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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 in PubMed/Medline, Cochrane Library and PsycINFO from inception of the data bases until 02/20/2012, without language/time restrictions. Key words 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 (n=762) in adults with standardized criteria-defined psychotic depression 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 and 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 risk ratios (RR) with 95% confidence intervals (CI), numbers-needed-to-treat/harm (NNT/NNH) and effect sizes (ES).

Results—Antipsychotic-antidepressant co-treatment outperformed antidepressant monotherapy regarding less study-defined inefficacy (N=6, n=378, RR:0.76, CI:0.60,0.96, p=0.03, I²=34%; NNT=7, CI:4-20, p=0.009) and Clinical Global Impressions-Severity (N=4, n=289, ES:-0.25, CI:-0.49,-0.02, p=0.03, I²=0%), with trend-level superiority for depression ratings (N=5, n=324,

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ES:-0.20, CI:-0.44,0.03, $p=0.09$, $I^2=10\%$), but not psychosis ($N=3$, $n=161$, ES:-0.24, CI:-0.85,0.38, $p=0.45$, $I^2=70\%$). Antidepressant-antipsychotic co-treatment also outperformed antipsychotic monotherapy regarding less study-defined inefficacy ($N=4$, $n=447$, RR:0.73, CI: 0.63,0.84, $p<0.0001$, $I^2=0\%$; NNT=5, CI:4-8, $p<0.0001$) and depression ($N=4$, $n=428$, ES:-0.49, CI:-0.75,-0.23, $p=0.0002$, $I^2=27\%$), while anxiety ($p=0.11$) and psychosis ratings ($p=0.06$) only trended favoring co-treatment. All-cause-discontinuation and reported side effect rates were similar, except for more somnolence with antipsychotic-antidepressant co-treatment versus antidepressants ($p=0.02$). Only one open, 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 of either 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.

Keywords

Depression; Psychosis; Antidepressants; Antipsychotics; Cotreatment; Combination; Efficacy; Meta-analysis

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

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 ($N=1$) or 2 antidepressants with each other ($N=4$). Based on these limited data, the investigators concluded that the combination of an antipsychotic plus antidepressant was not more effective than antidepressant monotherapy, but that antidepressant-antipsychotic cotreatment was superior to antipsychotic monotherapy.⁵ Several larger, randomized controlled studies⁷⁻⁹ have been conducted since, but no meta-analytic update has been reported on the clinically relevant issue of whether or not antidepressants and antipsychotics should be combined for the treatment of psychotic depression. Moreover, that meta-analysis⁶ 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, 27% of patients relapsed within 2 months after discontinuation of perphenazine who had responded to a 5-week combination treatment of fluoxetine plus perphenazine and who had remained stable for an additional three months prior to perphenazine discontinuation.¹⁰

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 combination treatment would be superior to monotherapy with either an antidepressant or antipsychotic 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 non-psychotic depression.¹¹

Methods

Search

We conducted an electronic search in PubMed/Medline, Cochrane Library and PsycINFO, without language or time restrictions, for double-blind, randomized controlled trials (DBRCT) comparing antipsychotic (AP)-antidepressant (AD) combination therapy with monotherapy with an agent from either of the two 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 two authors 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, i.e., lack of improvement, as well as in inefficacy of maintenance treatment, i.e., 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 three 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 analyzed." For studies where inefficacy or all-cause-discontinuation results were only provided 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 antipsychotic¹³) or who had at least 1 post baseline assessment, we re-calculated the

outcome in the intent-to-treat sample by counting the remaining patients who had not reached the pre-determined study time point as non-responders or drop-outs, 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 only included data from studies in which data for >80% of the originally randomized patients were available and only when the magnitude of dropout rates was comparable, i.e. <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 (SMD) yielding Hedges's *g* as an effect size (ES) measure, both along with their 95% confidence intervals (CI). To combine studies, the random effects model by Der-Simonian and Laird¹⁴ was used in all cases, which is more conservative than fixed effects models. For simplicity, each group comparison was counted as one "study" in the meta-analysis, even if two group comparisons were derived from a single, 3-arm study (e.g.⁷). Similarly, a pooled safety analysis¹⁵ from 2 separate studies were counted as 2 studies, although, due to prior pooling by the authors, only one 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 I^2 values 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, i.e., tricyclic or tetracyclic antidepressant (TCA) vs. non-TCA, and type of antipsychotic, i.e., first-generation antipsychotic (FGA) vs. second-generation antipsychotic (SGA).

All meta-analytic calculations were performed with RevMan 5.1, a meta-analytic standard software used by the Cochrane collaboration. All analyses were two-tailed, with alpha set at 0.05.¹⁷

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 paper reviews of the remaining 52 articles and found two more articles^{12,18} from the references sections. Of these 54 articles, 10 articles reported on acute randomized controlled trials comparing either AD +AP versus AD or AD+AP versus AP treatment in patients with major depressive disorder with psychotic features. One additional article¹⁹ reported on the maintenance efficacy of AD

+AP versus AD 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 identified by the search with acute treatment trials, we excluded 3 articles: one²⁰ because patients with psychotic depression represented only 31% of the randomized sample and it was not possible to obtain from the authors data just for the psychotic depression subgroup; another one¹⁸ 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 obtainable; and a final one²¹ because data contained in this article were from a preliminary analysis and contained in the larger sample reported elsewhere¹². Of the seven remaining articles, two articles^{7,22} reported on three study groups yielding two meta-analytic comparisons, designated with the letter a and b, respectively. Another article¹⁵ reported on 2 studies, so we designated them as Rothschild 2004a and Rothschild 2004b for efficacy outcomes and Rothschild 2004c for the pooled side effect data. Thus, our final acute treatment data set included seven publications reporting on eight studies, yielding 10 different comparisons of antipsychotic-antidepressant cotreatment versus either antidepressant or antipsychotic monotherapy.

The eight acute phase studies with 10 treatment comparisons included a total of 762 analyzable patients (range: 36-259 per study). Five studies with six comparisons (60%) compared AD+AP cotreatment against AD monotherapy (Spiker et al. 1985a²¹; Anton et al. 1990¹²; Mulsant et al. 2001¹³; Kunzel et al. 2009⁸; Wijkstra et al. 2010a⁷; Wijkstra et al. 2010b⁷) and 4 studies with four comparisons (40%) compared AD+AP against AP monotherapy (Spiker et al. 1985b²²; Rothschild et al. 2004a¹⁵; Rothschild et al. 2004b¹⁵; Meyers et al. 2009⁹). All studies examined AD-AP cotreatment vs. 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 (RDC) (N=1), Disorders (DSM)-III (N=2), DSM-IV (N=4) or International Statistical Classification of Diseases and Related Health Problems (ICD)-10 (N=1). In addition, one 4-month extension study including 59 patients who had completed a 7-week acute phase trial⁶ reported on the maintenance efficacy of AD +AP cotreatment vs. AD monotherapy.¹⁹

RCTs comparing AP+AD versus AD monotherapy

Five acute phase studies with six comparisons including 337 patients compared AP+AD vs. AD (mean age: 53.5 years, 48.9% male, 83% White). All were randomized, double blind trials including 36-88 analyzable patients. Four trials with four comparisons compared an FGA plus TCA with a TCA, and one study with three arms compared an SGA plus non-TCA (SNRI) with either a TCA or a non-TCA (SNRI). Study and patient characteristics are described in Table 1.

Study-Defined Inefficacy (see Figure 1)—Across all studies, AD+AP cotreatment was associated with significantly less study-defined inefficacy than AD monotherapy (N=6,

n=378, RR:0.76, CI:0.60, 0.96, p=0.03, $I^2=34\%$; NNT=7, CI:4, 20, p=0.009). Although the results were not significantly heterogeneous, an *a priori* planned subgroup analysis was conducted investigating 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 and monotherapy treatment (N=4, n=215, RR:0.9, CI:0.72, 1.13, p=0.37, $I^2=0\%$). On the other hand, when an SGA was added to an AD, this was associated with significantly less study-defined inefficacy than AD monotherapy (N=2, n=163, RR:0.60, CI:0.42, 0.85, p=0.004, $I^2=0\%$; NNT=5, CI:3, 25, p=0.02). Although the overall results for the SGA combination group were significant, this level of significance was only reached when a non-TCA AD was used (p=.004), whereas the results only trended in favor of the SGA + non-TCA combination when a TCA comparator was used (p=0.22), but these subsamples were small.

All Cause Discontinuation—There was no significant difference in all cause discontinuation across all studies (N=5, n=342, RR:0.89, CI:0.62, 1.29, p=0.55, $I^2=0\%$). There was also no difference within any of the 3 treatment subgroups.

Other Outcomes (see Table 2)—There was a significant difference in Clinical Global Impression-Severity (CGI-S) scores favoring combination therapy (N=4, n=289, ES:-0.25, CI:-0.49, -0.02, p=0.03, $I^2=0\%$). There was a trend towards superiority of antipsychotic augmentation of antidepressants in depression ratings (N=5, n=324, ES=-0.20, CI:-0.44, 0.03, p=0.09, $I^2=10\%$). There was no significant difference in psychosis ratings (N=3, n=161, ES=-0.24, CI: -0.85, 0.38, p=0.45, $I^2=70\%$). AD+AP cotreatment was associated with higher rates of somnolence (N=3, n=255, RR:2.79, CI:1.14, 6.79, p=0.02, $I^2=15\%$, NNH: not significant), but there were no additional between-group differences in side effects rates involving at least three studies/group comparisons: blurry vision (N=3, n=201, RR:0.43, CI:0.09, 2.11, p=0.30, $I^2=66\%$), dry mouth (N=4, n=293, RR:1.13, CI:0.76, 1.68, p=0.54, $I^2=48\%$), dizziness (N=4, n=293, RR:1.36, CI:0.93, 1.98, p=0.11, $I^2=0\%$), tremor (N=3, n=255, RR:0.62, CI:0.29, 1.30, p=0.20, $I^2=0\%$), and constipation (N=4, n=293, RR: 1.19, CI:0.85, 1.66, p=0.31, $I^2=0\%$).

Finally, in the 4-month open extension study¹⁹, 59 of the originally randomized patients continued in the maintenance treatment (quetiapine plus venlafaxine: n=26; venlafaxine: n=13; imipramine: n=20). During the four months of treatment, the response status remained constant in 86.4% of patients, remission status increased from 59.3% to 86.8%, and only two patients (3.8%) relapsed, one in the imipramine group and one in the cotreatment group. None of these outcomes, or any symptom changes or adverse effects differed significantly across the three small treatment groups. However, weight gain was considerable in all three groups, i.e., 6.4 kg and 6.7 kg with venlafaxine and imipramine, respectively, and 10.1 kg in the combination treatment group, translating into rates of weight gain 7% of 55%, 57% and 84%, respectively.

RCTs comparing AP+AD versus AP monotherapy

Four studies including 447 patients compared AP+AD vs. AP (mean age: 48.4 years, 41.6% male, 76.1% White). All were randomized, double blind trials including 39-259 analyzable

patients. Three trials compared an SGA plus non-TCA (SSRI) with a non-TCA (SSRI), and one study compared a FGA plus TCA with an FGA. Study and patient characteristics are described in Table 3.

Study-Defined Inefficacy (see Figure 2)—There was a significant difference in study-defined inefficacy favoring the AD augmentation of an AP versus AP monotherapy (N=4, n=447, RR:0.73, CI:0.63, 0.84, $p<0.0001$, $I^2=0\%$; NNT=5, CI: 4, 8, $p<0.0001$) The results were significant for the addition of a TCA to an FGA (N=1, n=39, RR:0.52, CI 0.27, 0.97, $p=0.04$; NNT=3, CI: 2, 20) as well as for the addition of an SNRI to an SGA (N=3, n=408, RR:0.74, CI:0.64, 0.86, $p<0.0001$, $I^2=0\%$; NNT=5, CI:4,10).

All Cause Discontinuation—There was no significant difference in all cause discontinuation across all studies (N=4, n=447, RR:0.82, CI:0.62, 1.08, $p=0.16$, $I^2=26\%$). There was also no difference in any of the 2 subgroups.

Other Outcomes (see Table 2)—Cotreatment outperformed monotherapy in depression ratings (N=4, n=428, ES:-0.49, CI:-0.75, -0.23, $p=0.0002$, $I^2=27\%$), but there was only trend level superiority in psychosis (N=4, n=429, ES=-0.35, CI:-0.7, 0.01, $p=0.06$, $I^2=57\%$) and anxiety ratings (N=3, n=169, ES=-0.39, CI -0.88, 0.09, $p=0.11$, $I^2=55\%$). There were limited side effect data available, but there were no differences between the treatment groups for somnolence (N=3, n=408, RR:1.02, CI:0.74, 1.41, $p=0.90$, $I^2=0\%$), and weight gain (N=3, n=408, RR:0.81, CI:0.35, 1.88, $p=0.63$, $I^2=44\%$).

Discussion

This is the largest meta-analysis evaluating the comparative efficacy of antidepressant-antipsychotic cotreatment vs. monotherapy with either an antidepressant or antipsychotic for patients with psychotic depression. Compared to the previous meta-analysis that included 243 analyzable patients⁶, we included an additional 519 patients (+114%) from three more recent, larger trials⁷⁻⁹ as well as one older study not included in the prior analyses¹². In addition, due to lacking data, the previous systematic review only yielded a meta-analysis of one single outcome, study-defined inefficacy⁶. In this 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 antipsychotic-antidepressant cotreatment for psychotic depression.

In line with our hypothesis, antipsychotic-antidepressant cotreatment was superior to monotherapy with either antipsychotics or antidepressants. This finding is consistent with clinical practice and recent guidelines,⁵ although the latter lacked sufficient trial evidence to back up the recommendation. Based on insufficient data, the previous meta-analysis had only been able to demonstrate superiority for antidepressant augmentation of antipsychotics compared to antipsychotic monotherapy regarding study-defined efficacy, yet the included studies were all small and the heterogeneity was large. In the updated meta-analysis that contains several 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-analysis⁶, findings are consistent in the sense that FGA augmentation remained non-significant and only the addition of an SGA (quetiapine) was superior to antidepressant monotherapy (although this was only true when added to venlafaxine, not when added to imipramine). This finding highlights that there is a need for additional studies to help tease apart the effectiveness of different combinations, at least at the level of FGA or SGA or TCA vs. non-TCA augmentation and/or comparison. This is relevant, as several SGAs appear to be efficacious for the treatment of unipolar depression¹¹ as well as for bipolar depression²³. By contrast, there have been some suggestions that FGAs may be associated with a tendency to aggravate depression or lead to dysphoria, at least in monotherapy²⁴. 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 group.

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 drop outs to be excluded from the analyses if there was also no more than a 15% difference in dropout rates between randomized arms. This 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 patient, the latter of which were particularly underreported. For example, less than three studies/group comparisons reported on the important outcomes of extrapyramidal side effects and akathisia, and only three studies 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 antipsychotic-antidepressant cotreatment is superior to monotherapy with either antidepressant or antipsychotic medications for the acute treatment of psychotic depression, only one, small extension study of a randomized trial,¹⁹ compared the combination treatment to monotherapy for another 15 weeks in responders to the original 7-week acute phase trial, assessing the pressing question 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 its limitations. Although we had more than twice as many patients in this than in the prior meta-analysis, 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 not provided at all. Moreover, data are only available for a limited set of individual antipsychotics and antidepressants, with a strong need for studies that include non-TCAs and SGAs, which have become 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, i.e., significantly less study-defined inefficacy, and the key secondary outcome, i.e., similar all-cause discontinuation rates, were not significantly heterogeneous. Moreover, the results for these two important, efficacy and tolerability/acceptability outcomes were based on full randomized ITT samples only.

Conclusion

In summary, this meta-analysis found that for the acute treatment of psychotic depression the combined use of antidepressants plus antipsychotics was superior to either monotherapy strategy. Nevertheless, the number of studies and of the tested combinations was 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. This is particularly relevant, as at least a subgroup of patients with psychotic depression may seem to have a high chance of developing psychosis again when relapsing into another major depressive episode²⁸. To facilitate better comparability across trials, ideally, the field should agree on a pragmatic set of in- and exclusion criteria and on standardized outcomes of response, remission and relapse in patients with psychotic depression.

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Clinical Points

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

Figure 1. Antipsychotic + Antidepressant Versus Antidepressant: Study Defined Inefficacy

Figure 2. Antipsychotic + Antidepressant Versus Antipsychotic : Study Defined Inefficacy

Table 1
Randomized Controlled Trials Comparing Antidepressant-Antipsychotic Cotreatment with Antidepressant Monotherapy

Study	Duration	Population	Mean Age, (SD) [range]	Male Gender, N (%)	White Race, N (%)	Drug	Mean Dose mg/day (SD)	N*	Rating Scales	Outcome Measures	Comments
Acute Phase Studies											
Spiker 1985a	7-day washout, 5 wks	RDC diagnosis MDD + psychotic subtype on basis of delusion, SADS 4, HAM-D 15	44.1 (13) [18-65]	22 (37.9)	54 (93)	Amitriptyline + Perphenazine Amitriptyline	170(45.5)+54.2(16.8) 217.6 (46.7)	22 19	HAM-D-17 Delusional Rating Scale BPRS Raskin Global Rating Scale Psychoticism subscale Anxiety/Agitation subscale	Responder=no longer depressed or delusional (delusional rating score=1, HAM-D 6)	Demographics for total sample (n=58); 49/58 (84%) of randomized group diagnosed w/ unipolar depression, 35/41 (85%) with psychosis and depression ratings
Anton 1990	4 wks	Inpatients, DSM-III Criteria MDD with psychosis, HAM-D>18	46.1(11.5) 44.4(12.4)	16(76) 16(94)	12(57) 12(71)	Amitriptyline + Perphenazine Amoxapine	209.5 + 33.5 411.8 (calculated)	25 21	HAM-D-17, BPRS, BPRS thought disorder subscale, CGI-I, CGI-S	HAM-D >50%, BPRS > 50%, CGI-S marked or moderate or marked, CGE of slight or no illness	Demographic + efficacy data in those completing 2 wks treatment (n=38); 32/38 (84%) diagnosed w/ unipolar depression, 38/46 (83%) of randomized sample included in CGI-S, psychosis, + side effect measures
Mulsant 2001	16 wks	DSM-III-R MDD with psychotic features (delusions or hallucinations), HAM-D 18	74 (8) 71 (10) [50]	4 (29) 4 (25)	14(100) 15(94)	Nortriptyline + Perphenazine Nortriptyline + Placebo	63.2(45.2) + 18.9(5.1) 76.3 (34.6) + 19.3(5.1)	17 19	HAM-D, BPRS, BPRS psychoticism subscale, Simpson-Angus Scale, Barnes Akathisia Scale, AIMS	Full responder =resolution of both depression and psychosis (total score 10 on HAM-D and scores of 1 or 2 for BPRS item 11,12, and 15)	Demographic, treatment, efficacy, side effect data in participants completing 4 wks of nortriptyline plus 2 wks of placebo or perphenazine treatment (30/36) (83%) of randomized sample; 14/17 (82%) in combo group, 16/19 (84%) in monotherapy group
Wijkstra 2010 a+b	4-day washout, 7 wks	Inpatients, DSM-IV MDD with psychosis, HAM-D –17 18	50.6(11.2) 51.6 (9.6) 49.5 (12) [18-65]	19(46.3) 19(45.2) 22(56.4)	No data	Venlafaxine + Quetiapine Imiprimine Venlafaxine	373.4(11.2) + 598.9(15) 254.4(101.1) 372.3 (14.2)	41 42 39	HAM-D-17, CGI	Primary: Response 50% ↓ in HAM-D score from baseline and final HAM-D 14. Secondary: improvement on CGI, differences in mean changes in HAM-D and CGI, absence of psychotic features, time to response	CGI, depression and side effect measures based on entire sample.41 patients in the AP+AD group used twice in the analyses as co-treatment group.
Kunzel 2009	3-day washout, 6 wks	ICD-10 depressive episode with psychotic symptoms, HAM-D-24 >17	51.4 (12.7) 50.6 (13.3) [18]	15(45.5) 8 (33.3)	No data	Trimipramine Amitriptyline + Haloperidol	356.1 (61.2) 184.8(23.6) 6.3(1.8) (doses at wk 6)	49 43	HAM-D-24, MADRS, CGI, Paranoid-Depression, Calgary Depression Scale,	Response decrease HAM-D-24 50%, Remission HAM-D-24 8	Demographics only provided for 57 patients (per protocol sample). 92/92 (100%) of ITT sample included in efficacy, all cause d/c,

Study	Duration	Population	Mean Age, (SD) [range]	Male Gender, N (%)	White Race, N (%)	Drug	Mean Dose mg/day (SD)	N*	Rating Scales	Outcome Measures	Comments
Total	4-16 (mean:7.6) wks		Mean: 53.3 years	Mean: 48.9%	Mean: 83% (3 studies)	FGA+TCA vs non-TCA=4 SGA+non-TCA vs TCA=1 SGA+non-TCA vs non-TCA=1		337	Extrapryramidal motor symptom scale, Barnes Akathisia Scale Extrapryramidal motor symptom scale, Barnes Akathisia Scale Extrapryramidal motor symptom scale, Barnes Akathisia Scale Extrapryramidal motor symptom scale, Barnes Akathisia Scale	symptom scale, Barnes Akathisia Scale symptom scale, Barnes Akathisia Scale symptom scale, Barnes Akathisia Scale symptom scale, Barnes Akathisia Scale	six effect measures. of ITT included in pathology ratings, (those completing 2 wks).
Maintenance Phase Studies											
Wijkstra 2010 c	15 weeks following a 7 week acute study	Same as in Wijkstra et al. 2010a and b	51.3	31 (52.5)	No data	Venlafaxine + Quetiapine Imiprimine Venlafaxine		26 20 13	HAM-D-17, CGI	Maintenance of response: 50% ↓ in HAM-D + HAM-D 14; Remission: HAM-D 7; Relapse: <50% ↓ in HAM-D + HAM-D > 14	59/122 originally randomized patients were responders after 7 wks of treatment and treated for an additional 15 wks; 89.8% completers; 86.4% maintained response; 3.8% relapsed.

randomized number of subjects;

: change; AIMS: Abnormal Involuntary Movement Scale; BPRS: Brief Psychiatric Rating Scale; CGI-I: Clinical Global Impressions-Improvement Scale; CGI-S: Clinical Global Impressions-Severity Scale; DSM: Diagnostic and Statistical Manual; FGA: first-generation antipsychotic; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: Hamilton Depression Rating Scale; ICD: International Classification of Diseases; ITT: intent-to-treat; MADRS: Montgomery-Asberg Depression Scale; MDD: major depressive disorder; RDC: Research Diagnostic Criteria; SADS: Schedule for affective disorders and schizophrenia; SGA: second-generation antipsychotic; TCA: tricyclic antidepressant

Table 2
Effect Sizes for Psychopathology Outcomes and Risk Ratios for Adverse Events

Antidepressant + Antipsychotic versus Antidepressant							Antidepressant +Antipsychotic versus Antipsychotic						
Outcome	N	n	Hedges g	95% CI	I ² %	P-Value	Outcome	N	n	Hedges g	95% CI	I ²	P-Value
CGI-S	4	289	-0.25	-0.49, -0.02	0%	0.03	-	-	-	-	-	-	-
Depression	5	324	-0.20	-0.44, 0.03	10%	0.09	Depression	4	428	-0.49	-0.75, -0.23	27%	0.0002
Psychosis	3	161	-0.24	-0.85, 0.38	70%	0.45	Psychosis	4	429	-0.35	-0.7, 0.01	57%	0.06
-	-	-	-	-	-	-	Anxiety	3	169	-0.39	-0.88, 0.09	55%	0.11
Outcome	N	n	RR	95% CI	I ² %	P	Outcome	N	n	RR	95% CI	I ² %	P
Blurry Vision	3	201	0.43	0.09, 2.11	66%	0.30	-	-	-	-	-	-	-
Dry Mouth	4	293	1.13	0.76, 1.68	48%	0.54	-	-	-	-	-	-	-
Dizziness	4	293	1.36	0.93, 1.98	0%	0.11	-	-	-	-	-	-	-
Tremor	3	255	0.62	0.29, 1.30	0%	0.20	-	-	-	-	-	-	-
Constipation	4	293	1.19	0.85, 1.66	0%	0.31	-	-	-	-	-	-	-
Somnolence	3	255	2.79	1.14, 6.79	15%	0.02	Somnolence	3	408	1.02	0.74, 1.41	0%	0.90
							Weight Gain	3	408	0.81	0.35, 1.88	44%	0.63

CI: confidence interval; N: number of studies; n: number of subjects; RR: Risk Ratio; bolded p-values <0.05; outcomes only reported here if at least 3 comparisons could be analyzed

Table 3
Randomized Controlled Trials Comparing Antidepressant-Antipsychotic Cotreatment with Antipsychotic Monotherapy

Study	Duration	Population	Mean Age (SD) [range]	Male Gender, N (%)	White Race, N (%)	Drug	Mean Dose mg/day (SD)	N*	Rating Scales	Outcome Measures	Comments
Spiker 1985b	7-day washout, 5 wks	Ages 18-65, RDC diagnosis MDD +psychotic subtype on basis of delusion, SADS 4, HAM-D 15	44.1 (13) [18-65]	22 (37.9)	54 (93)	Amiripityline v+ Perphenazine	170(45.5) + 54.2(16.8) 49.8 (15.4)	22 17	HAM-D-17, Delusional Rating Scale BPRS, Raskin Global Rating Scale, Psychoticism subscale, Anxiety/agitation subscale	Responder=no longer depressed or delusional (delusional rating score=1, HAM-D 6)	Demographics for total sample (n=58): 49/58 (84%) of randomized group diagnosed w/ unipolar depression. 34/39 (87%) of randomized sample included in psychosis, depression, and anxiety ratings. 22 patients in the AP+AD group used twice in the analyses as treatment group
Rothschild 2004a	3-9 day screening, 8wks	DSM IV MDD with psychosis, HAM-D-24 score 20	40.7 (12.6) [18]	60(48.4)	71(57.3)	Olanzapine + Fluoxetine Olanzapine	12.4(4) + 23.5(9.8) 11.9 (3.9)	25 48	HAM-D-24, HAM-A, BPRS total, BPRS positive, CGI-S depression, CGI-S psychosis CGI-S overall, Simpson-Angus Scale, Barnes Akathisia Scale, AIMS	Response defined as 50% decrease on HAM-D-24 at endpoint from baseline	Demographics based on n=124, i.e., including placebo group, 65/73 (89%) of randomized sample with depression, psychosis, anxiety ratings, 149/149 (100%) included in side effect analyses
Rothschild 2004b	3-9 day screening, 8wks	DSM IV MDD with psychosis, HAM-D-24 score 20	41.1 (10.4) [18]	62(49.6)	77(61.6)	Olanzapine + Fluoxetine Olanzapine	13.9(4.3) + 22.6(6.9) 14(4.5)	23 53	HAM-D-24, HAM-A, BPRS total, BPRS positive, CGI-S depression, CGI-S psychosis, CGI-S overall, Simpson-Angus Scale, Barnes Akathisia Scale, AIMS	Response defined as 50% decrease on HAM-D-24 at endpoint from baseline	Demographics based on n=125, i.e., including placebo group, 70/76 (92%) of randomized sample with depression and anxiety ratings, 71/76 (93%) with psychosis ratings. 149/149 (100%) included in side effect analyses
Meyers 2009	12 wks	In- or outpatient, SCID confirmed DSM-IV MDD with psychotic features, 1 delusional belief, 2 on 1 of the conviction items of the Delusional Assessment Scale, 3 on delusion severity rating item of the	57.4 (18) 58.5(17.5) [18]	46(35.7) 47(36.2)	110(85.3) 108(83.1)	Olanzapine + Sertraline Olanzapine + Placebo	14.7 (4.7) + 169.7(35) 14.3(5.3) + 168.9(44.1)	129 130	HAM-D-17, SADS, CGI-S-used to define insufficient response, Udvalg for Kliniske Undersogelser (UKU) scale, Simpson-Angus Scale, Barnes Akathisia Scale, AIMS	Remission defined as HAM-D 10 at 2 consecutive assessments and SADS delusional item score of 1 at second assessment (1 week remission of delusion required)	No enforced washout period. 259/259 (100%) of randomized patients with depression ratings and side effect measures Required delusion.

Study	Duration	Population	Mean Age (SD) [range]	Male Gender, N (%)	White Race, N (%)	Drug	Mean Dose mg/day (SD)	N*	Rating Scales	Outcome Measures	Comments
Total	5-12 (mean:8.3) wks	SADS, HAM-D-17 SADS,2HAM-D-17	Mean: 48.4 years	Mean 41.6%	Mean: 76.1%	FGA+TCA vs FGA=1 SGA+non-TCA vs SGA =3		447			22 patients in the AP+AD group used twice in the analyses as co-treatment group

* randomized number of subjects;

: change; AIMS: Abnormal Involuntary Movement Scale; AD: antidepressant; AP: antipsychotic; BPRS: Brief Psychiatric Rating Scale; CGI-I: Clinical Global Impressions-Improvement Scale; CGI-S: Clinical Global Impressions-Severity Scale; DSM: Diagnostic and Statistical Manual; FGA: first-generation antipsychotic; HAM-A: Hamilton Anxiety Rating Scale; HAM-D: 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 Disorders; SGA: second-generation antipsychotic, TCA: tricyclic antidepressant