restricted to randomized, double-blind trials (SMD 0.33; 95% CI 0.11 to 0.54, $P = 0.003$) to low risk of bias-trials (SMD 0.36; 95% CI 0.13 to 0.59, $P = 0.002$), to trials excluding patients with BD (SMD 0.30; 95% CI 0.07 to 0.53, $P = 0.01$), and to RCTs of MDD patients treated with standard doses (SMD 0.25; 95% CI 0.04 to 0.46, $P = 0.02$). In trials limited to nonresponders, the direction of effect remained but effect sizes were lower (SMD 0.13; 95% CI –0.18 to 0.44, $P = 0.42$).

Secondary Outcomes. Secondary outcome analyses based on remission and response supported the superiority of combination treatment over monotherapy: odds ratios of 1.63 (95% CI 1.25 to 2.12, $P < 0.001$), and of 1.68 (95% CI 1.32 to 2.14, $P < 0.001$), respectively. In a meta-analysis confined to continuous data (rating scale differences) a similar effect emerged (SMD –0.20; 95% CI –0.37 to –0.03, $P = 0.02$). Primary and secondary outcomes, as well as subgroup analyses, are presented in Table 2.

Tolerability

Regarding both dropouts, due to any reason and to dropouts due to adverse effects, fewer patients dropped out in monotherapy arms (OR 0.82; 95% CI 0.62 to 1.08 and OR 0.90; 95% CI 0.53 to 1.53, respectively). Results were not significant and high P values indicate a possible role of chance (0.16 and 0.70, respectively).

Heterogeneity

Between-study heterogeneity was substantial in the primary outcome meta-analysis ($I^2 = 63\%$, $\tau^2 = 0.08$, Figure 2) and in most of the subgroup analyses. In some subgroup analyses and secondary outcomes I^2 indicated lower heterogeneity between studies, especially in dropout analyses ($I^2 = 0\%$) and analyses restricted to studies of patients with MDD only ($I^2 = 49\%$). Heterogeneity as measured by tau-squared varied from 0.07 to 0.12 in primary outcome and primary outcome subgroup analyses. Accordingly, Tau ranged from 0.26 to 0.35, indicating that the standard deviation of the weighted SMD estimate was about equal to the effect size.

Publication Bias

The funnel plot of studies included in the primary outcome analysis did not rule out publication bias. Eggers test was borderline negative ($df = 34$, $P = 0.07$), a trim and fill procedure (Duval and Tweedie) with 9 studies trimmed to the left of the mean resulted in a reduced effect size (0.16; 95% CI 0.02 to 0.29). Forty-four studies with an effect size

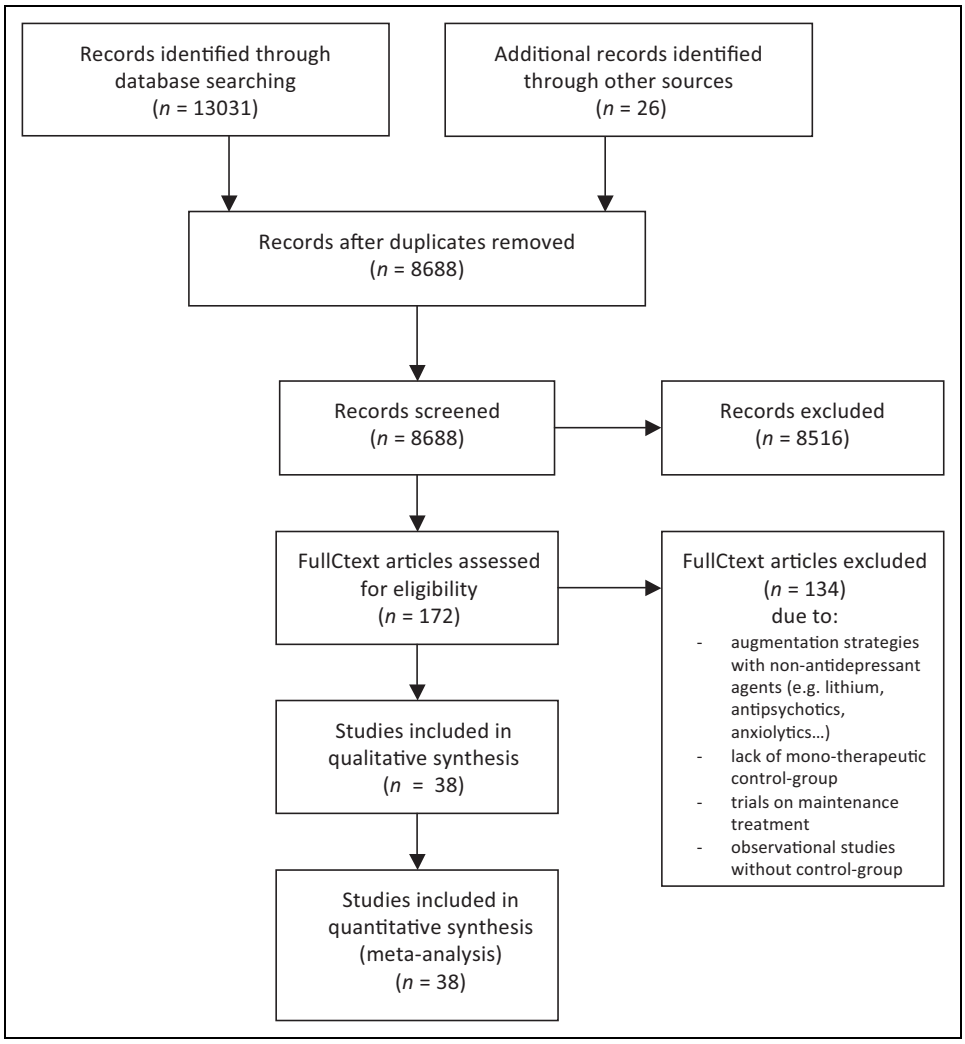

Figure 1. Flow chart of trials considered, eliminated, and included in study (adapted from PRISMA).

of 0 would be necessary to reduce the overall effect to 0.1 (Orwin's fail-safe *N*).

Trials selected had an average power of 26.4% (9.3% to 98.6%) to detect an effect size of 0.29 (SMD)–the primary outcome effect estimate.

Post Hoc Analyses

Two different modalities of monotherapy were compared with add-on combination treatment: continuation of monotherapy (10 studies) and switch to another monotherapy (2 studies). Both favoured add-on combination SMD (0.39; 95% CI 0.25 to 0.52, compared with 0.35; 95% CI 0.01 to 0.69).

Another post hoc analysis revealed similar effects in samples of only patients with MDD (SMD 0.30; 95% CI 0.15 to 0.44) (23 studies). The difference between combination and monotherapy was more pronounced in treatment-naive patients than in patients with treatment-resistant depression (TRD) (SMD 0.41; 95% CI 0.10 to 0.72) [6 studies], compared with 0.13; 95% CI –0.18 to 0.44 [8 studies]; randomized, double-blind studies, patients with MDD only).

Combination of a monoamine reuptake inhibitor (SSRI, SNRI, and TCA) with an antagonist of the presynaptic α2-autoreceptor (mianserin, mirtazapine, and trazodone) (13 studies) resulted in a statistically, significantly higher effect than other combinations (24 studies) (SMD 0.47; 95% CI 0.24 to 0.71, compared with SMD 0.17; 95% CI 0.02 to 0.32, $P = 0.03$). Restriction of this analysis to randomized, double-blind studies only consolidated the finding (SMD 0.54; 95% CI 0.29 to 0.79 [10 studies], compared with SMD 0.04; 95% CI –0.27 to 0.35 [8 studies]; $P = 0.01$); $I^2 = 47\%$) (Figure 3).

The fourth post hoc analysis confirmed an advantage of combination over monotherapy in patients with BD as well (SMD 0.30; 95% CI 0.07 to 0.53).

Meta-Regressions and Moderator Analyses

Average imipramine-equivalent doses were 269.8 mg (SD 134.1 mg) in combination arms and 170.1 mg (SD 72.9 mg) in monotherapy arms, a ratio of 1.6:1 ($n = 35$ studies). In meta-regression, dosage difference was substantially

Table 1. Characteristics of trials.

Author	Year	Diagnosis	*n*	Follow-up, weeks	Combination, *n* (ITT)	Monotherapy, *n* (ITT)	Randomized	Blindedness	Non-Responder only	Risk of bias	depression severity at baseline
Bares et al[49]	2013	MDD, DSM IV, at least Stage I criteria for resistant depression	61	6	variable, $n = 31$	variable, $n = 29$,	y	open	y	unknown/ high	MADRS, C: 28.6+/-3.2, M: 28.4+/-3.2
Blier et al[50]	2009	MD, DSM-IV	61	6	Mirtazapine (15 − 45 mg/day) + paroxetine (10 to 30 mg/ day), $n = 21$,	Paroxetine(10-30 mg), N = 19, //Mirtazapin(15-45 mg), N = 21,	y	double		low	MADRS, C: 34.4+/-7.2, M:32.2+/-5.9//32.0+/ − 6.4
Blier et al[15]	2010	MDD, DSM-IV	105	6	Mirtazapine (30 mg/day) + fluoxetine (20 mg/day), $n =$ 25, //mirtazapine (30mg/ day) + venlafaxine (75 mg increased to 225 mg/day), $n = 26$, //mirtazapine + bupropion (150 mg/day), $n = 26$	Fluoxetine(20 mg/day), N = 28,	y	double		low	MADRS, C: 32.4+/ − 5// 31.7+/ − 4.1//31.0+/ − 4.1, M:31.8+/ − 4.8 HAMD17, C:22.4+/ − 3.5//22.6+/-3.1//21.7+/ − 2.6, M: 22.6+/ − 3.0
Carpenter et al[51]	2002	major depressive episode, DSM-IV	26	4	Mirtazapine (15 to 30 mg/day) + primary antidepressant, $n = 11$	Primary antidepressant agents were continued at their pre-study doses throughout the augmentation trial (bupropion 450 mg, citalopram30 to 60 mg, fluoxetine 40 to 50 mg, fluvoxamine 300 mg, paroxetine 30 to 40 mg, sertraline 100 to 200 mg, venlafaxine 200 to 300 mg/ day), $n = 15$	y	double	y	low	HRSD-17, C:21.9+/ − 3.8, M: 22.5+/ − 5.8
Cha et al[52]	1998	DSM IV	36	6	Dothiepin (75 mg/day, dose increase due to clinical state) + sertraline (75 mg/ day, dose increase due to clinical state), $n = 20$	Dothiepin (150 mg/day, dose increase due to clinical state), $n = 16$	y	open		unknown/ high	HAM-D-17, C: 22.9+/ − 6.0, M: 21.0 +/ − 4.8
Dam et al[53]	1998	depression, ICD-10, moderate-to-severe degree (corresponding to a DSM-III-R diagnosis of MDD)	34	6	Mianserin (30 mg/day) + fluoxetine (20 mg/day), $n = 16$	Fluoxetine (20 mg/day), $n =$ 18,	y	double		unknown/ high	HAMD-D, median (range), C: 25.0(20 − 34), M: 21.5(17 − 30)
Ebert et al[54]	1995	dysthymia + superimposed episode of MDD, DSM-III-R, resistant to antidepressant therapy	36	6	Fluvoxamine (300 mg/day) + moclobemide (600 mg/day), $n = 18$	Fluvoxamine (300 mg/day), n = 18	n	single (raters)	y	unknown/ high	HDRS(21items), C: 25.2+/ − 2.7, M: 25.4+/ − 3.7
Fang et al[55,56]	2010 and 2011	MDD, DSM-IV, stage 2 TRD	197	8	Paroxetine (20mg/ day) + trazodone (100mg/ day), $n = 47$	Venlafaxine-XR (225 mg/d), n = 50, // mirtazapine (45 mg/ d), $n = 55$, // paroxetine (20 mg/d), $n = 45$	y	double	y	unknown/ low	HRSD-17, 24.6+/ − 5.8 (only whole − sample data)

(continued)

Table 1. (continued)

Author	Year	Diagnosis	*n*	Follow-up, weeks	Combination, *n* (ITT)	Monotherapy, *n* (ITT)	Randomized	Blindedness	Non-Responder only	Risk of bias	depression severity at baseline
Fava et al[25]	1994	MDD, DSM-III-R- Patient Version, refractoriness to initial fluoxetine	27	4	Fluoxetine (20 mg/day) + desipramine (25 to 50 mg/day), *n* = 12	Fluoxetine (40 to 60 mg/day), *n* = 15	y	double	y	unknown/high	HAM-D-17, C: 17.5+/-4.7, M: 16.2+/ − 3.9
Fava et al[18]	2002	MDD, DSM-III-R—Patient Edition	67	4	Fluoxetine (20 mg/day) + desipramine (25 to 50 mg/day), *n* = 34	Fluoxetine (40 to 60 mg/day), *n* = 33	y	double	y	unknown/high	HAM-D-17, C: 19.6+/-3.1, M: 17.7+/ − 3.4
Ferreri et al[57]	2001	MDD, DSM III-R, fluoxetin nonresponders	103	6	Fluoxetine (20 mg/day) + mianserine (60 mg/day), *n* = 32	Mianserine (60 mg/day), *n* = 33, //fluoxetine (20 mg/day), *n* = 38	y	double	y	low	HAMD-17, C: 27.7 + 1.9; M: 27.1 + 2.52//26.9 + 1.9
Gonul et al[58]	2005	MDD, DSM-IV, resistant to initial SSRI-treatment + consecutive venlafaxine-XR	39	8	Venlafaxine-XR (225 mg/day) + sertraline (50 to 100 mg/day), *n* = 19	Venlafaxine-XR (225 to 375 mg/day), *n* = 19	n	open	y	unknown/high	HAMD-D, C: 23.8+/ − 3.1, M: 24.5+/ − 2.3
Gulrez et al[59]	2012	MDD, DSM-IV-TR, partial responders to SSRI treatment	60	4	SSRI (escitalopram 10 to 30 mg/day//citalopram 20 to 60 mg/day//paroxetine 25 to 75 mgday//sertraline 50 to 200 mg/day) + bupropion-SR (300 mg/day), *n* = 30	SSRI (dosing see left) + placebo, *n* = 30	y	single	y	unknown/high	HDRS, C: 17.80 +/ − 0.60, M: 17.57 +/ − 0.48
Lam et al[60]	2004	MDD, DSM-IV, resistant to minimum 1 antidepressant	61	6	Citalopram (mean 33.1 +/ − 9.7 mg/day) + bupropion-SR (248.8+/ − 72.4 mg/day), *n* = 32	Citalopram (mean 38.8+/ − 13.2 mg/day) or bupropion-SR (283.3+/ − 68.5 mg/day), *n* = 29	n	open	y	unknown/high	SIGH-SAD, C: 30.0 +/ − 5.7, M: 31.2 +/ − 7.8
Lauritzen et al[61]	1992	Hamilton Depression Rating Scale score of >16 and (or) a Melancholia Scale score of >15. Inclusion: patients with depression from 18 to 67 years of age 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 patients with depression older than 67 years of age	40	6	Imipramine (50 to 100 mg/day according to target plasma level 200 nmol/l) + mianserine (30 mg/day), *n* = 22	Imipramine (50 to 100 mg/day according to target plasma level 200nmol/l), *n* = 18	y	double		low	HAM-D-17, median (25 − 75%), C: 25.2(21.0 − 27.0), M: 22.4(19.0 − 29.0)
Leuchter et al[62]	2009	MDD, DSM-IV	220	6	Escitalopram (10 mg/day) + bupropion XL (300 mg/day), *n* = 74 (PP; ITT not indicated)	Escitalopram(10 mg/day), *n* = 73 (PP; ITT not indicated), // bupropion XL (300 mg/day), *n* = 73 (PP; ITT not indicated)	y	open		Unknown/high	HAM-D-17, C: 20.4+/-4.3, M: 20.6+/-4.4, 21.7+/ − 4.0
Licht and Qvitzau,[38]	2002	MDD, DSM-IV	293	5	Sertraline(100 mg/day) + mianserine (30 mg/day), *n* = 98	Sertraline (100 mg/day), *n* = 98, //sertraline (200 mg/day), *n* = 97	y	double	y	low	HDRS-17, median(quartiles) C: 23(21 − 26), M: 23(21-26)//23(22 − 26)

(continued)

Table 1. (continued)

Author	Year	Diagnosis	*n*	Follow-up, weeks	Combination, *n* (ITT)	Monotherapy, *n* (ITT)	Randomized	Blindedness	Non-Responder only	Risk of bias	depression severity at baseline
Liu et al[63]	2000	Depression, CCMD-2−R	70	6	Fluoxetine (20 −to 40 mg/day) + amitriptyline (50 to 150 mg/day), *n* = 35	Fluoxetine (20 to 40 mg/day), *n* = 35	y	single (Pat. only)		unknown/high	HAMD, C: 20.7+/ − 2.5, M: 29.1+/ − 3.1
Maes et al[17]	1996	MD, DSM-III-R	22	4	Fluoxetine (20 mg/day) + trazodone (100 mg/day), *n* = 12	Trazodone (100 mg/day), *n* = 10	y	double		unknown/high	HAM-D-17, no baseline-data specified
Maes et al[16]	1999	MDD, DSM-III-R	23	5	Fluoxetine(20 mg/day)+Mianserine(30 mg/day), N = 11,	Fluoxetine (20 mg/day), *n* = 12	y	double		low	HAM-D-17, C: 23.7 +/ − 4.2, M: 21.0 +/ − 4.6
Matreja et al[40]	2012	MDD, ICD-10, and DSM-IV	60	6	SSRI (escitalopram 10 to 30 mg, citalopram 20 to 60 mg, sertraline 50 to 150 mg, fluoxetine 20 to 40 mg, paroxetine 10 to 50 mg/day) + low-dose mirtazapine (7.5 mg/day), *n* = 30	SSRI (escitalopram 10 to 30 mg, citalopram 20 to 60 mg, sertraline 50 to 150 mg, fluoxetine 20 to 40 mg, paroxetine 10 to 50 mg/day), *n* = 30	y	open		unknown/high	HRDS-17, C: 20.53 ± 0.47, M: 20.76 ± 0.32
Medhus et al[64]	1994	Major depressive episode, DSM-111, after treatment with adequate doses of a TCA	37	3	TCA (at least 150 mg/day or maximum tolerable dose/range: 100 to 200 mg/day) + mianserin (60 mg/day), *n* = 18	TCA (at least 150 mg/day or maximum tolerable dose/range: 75 to 225 mg/day) + placebo, *n* = 19	y	double	y	unknown/high	MADRS, C: 32.6 +/ − (4.3), M: 31.7 +/ − (5.6)
Murphy[39]	1977	Depressive illness of sufficient severity to justify treatment with a TCA	173	4	Clomipramine (10 mg/day) + desipramine (25 mg/day), *n* = 58	Clomipramine (10 mg/day), *n* = 57, //desipramine (25 mg/day), *n* = 58	y	double		low	clinical depression rating scale-17 item, mean scores, C: 22.98, M: 24.06//23.71
Nelson et al[65]	2004	Yale Depression Inventory, unipolar nonpsychotic MDD	39	6	Desipramine (target plasma level 160 ng/ml) + fluoxetine (20 mg/day), *n* = 13	Fluoxetine (20 mg/day), *n* = 14, //desipramine (target plasma level 160 ng/ml), *n* = 12	y	double		low	MADRS, C: 32 +/ − 6.3, M: 37.2 +/ − 7.1//38.3 +/ − 7.5
O'Brien et al[66]	1993	Research diagnostic criteria for MDD	79	6	AMI (150 mg/day) + TCP (30 mg/day), *n* = 25	Amitriptyline (150 mg/day), *n* = 28, //tranylcypromine (30 mg/day), *n* = 26	y	double		unknown/high	HRSD: C: 22.0 +/ − 4.9, M: 24.1 +/ − 6.0// 20.8 +/ − 4.9
STAR*D (step 2)[45-47]	2006	nonpsychotic MDD, DSM-IV	1006	12(-14)	Bupropion-SR (200 mg increased to 400 mg/day) + citalopram (mean 54.9 [SD 10.9] mg/day), *n* = 279	Bupropion-SR (150 mg increased to 400 mg/day), *n*=239, //sertraline (50 mg increased to 200 mg/day), *n* = 238, //venlafaxine-ER (75 mg increased to 375 mg/day), *n* = 250	limited	single (remission) /open (response)	(y)	unknown/high	HRSD-17, C: 15.4+/ − 6.8, M: 18.5+/ − 7.7//19.3+/ − 6.9//18.9+/ − 7.3 QIDS − SR − 16, C: 11.2 +/ − 4.7, M: 13.3+/ − 5.1//13.3+/ − 4.7// 13.1+/ − 5
STAR*D (step 4)[45,46,48]	2006	nonpsychotic MDD, DSM-IV	109	12 (−14)	Venlafaxine-ER (37.5 mg increased to 300 mg/day) + mirtazapine (15 mg increased to 45 mg/day), *n* = 51	Tranylcypromine (10 mg increased to 60 mg/day), *n* = 58	limited	single (remission) /open (response)	y	unknown/high	HDRS, C: 19.7+/ − 5.5, M: 19.6+/ − 7.6 QIDS-SR − 16, C: 14.9 +/ − 4.1, M: 13.6 +/ − 5.1
Stewart et al[67]	2014	MDD, DSM-IV-TR	245	12	Escitalopram (40 mg/d) + bupropion (450 mg/d), *n* = 78	Escitalopram (40 mg/d), N = 84, // Bupropion (450mg/d), N = 83,	y	double		low	HAM-D-17, C: 20+/-4, M: 20+/-5

(continued)

Table 1. (continued)

Author	Year	Diagnosis	*n*	Follow-up, weeks	Combination, *n* (ITT)	Monotherapy, *n* (ITT)	Randomized	Blindedness	Non-Responder only	Risk of bias	depression severity at baseline
Raisi et al[68]	2007	MDD, DSM-IV	45	8	Nortriptyline (50 mg/day) + citalopram (40 mg/day), *n* = 23	Citalopram (40 mg/day), *n* = 22	y	double		unknown/ high	HAM-D-17, C: 30.80+/-4.16, M: 31.2+/-5.07
Rush et al[69]	2011	DSM-IV-TR, recurrent or chronic (current episode lasting at least 2 years), MDD	665	12	Bupropion-SR (150 to 400 mg/day) + escitalopram (10 to 20 mg/day), *n* = 221, // venlafaxine-ER (150 to 300 mg/day) + mirtazapine (15 to 45 mg/day), *n* = 220	Escitalopram (10 to 20 mg/ day), *n* = 224	y	single		low	HAM-D, C: 23.8+/-4.6// 24.3+/-5.0, M: 23.4+/-4.9
Tanghe et al[70]	1997	DSM-III R, major depressive episode, resistant to minimum 2 antidepressants	39	4	Moclobemide (200600 mg/ day) + amitriptyline (increased to 280 mg/day), *n* = 20	Moclobemide (200 to 600 mg/ day), *n* = 19, //amitriptyline (increased to 280 mg/day), *n* = 19	y	double	y	unknown/ high	MADRS, C: 41.8+/-6.08, M: 41.26+/-8.22// 39.16+/-5.1
Tong and Lan[71]	2005	Comorbid depression and anxiety disorder, DSM-IV	63	6	Fluoxetine (20 +/- 4 mg/day) + maprotiline (139 +/- 20 mg/day), *n* = 31	Venlafaxine (204 +/- 44 mg/ day), *n* = 32	n	open		unknown/ high	HAM-D, data not available
Vezmar et al[72]	2009	MD, DSM-IV	22	2 (response) – 4/6 (remission)	Amitriptyline (75 mg/day) + fluvoxamine (100 mg/day), *n* = 7	Amitriptyline (75 mg/day), *n* = 9, //fluvoxamine (100 mg/day), *n* = 6	y	open		unknown/ high	HAM-D, C: 28.0+/-5.5, M: 29.3+/-5.8//29.2+/-8.1
White et al[73]	1980	minor or MDD	30	4	AMI (50 to 150 mg/day) + TCP (10 to 15 mg/day), *n* = 10,	Amitriptyline (75 to 300 mg/ day), *n* = 9, // tranylcypromine(10 to 20 mg/day), *n* = 11	y	open		unknown/ high	HAM-D, no baseline-data specified
Xu et al[24]	2004	comorbid depression and anxiety disorder, DSM-IV	84	8	Fluoxetine (20 mg/day) + amitriptyline (112.5 mg/ day), *n* = 28	Fluoxetine (20 mg/day), *n* = 28, //amitriptyline (75 to 150 mg/day), *n* = 28	y	single (Pat. only)		unknown/ high	SDS, data not available
Yang et al[74]	2005	refractory depression	36	6	Citalopram (20 mg increased to 40 mg/day) + amitriptylin (50 mg/day), *n* = 20	Citalopram (20 mg increased to 40 mg/day), *n* = 16	y	single	y	unknown/ high	HAM-D, C: 28.9 + /-6.3, M: 28.5 + /-6.8
Yazicioglu et al[75]	2006	MDD, DSM-IV	43	10	Reboxetine (4 mg increased to 8 mg/day) + sertraline (50 mg/day), *n* = 21	Venlafaxine-XR(75 mg increased to 150 mg/day), N = 22,	y	open		unknown/ high	HDRS-17, C: 18.1 + /-1.7, M: 18.3 + /-1.6
Young et al[76]	1979	mild or moderate depression not requiring ECT or inpatient admission	135	6	Trimipramine (mean 102 mg/ day) + phenelzine (mean 44 mg/day) // trimipramine (mean 96 mg/day) + isocarboxazide (mean 30 mg/day), *n* = 51	Trimipramine (mean 106 mg/ day) + placebo//phenelzine (mean 45 mg/day) + placebo//isocarboxazide (mean 32 mg/day) + placebo, *n* = 84	y	double		unknown/ high	HDRS, mean score, C: 22.9//26.6, M: 22.5// 24.8//24.8
											HAM-D range: 15.4 – 31.2, MADRS range: 28.4 – 41.8

AMI = amitriptyline; CCMD-2-R = Chinese Classification of Mental Disorders, Second Edition, Revised; DSM = Diagnostic and Statistical Manual of Mental Disorders;
ECT = electroconvulsive therapy; ICD = International Classification of Diseases; ITT = intention-to-treat population; MDD = major depressive disorder;
PP = per-protocol population; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; TCP = tranylcypromine;
TRD = treatment-resistant depression

Table 2. Results and outcomes across subgroup analyses

	Primary outcome	Secondary outcomes				
	SMD	Remission	Response	SMD at study endpoint	Dropouts	Dropouts due to AE
Results	SMD (95% CI)	OR (95% CI)	OR (95% CI)	SMD (95% CI)	OR (95% CI)	OR (95% CI)
Whole sample (38 studies)	0.29 (0.16 to 0.42); $n = 4342$ (36 studies)	1.63 (1.24 to 2.08); $n = 3884$ (27 studies)	1.68 (1.32 to 2.14); $n = 3769$ (29 studies)	–0.20 (–0.37 to –0.03); $n = 2989$ (20 studies)	0.82 (0.62 to 1.08]; $n = 2044$ (29 studies)	0.90 (0.53 to 1.53); $n = 2857$ (17 studies)
rand.db. (20 studies)	0.33 (0.11 to 0.54); $n = 1643$ (18 studies)	1.63 (1.07 to 2.48); $n = 1287$ (12 studies)	2.38 (1.50 to 3.77); $n = 1130$ (12 studies)	–0.13 (–0.61 to 0.36); $n = 441$ (6 studies)	0.79 (0.59 to 1.07); $n = 1405$ (16 studies)	0.87 (0.51 to 1.48); $n = 883$ (10 studies)
Non(rand.db.) (18 studies)	0.27 (0.09 to 0.44); $n = 2699$ (18 studies)	1.65 (1.15 to 2.37); $n = 2597$ (15 studies)	1.35 (1.04 to 1.75); $n = 2639$ (17 studies)	–0.23 (–0.41 to –0.05); $n = 2548$ (14 studies)	1.03 (0.49 to 2.19); $n = 639$ (13 studies)	0.89 (0.34 to 2.34); $n = 1974$ (7 studies)
rand.db. nonresponder (8 studies)	0.13 (–0.18 to 0.44); $n = 808$ (8 studies)	1.22 (0.71 to 2.07); $n = 713$ (6 studies)	1.53 (0.87 to 2.68); $n = 619$ (4 studies)	0.01 (–0.81 to 0.82); $n = 157$ (4 studies)	0.65 (0.37 to 1.14); $n = 450$ (5 studies)	0.94 (0.23 to 3.83); $n = 156$ (3 studies)
Low risk of bias (11 studies)	0.30 (0.09 to 0.50); $n = 1773$ (11 studies)	1.84 (1.18 to 2.89); $n = 1537$ (8 studies)	2.00 (1.27 to 3.14); $n = 1528$ (10 studies)	–0.21 (–0.54 to 0.11); $n = 975$ (4 studies)	0.73 (0.52 to 1.04); $n = 956$ (8 studies)	0.72 (0.39 to 1.32); $n = 1408$ (8 studies)
High /unknown risk of bias (27 studies)	0.25 (0.09 to 0.42); $n = 2569$ (25 studies)	1.54 (1.08 to 2.18); $n = 2347$ (19 studies)	1.57 (1.16 to 2.12); $n = 2241$ (19 studies)	–0.19 (–0.39 to 0.01); $n = 2014$ (16 studies)	0.99 (0.63 to 1.54); $n = 1088$ (21 studies)	1.25 (0.67 to 2.34); $n = 1449$ (9 studies)
Exclusion of patients with bipolar disorder (12 studies)	0.30 (0.07 to 0.53); $n = 1661$ (12 studies)	2.13 (1.28 to 3.55); $n = 1661$ (12 studies)	1.59 (1.00 to 2.53); $n = 1210$ (8 studies)	–0.17 (–0.47 to 0.12); $n = 1114$ (6 studies)	0.84 (0.56 to 1.27); $n = 700$ (8 studies)	0.61 (0.29 to 1.27); $n = 1253$ (7 studies)
Patients with MDD rand.db. (15 studies)	0.25 (0.04 to 0.46); $n = 1382$ (14 studies)	1.63 (1.07 to 2.48); $n = 1287$ (12 studies)	1.94 (1.27 to 2.97); $n = 869$ (8 studies)	–0.14 (–0.55 to 0.26); $n = 499$ (7 studies)	0.78 (0.55 to 1.09); $n = 1019$ (11 studies)	0.96 (0.50 to 1.85); $n = 680$ (8 studies)

Primary outcome: SMD > 0 in favour of combination. Secondary outcomes: OR > 1 designates superiority of combination treatment; SMD < 0 designates superiority of combination treatment. Study number in the first column refers to the number of studies in a subgroup: for example, there are 20 randomized double-blind studies. Note, depending on design specifics, studies from column 1 may not be included in all outcome analyses (for example, only 10 randomized double-blind studies reported data on the number of dropouts due to adverse effects).
AE = adverse events; MDD = major depressive disorder; rand.db. = randomized, double-blind trials; SMD = standardized mean difference

associated with SMD (slope 0.0014; 95% CI 0.00003 to 0.0028, $P = 0.045$, $n = 34$). A similar result emerged for dosage ratio (slope 0.286; 95% CI 0.0285 to 0.543, $P = 0.029$, $n = 35$).

Meta-regression revealed no association of duration of follow-up in weeks with SMD (slope –0.01; 95% CI –0.06 to 0.04, $P = 0.60$, $n = 36$).

Moderator analyses of dichotomized variables did not result in strong signals: randomized, compared with nonrandomized trials ($P = 0.66$); low, compared with non-low risk of bias studies ($P = 0.46$); and treatment resistant, compared with nontreatment-resistant patient samples ($P = 0.78$) (Table 2).

Discussion

Our study yielded 3 main results. First, combination treatment seems to be superior to monotherapy. Second, combination treatment is not associated with substantially more dropouts. Third, the combination of monoamine reuptake inhibitors and α2-adrenergic receptor antagonists seems to be superior to other AD combinations.

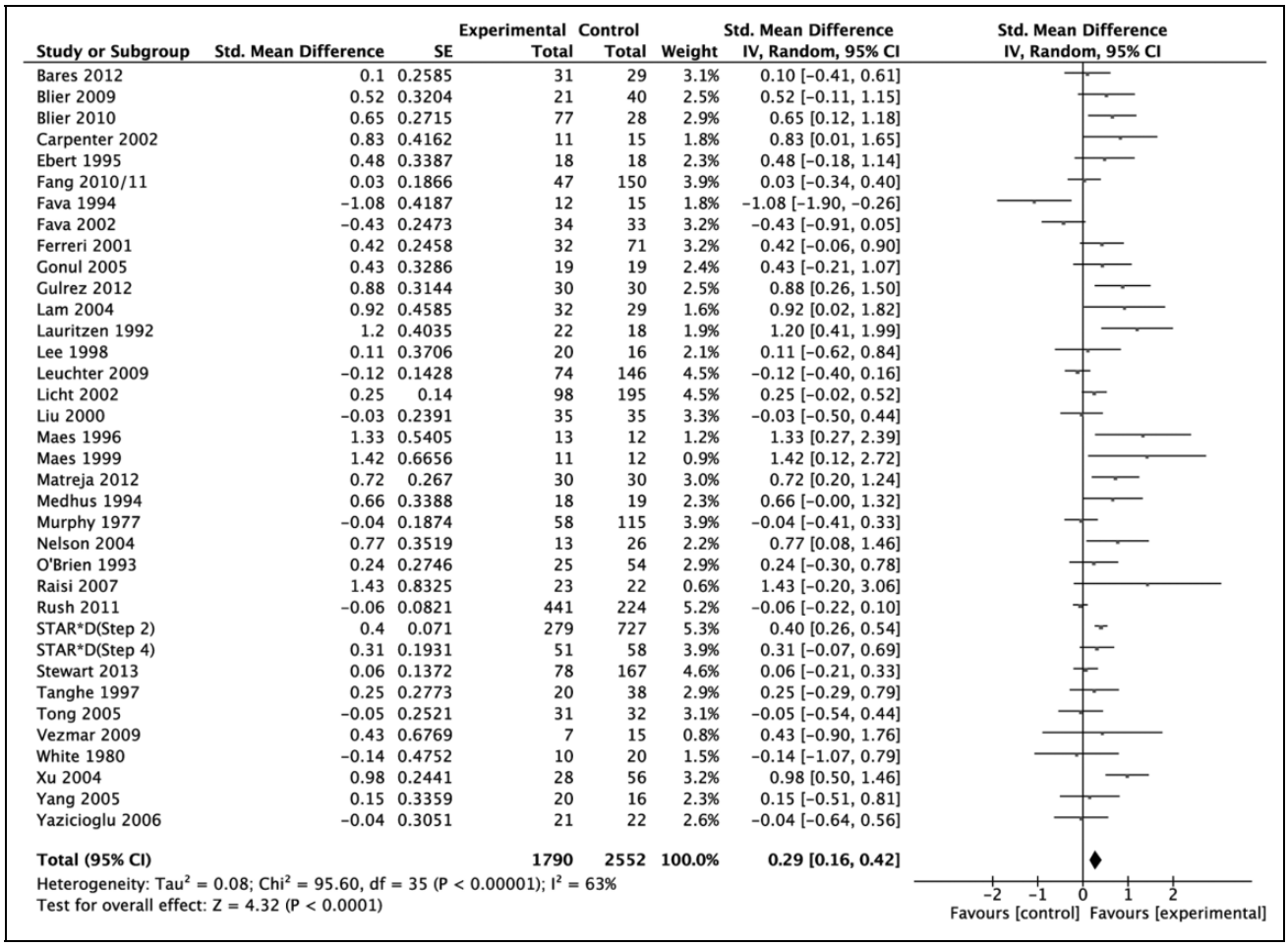

Figure 2. Primary outcome: treatment effect as measured in standardized mean difference weighted according to random effects analysis.

In this area of research an SMD of about 0.3, as estimated in this meta-analysis, is substantial, particularly because it emerged from comparisons between active treatments. Even when compared with placebo, AD monotherapy has effect sizes of no more than about 0.3.[26] Thus, even the lower end of the effect size confidence interval of the primary outcome, 0.16, indicates a non-negligible effect in AD pharmacotherapy. In the same vein, the subgroup analysis regarding remission lead to number needed to treat estimate of 9 (6 to 21) for combination treatment in comparison with monotherapy. In contrast, regarding dropouts, the point estimate of number needed to harm amounts to 50 (not significant).

Some, but not all, previous reviews judged combination therapy to be superior.[20,27-31] Nevertheless, owing to small numbers of studies, or in the absence of meta-analyses, differences were not quantified or the role of chance was not estimated. Unfortunately, previous reviews did not quantify adverse effects but some, largely on theoretical grounds, highlighted increased risks of adverse events during combination therapy.[20,28,29] Thus, our tolerability analyses are of clinical importance: while monotherapy resulted in fewer dropouts due to any reason to adverse events, both effects were small and *P* values were high. The results refute our hypothesis of lower tolerability during combination treatment.

Regarding other treatment strategies in TRD, studies support lithium augmentation and augmentation with atypical antipsychotics.[32,33] However, switching to another AD cannot be considered evidence based. Bschor and Baethge,[34] in a systematic review and meta-analysis found switching not to be superior to continuation of initial ADs. Similarly, our subgroup analyses showed the advantage of add-on combination treatment to be more pronounced when compared with switching, than to continuation of monotherapy. As a result, it seems justified to particularly prefer combining ADs, compared with switching to another AD. It is important to note that, in our analysis, combination treatment in TRD was only marginally and not statistically, significantly effective in comparison with monotherapy. The finding may prove clinically useful anyway for 2 reasons. First, patients with TRD are a difficult-to-treat subgroup—and one that is probably frequently subjected to combination treatment—and any approach that shows some potential may have clinical merit. Second, the effect estimated in our study could be real even in the absence of statistical significance, mainly

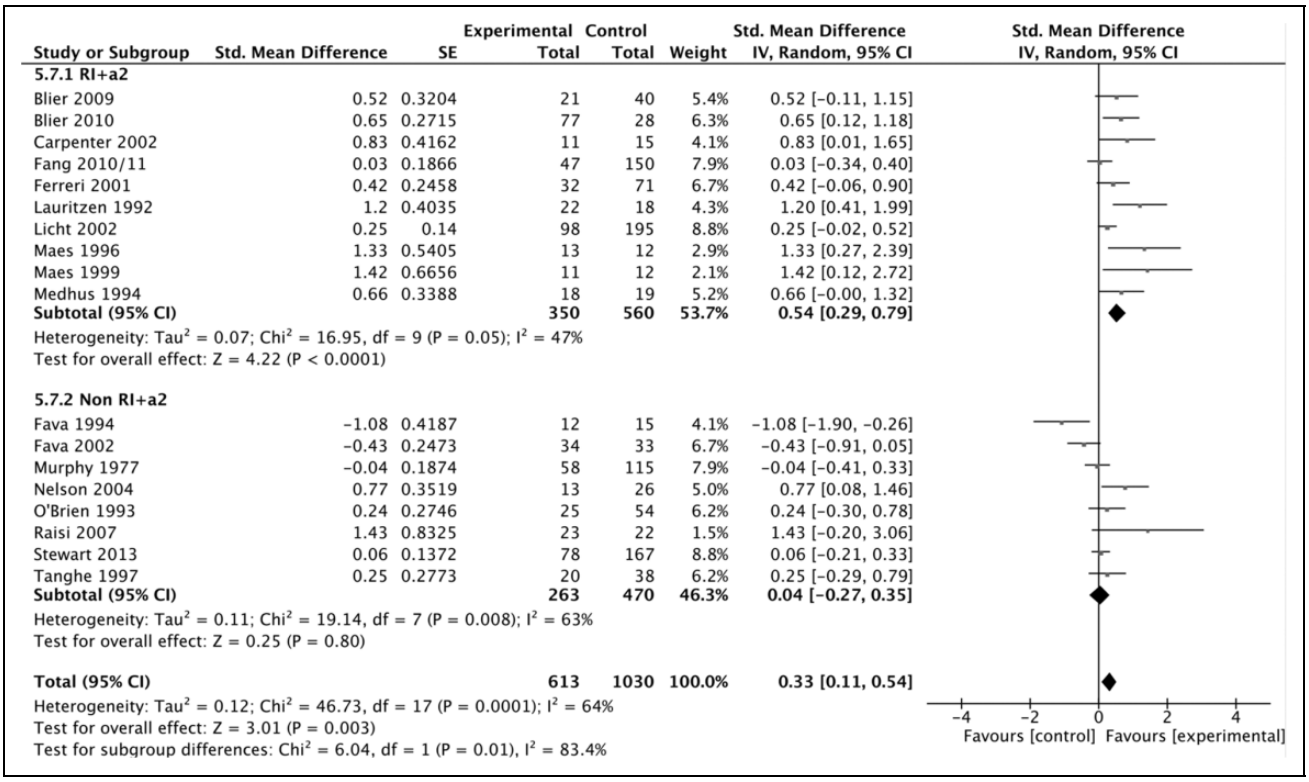

Figure 3. Primary outcome: treatment effect as measured in standardized mean difference (SMD) subgroup analysis: RI+α2 versus other pharmacologic combinations. Randomized, double-blind trials only weighted according to random effects analysis.

because the positive results in our various comparisons between combination and monotherapy increase the a priori probability of superiority in patients with TRD as well. In any event, additional methodologically rigorous research on this topic is essential.

Combinations of monoamine reuptake inhibitors and α2-adrenergic receptor antagonists turned out to be particularly effective. On pharmacodynamic grounds, monoamine reuptake inhibitors may act synergistically with α2-adrenergic receptor antagonists. Reuptake inhibitors are thought to be limited in effect, because increased levels of monoamines in the synaptic cleft result in increased activation of inverse feedback by stimulation of presynaptic α2-adrenergic receptors.[35,36] However, this finding has to be viewed with caution as it resulted from a post hoc analysis.

In our regression model, dosage difference accounted for about one-half of the total difference in treatment effect. Still, it has to be borne in mind that several studies did not provide detailed data on dosages. However, if the dose difference is correct it is all the more remarkable that tolerability, as measured in dropouts, seems to be sufficient when ADs are combined. Additionally, in a systematic review, a dose–effect relation could be demonstrated for some, but not for all ADs.[37] Licht and Qvitzau,[38] comparing combination therapy to standard- and high-dose sertraline, found the latter to be the least effective regimen. However, more 3-armed studies including a standard-dose monotherapy arm, a high-dose monotherapy arm, and a combination arm are needed to shed light on the significance of dosage.

Murphy et al[39] examined application of ADs at subtherapeutic doses. Matreja et al[40] observed application of low-dose mirtazapine in combination treatment. Both were not part of the MDD subgroup analyses. These may simultaneously represent subgroup analyses of therapeutic AD dosing.

Limitations

First, this meta-analysis included studies covering different patient populations, ADs, dosages, or durations of treatment, as well as studies of different methodological rigour. However, as earlier studies were contradictory and many underpowered, we aimed at including as many publications as possible. Ioannidis et al[41] argue that in most cases, even in the presence of heterogeneity, quantitative synthesis may be preferable to approaches frequently found in narrative reviews, as long as limitations of meta-analyses are acknowledged. In this vein, had we limited our calculations to meta-analyses restricted to a small group of studies we would not have found preliminary evidence for the superiority of combining reuptake inhibitors with α2-autoreceptor antagonists.

I^2 values indicated substantial heterogeneity of effects. However, they are known to increase with accumulating *N*, additional tau-squared statistics were calculated, indicating a spread of data not unfamiliar in medical studies. The standard deviation had the same order of magnitude as the effect

size. Nevertheless, heterogeneity was carefully considered in various sensitivity and subgroup analyses of more homogeneous study samples, in using random effects models, in testing whether results remained robust after each study was left out, and in considering possible effects of publication bias. Finally, 2 meta-regressions and 3 additional moderator analyses addressed the role of possible confounders. Therefore, our study does not represent an analysis of broad, instead of narrow, inclusion criteria but rather several analyses of different grades of homogeneity regarding trials selected, narrow and broad. Although we acknowledge that different confounding factors are interconnected, unfortunately, we could not calculate a single meta-analysis adjusting for all covariates simultaneously.

The meta-analyses of double-blind randomized trials and double-blind randomized trials among patients with MDD supported our findings. In fact, the advantage of combination treatment became stronger. Similar results apply to the more homogeneous subgroup populations. Some factors causing variability in the group of studies included likely have made the sample as a whole more conservative (for example, selection of studies employing low dose combinations, or including a subgroup of patients with BD). Still, rather than to find an exact point estimate for the efficacy of combined ADs relative to monotherapy it was the primary aim of our study to determine whether there is a difference at all between these 2 treatment principles and whether such a difference would be outweighed by an increase in dropouts. Note, secondary outcome analyses using different effect estimates aimed at confirming or falsifying primary results and not at finding significant results. Every effect estimate has to be viewed as what it is—an estimate that makes sense only with its confidence interval.

Some of the trials ($N = 10$) required nonresponse to an initial period of AD monotherapy. Trials consisted of AD monotherapy of this agent (in continuation), compared with add-on therapy with an additional AD. Therefore, dropouts due to adverse effects may have been decreased in the monotherapy group, as patients may have dropped out during the pretrial period. In these studies, dropout rates may be biased against combination treatment—a methodological problem that strengthens our findings.

Further, it has been shown that the results of some meta-analyses are inflated. While Pereira and Ioannidis[42] confirmed that results of most meta-analyses represent true effects, they calculated that there may occur effect inflation, particularly in meta-analyses with sparse data. However, our study benefitted from many studies and events. With a sample size of 4300 patients for our primary outcome, there seems reason to believe that the results of our meta-analysis will be stable over time.[43]

It is possible that we did not include all relevant studies, but with MEDLINE, Embase, PsycINFO, and CENTRAL, 4 different large international databases were searched. It is doubtful that, in the field of combination treatment, publication bias is as important as it is in placebo studies of AD monotherapies. Nevertheless, adjusting for possible publication bias resulted in a weakened but still positive effect (SMD 0.16).

Finally, the limitations of our study will always be those of the included trials. For example, the trials that were published as blinded studies did not report on measures to ensure blinding. Therefore, it is difficult to judge the quality of blinding—a problem that has been shown to be prevalent in psychiatric research.[44] In addition, some of the study arms (step 2 in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Study[45-47]) were not meant to be directly compared, and step 2 and step 4 of the STAR*D trial[45-48] were sequential treatments among the same study population. It is, therefore, reassuring that results were supported by the analysis of trials with low risk of bias.

Conclusions

AD combination seems to be superior to monotherapy and this advantage does not come at the cost of higher rates of severe adverse events. Possible areas of application might be in particularly severe cases of depression and treatment-resistant populations (although in this population the effect estimate was low). Our results point to a possibly important role of higher dosage in combination therapy and to promising combinations of reuptake inhibitors with $\alpha 2$-autoreceptor antagonists. Still, even with our systematic search of ample and broad inclusion criteria we find a dearth of evidence in this field of research. Future research should focus on the clinically important field of TRD.

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Both Dr Henssler and Dr Bschor contributed equally to this work.

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Supplemental Material

The online supplements are available at http://cpa.sagepub.com/supplemental.

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