Are Antipsychotics or Antidepressants Needed for Psychotic Depression? A Systematic Review and Meta-Analysis of Trials Comparing Antidepressant or Antipsychotic Monotherapy With Combination Treatment

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ABSTRACT

Objective: To perform a meta-analysis of antidepressant-antipsychotic cotreatment versus antidepressant or antipsychotic monotherapy for psychotic depression.

Data Sources: We performed an electronic search (from inception of databases until February 28, 2011) in PubMed/MEDLINE, Cochrane Library, and PsycINFO, without language or time restrictions. Search terms were (*psychosis* OR *psychotic* OR *hallucinations* OR *hallucinating* OR *delusions* OR *delusional*) AND (*depression* OR *depressed* OR *major depressive disorder*) AND (*random* OR *randomized* OR *randomly*).

Study Selection: Eight randomized, placebo-controlled acute-phase studies in adults (N = 762) with standardized criteria–defined psychotic depression (including Research Diagnostic Criteria, *DSM-III*, *DSM-IV*, or *ICD-10*) were meta-analyzed, yielding 10 comparisons. Antidepressant-antipsychotic cotreatment was compared in 5 trials with 6 treatment arms (n = 337) with antidepressant monotherapy and in 4 trials with 4 treatment arms (n = 447) with antipsychotic monotherapy.

Data Extraction: Primary outcome was study-defined inefficacy; secondary outcomes included all-cause discontinuation, specific psychopathology ratings, and side effects. Using random effects models, we calculated relative risk (RR) with 95% confidence intervals (CIs), number-needed-to-treat/harm (NNT/NNH), and effect size (ES).

Results: Antidepressant-antipsychotic cotreatment outperformed antidepressant monotherapy regarding less study-defined inefficacy (no. of comparisons = 6; n = 378; RR = 0.76; 95% CI, 0.59–0.98; $P = .03$; heterogeneity [I^2] = 34%) (NNT = 7; 95% CI, 4–20; $P = .009$) and Clinical Global Impressions-Severity of Illness scores (no. of comparisons = 4; n = 289; ES = −0.25; 95% CI, −0.49 to −0.02; $P = .03$; $I^2 = 0\%$), with trend-level superiority for depression ratings (no. of comparisons = 5; n = 324; ES = −0.20; 95% CI, −0.44 to 0.03; $P = .09$; $I^2 = 10\%$), but not regarding psychosis ratings (no. of comparisons = 3; n = 161; ES = −0.24; 95% CI, −0.85 to 0.38; $P = .45$; $I^2 = 70\%$). Antidepressant-antipsychotic cotreatment also outperformed antipsychotic monotherapy regarding less study-defined inefficacy (no. of comparisons = 4; n = 447; RR = 0.73; 95% CI, 0.63–0.84; $P < .0001$; $I^2 = 0\%$) (NNT = 5; 95% CI, 4–8; $P < .0001$) and depression ratings (no. of comparisons = 4; n = 428; ES = −0.49; 95% CI, −0.75 to −0.23; $P = .0002$; $I^2 = 27\%$), while anxiety ($P = .11$) and psychosis ($P = .06$) ratings only trended toward favoring cotreatment. All-cause discontinuation and reported side-effect rates were similar, except for more somnolence with antidepressant-antipsychotic cotreatment versus antidepressants ($P = .02$). Only 1 open-label, 4-month extension study (n = 59) assessed maintenance/relapse-prevention efficacy of antidepressant-antipsychotic cotreatment versus antidepressant monotherapy, without group differences.

Conclusions: Antidepressant-antipsychotic cotreatment was superior to monotherapy with either drug class in the acute treatment of psychotic depression. These results support recent treatment guidelines, but more studies are needed to assess specific combinations and maintenance/relapse-prevention efficacy.

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According to recent estimates, approximately 20% of patients with a major depressive disorder have psychotic features.[1] This subtype, often referred to as *psychotic depression*, runs a more severe, debilitating course.[2,3] More recently, psychotic depression has been classified as a "primary" form of depression, differentiating it (together with unipolar depression, bipolar depression, and atypical depression) from conditions related to either stress-induced disorders or somatic disorders.[4] Historically, there has been conflicting evidence regarding the most appropriate and effective pharmacologic treatment of psychotic depression. According to the 2010 American Psychiatric Association *Guidelines for the Treatment of Patients With Major Depressive Disorder*, psychotic depression "typically responds better to the combination of an antipsychotic and an antidepressant medication rather than treatment with either component alone, although some research has shown comparable responses for antidepressive treatment or antipsychotic treatment alone."[5(p61)]

In 2006, a meta-analysis on the pharmacologic treatment of psychotic depression was published.[6] Although it included 10 studies published until 2004, only 5 randomized controlled trials, including 243 analyzable patients, compared antidepressant-antipsychotic cotreatment to either antidepressant or antipsychotic monotherapy. The other studies compared an antidepressant with placebo (1 study) or 2 antidepressants with each other (4 studies). On the basis of these limited data, the investigators concluded that the combination of an antipsychotic and an antidepressant was not more effective than antidepressant monotherapy but that antidepressant-antipsychotic cotreatment was superior to antipsychotic monotherapy.[5] Several larger, randomized controlled studies[7–9] have been conducted since, but no meta-analytic update has been conducted on the clinically relevant issue of whether or not

antidepressants and antipsychotics should be combined for the treatment of psychotic depression. Moreover, that prior meta-analysis[6] did not focus on adverse-effect outcomes or on the maintenance/relapse-prevention phase of psychotic depression. However, relapse prevention is a key treatment goal in psychotic depression. For example, in 1 study,[10] 27% of patients who had responded to a 5-week combination treatment of fluoxetine plus perphenazine and who had remained stable for an additional 3 months prior to perphenazine discontinuation relapsed within 2 months after discontinuation of perphenazine.

To update and extend the evaluation of the randomized controlled trial evidence for the efficacy and safety of pharmacologic treatment options for psychotic depression, we conducted a systematic review and meta-analysis on this issue. We hypothesized that antidepressant-antipsychotic combination treatment would be superior to monotherapy with either drug class due to complementary and, possibly, additive effects, especially when combining second-generation antipsychotics with antidepressants, as at least some agents have shown proven antidepressant efficacy as augmentation agents in nonpsychotic depression.[11]

Clinical Points

- Available evidence supports the use of antidepressant-antipsychotic combination treatment, rather than monotherapy with either an antipsychotic or antidepressant, for the acute management of psychotic depression.
- Data on specific antidepressant-antipsychotic combinations for the acute management of psychotic depression are too limited to allow for more detailed recommendations at this time.
- Evidence is lacking regarding the relative efficacy of antidepressant-antipsychotic combinations compared to monotherapy with either an antipsychotic or antidepressant for relapse prevention after an acute episode of psychotic depression.

METHOD

Search

We conducted an electronic search (from inception of databases until February 28, 2011) in PubMed/MEDLINE, Cochrane Library, and PsycINFO, without language or time restrictions, for double-blind, randomized controlled trials comparing antidepressant-antipsychotic combination therapy with monotherapy using an agent from either of the 2 medication classes in adults with major depressive disorder with psychotic features. Our search terms included (*psychosis* OR *psychotic* OR *hallucinations* OR *hallucinating* OR *delusions* or *delusional*) AND (*depression* OR *depressed* OR *major depressive disorder*) AND (*random* OR *randomized* OR *randomly*). The reference sections of relevant articles were screened for additional references, and we contacted authors to obtain specific results for patients with psychotic depression whenever such patients were part of a larger, more heterogeneous patient group and data were not reported separately. Moreover, corresponding authors of all included studies were contacted to provide additional data for the outcomes included in this meta-analysis. The 2 authors of this study independently identified and extracted data from the trials. Any inconsistency was discussed and resolved.

Outcome Parameters

The primary outcome of interest was study-defined inefficacy. We were interested separately in acute inefficacy, ie, lack of improvement, as well as in inefficacy of maintenance treatment, ie, illness recurrence or relapse. Secondary outcomes were all-cause discontinuation; specific-cause discontinuation; global illness severity; specific psychopathology scale scores for depression, psychosis, and anxiety; and side-effect rates. For an outcome to be included in the meta-analysis, data from at least 3 studies or comparisons had to be available. For the primary outcome of study-defined inefficacy and the key secondary outcome of all-cause discontinuation, we utilized the rule of "once randomized, then analyzed." For studies in which inefficacy or all-cause discontinuation results were provided only for patients who either completed at least a defined minimum duration of the trial (2 weeks[8,12] or 4 weeks of antidepressant plus 2 weeks of placebo or antipsychotic[13]) or had at least 1 postbaseline assessment, we recalculated the outcome in the intent-to-treat sample by counting the remaining patients who had not reached the predetermined study time point as nonresponders or dropouts, respectively.

However, as continuous psychopathology scale score outcomes and adverse-effect rates were reported only sparsely, we also conducted exploratory analyses of these outcomes, including studies that did not employ true last-observation-carried-forward analyses.[8,12,13] To minimize the chance of biasing the results, we included data only from studies in which data for > 80% of the originally randomized patients were available and when the magnitude of dropout rates was comparable, ie, < 15% difference between the study groups (see Table 1).

Meta-Analytic Calculations

We applied standard meta-analytic procedures as used by the Cochrane Collaboration throughout. For dichotomous data, we calculated the relative risk (RR), and for continuous data, we calculated standardized mean differences, yielding Hedges g as an effect size (ES) measure, both accompanied by their 95% confidence intervals (CIs). To combine studies, the random-effects model by DerSimonian and Laird,[14] which is more conservative than fixed-effects models, was used in all cases. For simplicity, each group comparison was counted as 1 "study" in the meta-analysis, even if 2 group comparisons were derived from a single 3-arm study (eg, see Wijkstra et al[7]). Similarly, a pooled safety analysis[15] from 2 separate studies was counted as 2 studies, although, due

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Table 1. Randomized Controlled Trials Comparing Antidepressant-Antipsychotic Cotreatment With Antidepressant Monotherapy

Study	Study Duration	Population	Mean Age (SD) [Range], y	Male Gender, N (%)	White Race, N (%)	Drug	Dose, Mean (SD), mg/d	N[a]
Acute-phase studies								
Spiker et al, 1985a[22]†	7-day washout, 5 weeks	RDC diagnosis; MDD + psychotic subtype on basis of delusions; SADS score ≥ 4; HDRS score ≥ 15	44.1 (13) [18–65]	22 (37.9)	54 (93)	Amitriptyline + Perphenazine	170 (45.5) + 54.2 (16.8)	22
						Amitriptyline	217.6 (46.7)	19
Anton and Burch, 1990[12]	4 weeks	Inpatients; *DSM-III* criteria; MDD with psychosis; HDRS score > 18	46.1 (11.5)	16 (76)	12 (57)	Amitriptyline + Perphenazine	209.5 + 33.5	25
			44.4 (12.4)	16 (94)	12 (71)	Amoxapine	411.8 (calculated)	21
Mulsant et al, 2001[13]	16 weeks	*DSM-III-R* criteria; MDD with psychotic features (delusions or hallucinations); HDRS score ≥ 18	74 (8)	4 (29)	14 (100)	Nortriptyline + Perphenazine	63.2 (45.2) + 18.9 (5.1)	17
			71 (10) [≥ 50]	4 (25)	15 (94)	Nortriptyline + Placebo	76.3 (34.6) + 19.3 (5.1)	19
Wijkstra et al, 2010a + b[7]†	4-day washout, 7 weeks	Inpatients; *DSM-IV* criteria; MDD with psychosis; HDRS-17 score ≥ 18	50.6 (11.2)	19 (46.3)	No data	Venlafaxine + Quetiapine	373.4 (11.2) + 598.9 (15)	41
			51.6 (9.6)	19 (45.2)		Imipramine	254.4 (101.1)	42
			49.5 (12) [18–65]	22 (56.4)		Venlafaxine	372.3 (14.2)	39
Künzel et al, 2009[8]	3-day washout, 6 weeks	*ICD-10* criteria; depressive episode with psychotic symptoms; HDRS-24 score > 17	51.4 (12.7)	15 (45.5)	No data	Trimipramine	356.1 (61.2)	49
			50.6 (13.3) [≥ 18]	8 (33.3)		Amitriptyline + Haloperidol	184.8 (23.6) + 6.3 (1.8) (doses at week 6)	43
Totals	4–16 weeks (mean = 7.6 weeks)		53.3	48.9	Mean = 83% (3 studies)	FGA + TCA vs non-TCA: no. = 4; SGA + non-TCA vs TCA: no. = 1; SGA + non-TCA vs non-TCA: no. = 1		337
Maintenance-phase study								
Wijkstra et al, 2010[7]†	15 weeks following a 7-week acute study	Same as in Wijkstra et al, 2010a + b	51.3	31 (52.5)	No data	Venlafaxine + Quetiapine		26
						Imipramine		20
						Venlafaxine		13

[a]Randomized number of subjects.
†Studies listed with an a or b indicate more than 1 study or more than 1 comparison in our meta-analysis.

to prior pooling by the authors, only 1 number went into the meta-analytic calculation. We explored study heterogeneity using the I^2 statistic, a measure estimating how much of the variance is explained by study heterogeneity.[16] Values for I^2 of 50% or higher were considered to reflect considerable heterogeneity. In such cases, we sought reasons explaining the heterogeneity, conducting sensitivity analyses. In the case of significant differences in categorical outcomes between groups, the number of participants needed to treat (NNT) or the number of participants needed to harm (NNH) was calculated as the inverse of the risk difference.

In addition to the primary analyses, we also examined a priori whether the results differed depending on the type of antidepressants, ie, tricyclic or tetracyclic antidepressant (TCA) versus non-TCA, and the type of antipsychotic, ie, first-generation antipsychotic (FGA) versus second-generation antipsychotic (SGA).

Rating Scales	Outcome Measures	Comments
HDRS-17 Delusion Rating Scale BPRS Raskin Global Rating Scale BPRS psychoticism subscale BPRS anxiety/agitation subscale	Responder: no longer depressed or delusional (delusional rating score = 1; HDRS score ≤ 6)	Demographics for total sample (N = 58); 84% (49/58) of randomized group diagnosed with unipolar depression; 85% (35/41) included in psychosis and depression ratings
HDRS-17 BPRS BPRS thought disorder subscale CGI-I CGI-S	Change in HDRS score > 50%; change in BPRS score > 50%; CGI-S score marked, or moderate or marked; Clinical Global Evaluation of slight or no illness	Demographic and efficacy data in those completing ≥ 2 weeks of treatment (n = 38); 84% (32/38) diagnosed with unipolar depression; 83% (38/46) of randomized sample included in CGI-S, psychosis, and side-effect measures
HDRS BPRS BPRS psychoticism subscale Simpson-Angus Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale	Full responder: resolution of both depression and psychosis (total score ≤ 10 on HDRS, and scores of 1 or 2 for BPRS items 11, 12, and 15)	Demographic, treatment, efficacy, and side-effect data included on participants completing 4 weeks of nortriptyline plus ≥ 2 weeks of placebo or perphenazine treatment, 83% (30/36) of randomized sample; 82% (14/17) in combo group; 84% (16/19) in monotherapy group
HDRS-17 CGI	Primary: response, ≥ 50% decrease in HDRS score from baseline and final HDRS score ≤ 14 Secondary: improvement on CGI, differences in mean changes in HDRS and CGI, absence of psychotic features, time to response	CGI, depression, and side-effect measures were based on entire sample; 41 patients in the antidepressant + antipsychotic group were used twice in the analyses as cotreatment group
HDRS-24 Montgomery-Asberg Depression Rating Scale CGI Paranoid Depression Scale Calgary Depression Scale Extrapyramidal Motor Symptom Scale Barnes Akathisia Scale	Response: decrease in HDRS-24 score ≤ 50%; Remission: HDRS-24 score ≤ 8	Demographics provided only for 57 patients (per protocol sample); 100% (92/92) of ITT sample included in efficacy, all-cause discontinuation, and side-effect measures; 96% (88/92) of ITT sample included in psychopathology ratings (those completing ≥ 2 weeks)
		41 patients in the antidepressant + antipsychotic group were used twice in the analyses as cotreatment group
HDRS-17 CGI	Maintenance of response: ≥ 50% decrease in HDRS score, plus HDRS score ≤ 14; Remission: HDRS score ≤ 7; Relapse: < 50% decrease in HDRS score, plus HDRS score > 14	59 of 122 originally randomized patients were responders after 7 weeks of treatment and were treated for an additional 15 weeks; 89.8% were completers; 86.4% maintained response; and 3.8% relapsed

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, FGA = first-generation antipsychotic, HDRS = Hamilton Depression Rating Scale, ITT = intent-to-treat, MDD = major depressive disorder, RDC = Research Diagnostic Criteria, SADS = Schedule for Affective Disorders and Schizophrenia, SGA = second-generation antipsychotic, TCA = tricyclic or tetracyclic antidepressant.

All meta-analytic calculations were performed with RevMan, version 5.1,[17] a meta-analytic standard software used by the Cochrane Collaboration. All analyses were 2-tailed, with α set at .05.

RESULTS

Our initial literature search in PubMed/MEDLINE yielded 756 articles as of February 28, 2011. By abstract review, we excluded 704 articles. We conducted full article reviews of the remaining 52 articles and found 2 more articles[12,18] from the references sections. Of these 54 articles, 10 articles reported on acute-phase randomized controlled trials comparing either antidepressant (AD) plus antipsychotic (AP) (AD + AP) combination treatment versus AD monotherapy or AD + AP combination treatment versus AP monotherapy in patients with major depressive disorder with psychotic features. One additional article[19] reported on the maintenance

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efficacy of AD + AP cotreatment versus AD monotherapy in a 4-month, open-label extension study of a 7-week, acute-phase study.[7] Additional searches of the Cochrane Library (yielding 326 Cochrane reviews, 60 "other reviews," and 482 clinical trials) and of PsychINFO (yielding 666 initial hits) did not uncover any additional relevant articles/studies.

Of the 10 articles with acute treatment trials identified by the search, we excluded 3. One article[20] was excluded because patients with psychotic depression represented only 31% of the randomized sample and it was not possible to obtain from the authors the data for just the psychotic depression subgroup. Another article[18] was excluded because one-third of the participants had bipolar disorder and separate data for patients with major depressive disorder with psychotic features were not provided or were not obtainable. A final article[21] was excluded because data contained in this article were from a preliminary analysis and were contained in the larger sample reported elsewhere.[12] Of the remaining 7 acute-treatment-phase articles, 2 articles[7,22] reported on 3 study groups, each article yielding 2 meta-analytic comparisons, designated with the letter "a" and "b," respectively. Another article[15] reported on 2 studies, so we designated them as Rothschild et al 2004a and Rothschild et al 2004b for efficacy outcomes and as Rothschild et al 2004c for the pooled side-effect data. Thus, our final acute-treatment-phase data set included 7 publications reporting on 8 studies, yielding 10 different comparisons of AD + AP cotreatment versus either AD or AP monotherapy.

The 8 acute-phase studies with 10 treatment comparisons included a total of 762 analyzable patients (range, 36–259 per study). Five studies with 6 comparisons (60%) compared AD + AP cotreatment versus AD monotherapy (Spiker et al, 1985a[22]; Anton and Burch, 1990[12]; Mulsant et al, 2001[13]; Künzel et al, 2009[8]; Wijkstra et al, 2010a[7]; Wijkstra et al, 2010b[7]), and 4 studies with 4 comparisons (40%) compared AD + AP cotreatment versus AP monotherapy (Spiker et al, 1985b[22]; Rothschild et al, 2004a[15]; Rothschild et al, 2004b[15]; Meyers et al, 2009[9]). All studies examined AD + AP cotreatment versus monotherapy with either drug class during the acute illness phase (mean study duration, 7.9 weeks; range, 4–16 weeks). Psychotic depression was diagnosed using standardized criteria in all studies, including the Research Diagnostic Criteria (1 study), *DSM-III* (2 studies), *DSM-IV* (4 studies), or *ICD-10* (1 study). In addition, one 4-month extension study[19] (including 59 patients who had completed a 7-week acute-phase trial[7]) reported on the maintenance efficacy of AD + AP cotreatment versus AD monotherapy.

Randomized Controlled Trials Comparing AD + AP Cotreatment Versus AD Monotherapy

Five acute-phase studies with 6 treatment comparisons (including 337 patients) compared AD + AP cotreatment versus AD monotherapy (mean age = 53.5 years, 48.9% male, 83% white). All studies were randomized double-blind trials including 36–88 analyzable patients. Four trials compared an FGA + TCA with a TCA, and 1 study with 3 arms compared an SGA + non-TCA (a serotonin-norepinephrine reuptake inhibitor [SNRI]) with either a TCA or a non-TCA (an SNRI). Study and patient characteristics are described in Table 1.

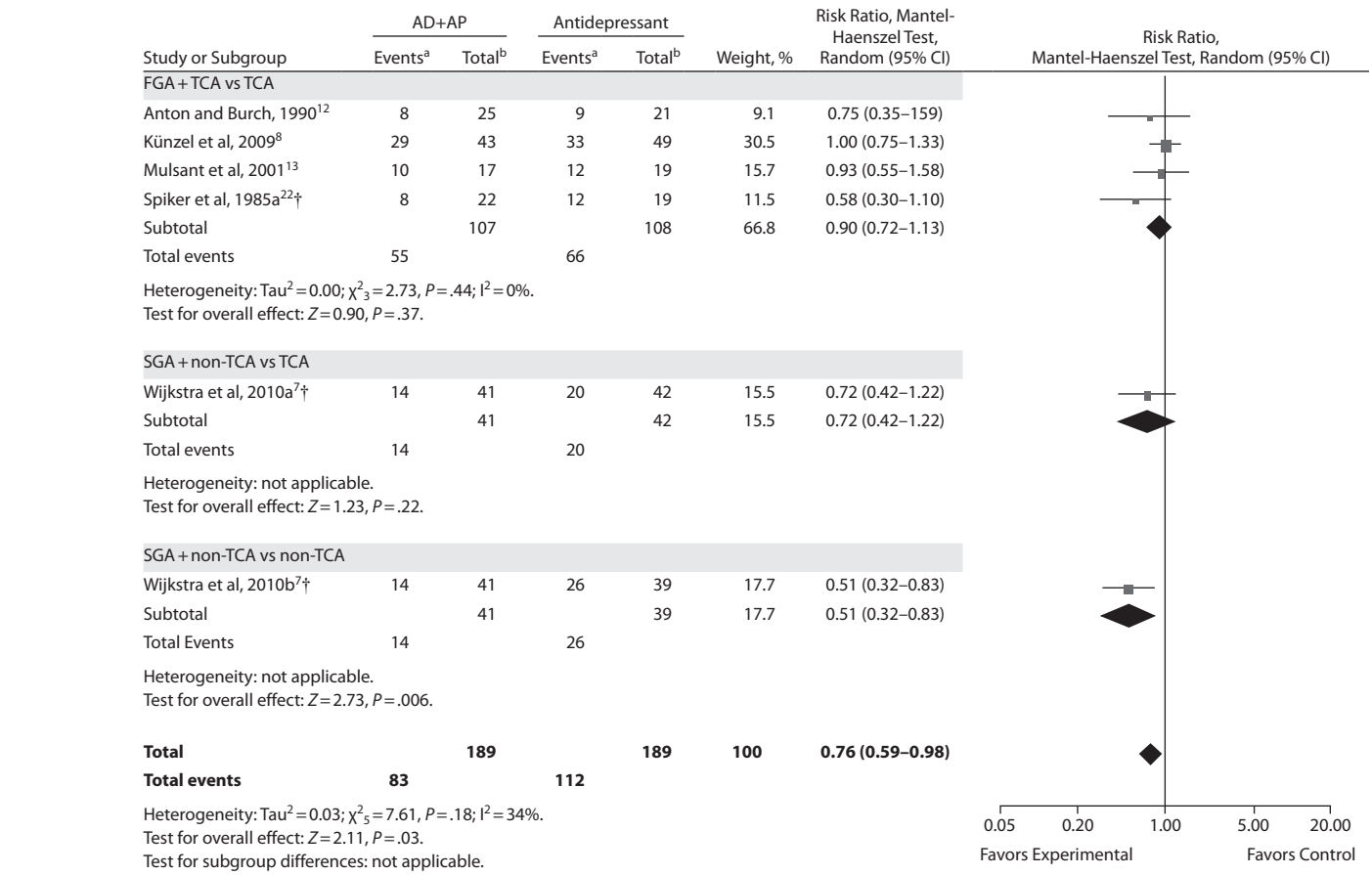
Study-defined inefficacy (Figure 1). Across all studies, AD + AP cotreatment was associated with significantly less study-defined inefficacy than AD monotherapy (no. of comparisons = 6; n = 378; RR = 0.76; 95% CI, 0.59–0.98; $P = .03$; $I^2 = 34\%$) (NNT = 7; 95% CI, 4–20; $P = .009$). Although the results were not significantly heterogeneous, an a priori planned subgroup analysis was conducted to investigate the effects of FGAs or SGAs as part of the combination group. For the FGA combination group, there was no significant difference between the combination treatment and monotherapy (no. of comparisons = 4; n = 215; RR = 0.9; 95% CI, 0.72–1.13; $P = .37$; $I^2 = 0\%$). On the other hand, when an SGA was added to an AD, this combination was associated with significantly less study-defined inefficacy than AD monotherapy (no. of comparisons = 2; n = 163; RR = 0.60; 95% CI, 0.42–0.85; $P = .004$; $I^2 = 0\%$) (NNT = 5; 95% CI, 3–25; $P = .02$). Although the overall results for the SGA combination group were significant, this level of significance was reached only when a non-TCA AD comparator was used ($P = .006$), whereas the results only trended in favor of the SGA + non-TCA combination when a TCA comparator was used ($P = .22$), but these subsamples were small.

All-cause discontinuation. There was no significant difference in all-cause discontinuation across all studies (no. of comparisons = 5; n = 342; RR = 0.89; 95% CI, 0.62–1.29; $P = .55$; $I^2 = 0\%$). There was also no difference within any of the 3 treatment subgroups.

Other outcomes (Table 2). There was a significant difference in Clinical Global Impressions-Severity of Illness (CGI-S) scores favoring combination therapy (no. of comparisons = 4; n = 289; ES = −0.25; 95% CI, −0.49 to −0.02; $P = .03$; $I^2 = 0\%$). There was a trend toward superiority of AP augmentation of an AD in depression ratings (no. of comparisons = 5; n = 324; ES = −0.20; 95% CI, −0.44 to 0.03; $P = .09$; $I^2 = 10\%$). There was no significant difference in psychosis ratings (no. of comparisons = 3; n = 161; ES = −0.24; 95% CI, −0.85 to 0.38; $P = .45$; $I^2 = 70\%$). Cotreatment with AD + AP was associated with higher rates of somnolence (no. of comparisons = 3; n = 255; RR = 2.79; 95% CI, 1.14–6.79; $P = .02$; $I^2 = 15\%$) (NNH not significant), but there were no additional between-group differences in side-effect rates involving at least 3 studies or group comparisons: blurry vision (no. of comparisons = 3; n = 201; RR = 0.43; 95% CI, 0.09–2.11; $P = .30$; $I^2 = 66\%$), dry mouth (no. of comparisons = 4; n = 293; RR = 1.13; 95% CI, 0.76–1.68; $P = .54$; $I^2 = 48\%$), dizziness (no. of comparisons = 4; n = 293; RR = 1.36; 95% CI, 0.93–1.98; $P = .11$; $I^2 = 0\%$), tremor (no. of comparisons = 3; n = 255; RR = 0.62; 95% CI, 0.29–1.30; $P = .20$; $I^2 = 0\%$), and constipation (no. of comparisons = 4; n = 293; RR = 1.19; 95% CI, 0.85–1.66; $P = .31$; $I^2 = 0\%$).

Finally, in the 4-month open-label extension study,[19] 59 of the originally randomized patients continued with

Figure 1. Antidepressant + Antipsychotic (AD + AP) Cotreatment Versus Antidepressant Monotherapy: Study-Defined Inefficacy



[a]Number of patients with the outcome. [b]Total number of patients per treatment arm.
†Studies listed with an a or b indicate more than 1 study or more than 1 comparison in our meta-analysis.
Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic, TCA = tricyclic or tetracyclic antidepressant.

Table 2. Effect Sizes (Hedges g) for Psychopathology Outcomes and Risk Ratios for Adverse Events

	Antidepressant + Antipsychotic Versus Antidepressant						Antidepressant + Antipsychotic Versus Antipsychotic					
Variable	No. of Comparisons	N	Hedges g	95% CI	I^2, %	*P* Value[a]	No. of Comparisons	N	Hedges g	95% CI	I^2, %	*P* Value[a]
Outcome[b]												
CGI-S	4	289	−0.25	−0.49 to −0.02	0	**.03**	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]
Depression	5	324	−0.20	−0.44 to 0.03	10	.09	4	428	−0.49	−0.75 to −0.23	27	**.0002**
Psychosis	3	161	−0.24	−0.85 to 0.38	70	.45	4	429	−0.35	−0.70 to 0.01	57	.06
Anxiety	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]	3	169	−0.39	−0.88 to 0.09	55	.11
			Risk Ratio						Risk Ratio			
Adverse event												
Blurry vision	3	201	0.43	0.09 to 2.11	66	.30	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]
Dry mouth	4	293	1.13	0.76 to 1.68	48	.54	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]
Dizziness	4	293	1.36	0.93 to 1.98	0	.11	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]
Tremor	3	255	0.62	0.29 to 1.30	0	.20	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]
Constipation	4	293	1.19	0.85 to 1.66	0	.31	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]
Somnolence	3	255	2.79	1.14 to 6.79	15	**.02**	3	408	1.02	0.74 to 1.41	0	.90
Weight gain	…[c]	…[c]	…[c]	…[c]	…[c]	…[c]	3	408	0.81	0.35 to 1.88	44	.63

[a]Bolded *P* values < .05. [b]Outcomes are reported here only if at least 3 comparisons could be analyzed. [c]Not applicable.
Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness scale.

maintenance treatment (quetiapine + venlafaxine: n = 26; venlafaxine: n = 13; imipramine: n = 20). During the 4 months of treatment, response status remained constant in 86.4% of patients, remission status increased from 59.3% to 86.8%, and only 2 patients (3.4%) relapsed, 1 in the imipramine group and 1 in the cotreatment group. None of these outcomes or any symptom changes or adverse effects differed significantly across the 3 small treatment groups. However, weight gain was considerable in all 3 groups, ie, 6.4 kg and 6.7 kg in the venlafaxine and imipramine groups, respectively, and 10.1 kg in the combination treatment group, translating into rates of weight gain ≥ 7% of 55%, 57%, and 84%, respectively.

Table 3. Randomized Controlled Trials Comparing Antidepressant-Antipsychotic Cotreatment With Antipsychotic Monotherapy

Study	Study Duration	Population	Mean Age (SD) [Range], y	Male Gender, N (%)	White Race, N (%)	Drug	Dose, Mean (SD), mg/d	N[a]
Spiker et al, 1985b[22]†	7-day washout, 5 weeks	RDC diagnosis; MDD + psychotic subtype on basis of delusions; SADS score ≥ 4; HDRS score ≥ 15	44.1 (13) [18–65]	22 (37.9)	54 (93)	Amitriptyline + Perphenazine	170 (45.5) + 54.2 (16.8)	22
						Perphenazine	49.8 (15.4)	17
Rothschild et al, 2004a[15]†	3–9 days of screening, 8 weeks	*DSM-IV* MDD with psychosis; HDRS-24 score ≥ 20	40.7 (12.6) [≥ 18]	60 (48.4)	71 (57.3)	Olanzapine + Fluoxetine	12.4 (4) + 23.5 (9.8)	25
						Olanzapine	11.9 (3.9)	48
Rothschild et al, 2004b[15]†	3–9 days of screening, 8 weeks	*DSM-IV* MDD with psychosis; HDRS-24 score ≥ 20	41.1 (10.4) [≥ 18]	62 (49.6)	77 (61.6)	Olanzapine + Fluoxetine	13.9 (4.3) + 22.6 (6.9)	23
						Olanzapine	14 (4.5)	53
Meyers et al, 2009[9]	12 weeks	Inpatient or outpatient; SCID-confirmed *DSM-IV* MDD with psychotic features; ≥ 1 delusional belief; ≥ 2 on 1 of the conviction items of the Delusion Assessment Scale; ≥ 3 on delusion severity rating item of the SADS; HDRS-17 score ≥ 21	57.4 (18)	46 (35.7)	110 (85.3)	Olanzapine + Sertraline	14.7 (4.7) + 169.7 (35)	129
			58.5 (17.5) [≥ 18]	47 (36.2)	108 (83.1)	Olanzapine + Placebo	14.3 (5.3) + 168.9 (44.1)	130
Totals	5–12 weeks (mean = 8.3 weeks)		Mean = 48.4 y	Mean = 41.6%	Mean = 76.1%	FGA + TCA vs FGA: no. = 1 SGA + non-TCA vs SGA: no. = 3		447

[a]Randomized number of subjects.
†Studies listed with an a or b indicate more than 1 study or more than 1 comparison in our meta-analysis.

Randomized Controlled Trials Comparing AD + AP Cotreatment Versus AP Monotherapy

Four studies including 447 patients compared AD + AP cotreatment versus AP monotherapy (mean age = 48.4 years, 41.6% male, 76.1% white). All studies were randomized double-blind trials including 39–259 analyzable patients. Three trials compared an SGA + non-TCA (a selective serotonin reuptake inhibitor [SSRI]) with an SGA, and 1 study compared an FGA + TCA with an FGA. Study and patient characteristics are described in Table 3.

Study-defined inefficacy (Figure 2). There was a significant difference in study-defined inefficacy favoring the AD augmentation of an AP versus AP monotherapy (no. of comparisons = 4; N = 447; RR = 0.73; 95% CI, 0.63–0.84; $P < .0001$; $I^2 = 0\%$) (NNT = 5; 95% CI, 4–8; $P < .0001$). The results were significant for the addition of a TCA to an FGA (no. of comparisons = 1; n = 39; RR = 0.52; 95% CI, 0.27–0.97; $P = .04$) (NNT = 3; 95% CI, 2–20), as well as for the addition of an SSRI to an SGA (no. of comparisons = 3; n = 408; RR = 0.74; 95% CI, 0.64–0.86; $P < .0001$; $I^2 = 0\%$) (NNT = 5; 95% CI, 4–10).

All-cause discontinuation. There was no significant difference in all-cause discontinuation across all studies (no. of comparisons = 4; N = 447; RR = 0.82; 95% CI, 0.62–1.08; $P = .16$; $I^2 = 26\%$). There was also no difference within any of the 2 subgroups.

Other outcomes (see Table 2). Cotreatment outperformed monotherapy in depression ratings (no. of comparisons = 4; n = 428; ES = –0.49; 95% CI, –0.75 to –0.23; $P = .0002$; $I^2 = 27\%$), but there was only trend-level superiority in psychosis ratings (no. of comparisons = 4; n = 429; ES = –0.35; 95% CI, –0.70 to 0.01; $P = .06$; $I^2 = 57\%$) and anxiety ratings (no. of comparisons = 3; n = 169; ES = –0.39; 95% CI, –0.88 to 0.09; $P = .11$; $I^2 = 55\%$). There were limited side-effect data available, but

Rating Scales	Outcome Measures	Comments
HDRS-17 Delusion Rating Scale BPRS Raskin Global Rating Scale BPRS psychoticism subscale BPRS anxiety/agitation subscale	Responder: no longer depressed or delusional (delusional rating score = 1; HDRS score ≤ 6)	Demographics for total sample (N = 58); 84% (49/58) of randomized group diagnosed with unipolar depression; 87% (34/39) of randomized sample included in psychosis, depression, and anxiety ratings; 22 patients in the antidepressant + antipsychotic group were used twice in the analyses as treatment group
HDRS-24 Hamilton Anxiety Rating Scale BPRS total BPRS positive CGI-S depression CGI-S psychosis CGI-S overall Simpson-Angus Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale	Response defined as ≥ 50% decrease on HDRS-24 from baseline to endpoint	Demographics based on n = 124, ie, including placebo group; 89% (65/73) of randomized sample included in depression, psychosis, and anxiety ratings; 100% (149/149) included in side effect analyses
HDRS-24 Hamilton Anxiety Rating Scale BPRS total BPRS positive CGI-S depression CGI-S psychosis CGI-S overall Simpson-Angus Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale	Response defined as ≥ 50% decrease on HDRS-24 from baseline to endpoint	Demographics based on n = 125, ie, including placebo group; 92% (70/76) of randomized sample included in depression and anxiety ratings, and 93% (71/76) included in psychosis ratings; 100% (149/149) included in side effect analyses
HDRS-17 SADS CGI-S used to define insufficient response Udvalg for Kliniske Undersøgelser (UKU) scale Simpson-Angus Scale Barnes Akathisia Scale Abnormal Involuntary Movement Scale	Remission defined as HDRS score ≤ 10 at 2 consecutive assessments and a SADS delusional item score of 1 at second assessment (1-week remission of delusion required)	No enforced washout period; 100% (259/259) of randomized patients included in depression ratings and side-effect measures; required delusion
		22 patients in the antidepressant + antipsychotic group were used twice in the analyses as cotreatment group

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, FGA = first-generation antipsychotic, HDRS = Hamilton Depression Rating Scale, MDD = major depressive disorder, RDC = Research Diagnostic Criteria, SADS = Schedule for Affective Disorders and Schizophrenia, SCID = Structured Clinical Interview for *DSM-IV* Axis I Disorders, SGA = second-generation antipsychotic, TCA = tricyclic or tetracyclic antidepressant.

there were no differences between the treatment groups for somnolence (no. of comparisons = 3; n = 408; RR = 1.02; 95% CI, 0.74–1.41; $P = .90$; $I^2 = 0\%$) and weight gain (no. of comparisons = 3; n = 408; RR = 0.81; 95% CI, 0.35–1.88; $P = .63$; $I^2 = 44\%$).

DISCUSSION

This meta-analysis is the largest to date evaluating the comparative efficacy of antidepressant-antipsychotic cotreatment versus monotherapy with either drug class alone for patients with psychotic depression. Compared to the previous meta-analysis[6] that included 243 analyzable patients, we included an additional 519 patients (an increase of 114%) from 3 more recent, larger trials[7–9] as well as 1 older study[12] not included in the prior analyses. In addition, due to lacking data, the previous systematic review[6] yielded a meta-analysis with only 1 single outcome, study-defined inefficacy. In our study, we also provide a meta-analysis of all-cause discontinuation, as well as exploratory analyses of other outcomes that shed additional light on the efficacy and tolerability of antidepressant-antipsychotic cotreatment for psychotic depression.

In line with our hypothesis, antidepressant-antipsychotic cotreatment was superior to monotherapy with either antipsychotics or antidepressants. This finding is consistent with clinical practice and recent guidelines,[5] although the latter[5] lacked sufficient trial evidence to back up the recommendation. Because of insufficient data, the previous meta-analysis[6] had been able to demonstrate superiority for antidepressant augmentation of antipsychotics compared to antipsychotic monotherapy only in terms of study-defined efficacy, yet the included studies were all small and the heterogeneity was large. In our updated meta-analysis that contains several

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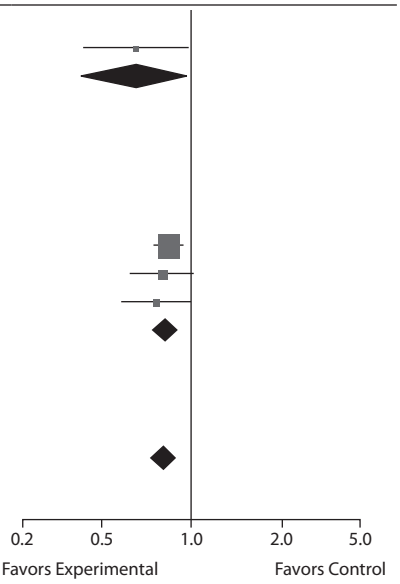
Figure 2. Antidepressant + Antipsychotic (AD + AP) Cotreatment Versus Antipsychotic Monotherapy: Study-Defined Inefficacy

Study or Subgroup	AD+AP Events[a]	AD+AP Total[b]	Antipsychotic Events[a]	Antipsychotic Total[b]	Weight, %	Risk Ratio, Mantel-Haenszel Test, Random (95% CI)
FGA + TCA vs FGA						
Spiker et al, 1985b[22]†	8	22	12	17	5.2	0.52 (0.27–0.97)
Subtotal		22		17	5.2	0.52 (0.27–0.97)
Total events	8		12			
Heterogeneity: not applicable. Test for overall effect: $Z = 2.06$, $P = .04$.						
SGA + non-TCA vs SGA						
Meyers et al, 2009[9]	75	129	99	130	68.0	0.76 (0.64–0.91)
Rothschild et al, 2004a[15]†	14	25	38	48	14.7	0.71 (0.49–1.03)
Rothschild et al, 2004b[15]†	12	23	42	53	12.1	0.66 (0.43–1.00)
Subtotal		177		231	94.8	0.74 (0.64–0.86)
Total events	101		179			
Heterogeneity: $Tau^2 = 0.00$; $\chi^2_2 = 0.49$, $P = .78$; $I^2 = 0\%$. Test for overall effect: $Z = 3.97$, $P < .0001$.						
Total		**199**		**248**	**100**	**0.73 (0.63–0.84)**
Total events	**109**		**191**			
Heterogeneity: $Tau^2 = 0.00$; $\chi^2_3 = 1.71$, $P = .64$; $I^2 = 0\%$. Test for overall effect: $Z = 4.34$, $P < .0001$. Test for subgroup differences: not applicable.						



[a]Number of patients with the outcome. [b]Total number of patients per treatment arm.
†Studies listed with an a or b indicate more than 1 study or more than 1 comparison in our meta-analysis.
Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic, TCA = tricyclic or tetracyclic antidepressant.

larger studies, we found antidepressant-antipsychotic cotreatment to be superior to either antidepressant or antipsychotic monotherapy, and the results were not heterogeneous. Although the addition of an FGA to a TCA had no advantage over TCA monotherapy in the prior meta-analysis,[6] the findings are consistent in the sense that FGA augmentation remained nonsignificant and only the addition of an SGA (quetiapine) was superior to antidepressant monotherapy (although this result was true only when the SGA was added to venlafaxine, not when added to imipramine). This finding highlights the need for additional studies to help tease apart the effectiveness of different combinations, at least at the level of FGA or SGA or TCA versus non-TCA augmentation and/or comparison. The evaluation of a larger number of individual drug combinations is relevant, as several SGAs appear to be efficacious for the treatment of unipolar depression[11] as well as for bipolar depression.[23] By contrast, there have been some suggestions that FGAs may be associated with a tendency to aggravate depression or lead to dysphoria, at least with monotherapy.[24] However, while results from 4 smaller studies suggest that FGA augmentation of TCAs does not provide superior efficacy compared to TCA monotherapy, no studies are available for FGA + non-TCA combinations compared to non-TCA monotherapy.

Regarding secondary outcomes, less stringent data were available, in that 3 studies[8,12,13] did not report on true intent-to-treat last-observation-carried-forward analysis. In exploratory analyses, we allowed for < 20% of patient dropouts to be excluded from the analyses if there was also no more than a 15% difference in dropout rates between randomized arms. The exclusion of some early dropouts from the analyses renders the findings more exploratory, highlighting that additional randomized controlled studies are needed that report on a diverse set of efficacy and tolerability outcomes in all randomized patients, the latter of which were particularly underreported. For example, fewer than 3 studies or group comparisons[7,8,12,13] each reported on the important outcomes of extrapyramidal side effects or akathisia, and only 3 studies[9,15] included information on patient- or physician-reported weight change, without sufficient data to calculate actual weight change in kilograms or body mass index. Moreover, not a single study assessed patient-reported efficacy outcomes, quality of life, or any other functional measures.

Importantly, even though this meta-analysis suggests that antidepressant-antipsychotic cotreatment is superior to monotherapy with either antidepressant or antipsychotic medications for the acute treatment of psychotic depression, only 1 small extension study[19] of a randomized trial[7] compared the combination treatment to monotherapy for another 15 weeks in responders to the original 7-week acute-phase trial, assessing the pressing questions of *if* and *for how long* the combination treatment should be continued to maintain efficacy and prevent illness recurrence. Such studies are urgently needed, given the fact that SGAs have been associated with weight gain and metabolic abnormalities that can have detrimental long-term health effects.[25–27]

The results of this meta-analysis need to be interpreted within the study's limitations. Although we had more than twice as many patients in this analysis as in the prior

meta-analysis,[6] still, most studies were small; methodologies, inclusion criteria, and outcomes (including the definition of "efficacy") varied; most trials investigated older agents (FGAs and TCAs); and specific psychopathology and adverse-event rates were not always provided for all randomized patients or were not provided at all. Moreover, data are available only for a limited set of individual antipsychotics and antidepressants, highlighting a strong need for studies that include non-TCAs and SGAs, which have become the standard of care. Furthermore, placebo-controlled trials in psychotic depression might lead to a selection bias of less severely ill patients. However, in the meta-analyzed trials, at least either antidepressant monotherapy or antipsychotic monotherapy was provided in addition to placebo, which might have reduced this potential selection bias. Additionally, we cannot exclude that negative studies in psychotic depression might not have been published. Nevertheless, despite this heterogeneity in methods, populations, and studied medications, the results for the primary outcome (ie, significantly less study-defined inefficacy) and the key secondary outcome (ie, similar all-cause discontinuation rates) were not significantly heterogeneous. Moreover, the results for these 2 important efficacy and tolerability/acceptability outcomes were based on full randomized intent-to-treat samples only.

CONCLUSION

In summary, this meta-analysis found that, for the acute treatment of psychotic depression, the combined use of antidepressants and antipsychotics was superior to either monotherapy strategy. Nevertheless, the number of studies and the number of tested combinations were quite limited. Therefore, more detailed studies testing more specific combinations are urgently needed to confirm that these results extend to multiple other combinations used in clinical practice. Moreover, randomized controlled maintenance and relapse-prevention studies are urgently needed to inform long-term treatment decisions in patients with psychotic depression. The additional study of combined antidepressant and antipsychotic versus monotherapy with each of these agents during the longer-term maintenance phase is particularly relevant, as at least a subgroup of patients with psychotic depression seems to have a high chance of developing psychosis again when relapsing into another major depressive episode.[28] To facilitate better comparability across trials, ideally, the psychiatric field should agree on a pragmatic set of inclusion and exclusion criteria and on standardized outcomes of response, remission, and relapse in patients with psychotic depression.

Drug names: fluoxetine (Prozac and others), fluoxetine-olanzapine (Symbyax), haloperidol (Haldol and others), imipramine (Tofranil and others), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), quetiapine (Seroquel), sertraline (Zoloft and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

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