Augmentation of Antidepressants With Atypical Antipsychotic Medications for Treatment-Resistant Major Depressive Disorder: A Meta-Analysis

George I. Papakostas, M.D.; Richard C. Shelton, M.D.; Juliana Smith, B.A.; and Maurizio Fava, M.D.

Objective: To examine the efficacy and overall tolerability of augmentation of standard antidepressants with atypical antipsychotic agents for treatment-resistant major depressive disorder.

Data Sources: MEDLINE/PubMed, EMBASE, the Cochrane database, and program syllabi from major psychiatric meetings held since 2000 as well as a number of online clinical trial results registries were searched. Makers of atypical antipsychotic agents who do not maintain an online clinical study results registry were contacted directly.

Study Selection: Double-blind, randomized, placebo-controlled clinical trials assessing adjunctive treatment of standard antidepressants with an atypical antipsychotic agent for treatment-resistant major depressive disorder were identified.

Data Extraction: Data were extracted with the use of a pre-coded form.

Data Synthesis: Data from 10 clinical trial reports involving a total of 1500 outpatients with treatment-resistant major depressive disorder were identified and combined using a random-effects model. Patients randomized to adjunctive treatment with an atypical antipsychotic agent were more likely to experience remission (risk ratio [RR] = 1.75, $p < .0001$) or clinical response (RR = 1.35, $p = .001$) than patients who received adjunctive placebo. Pooled remission and response rates for the 2 treatment groups were 47.4% vs. 22.3% and 57.2% vs. 35.4%, respectively. Although there was no difference in overall discontinuation rates ($p = .929$) or the rate of discontinuation due to inefficacy ($p = .133$) between the 2 treatment groups, the rate of discontinuation due to adverse events was lower among placebo-treated patients (RR = 3.38, $p < .0001$).

Conclusions: These results support the utility of augmenting standard antidepressants with atypical antipsychotic agents for treatment-resistant major depressive disorder. An obvious limitation of this work is the absence of data focusing on the use of aripiprazole and ziprasidone. Future short- as well as long-term studies comparing the efficacy, safety, and tolerability of this versus other adjunctive strategies are warranted.

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Corresponding author and reprints: George I. Papakostas, M.D., Massachusetts General Hospital, Department of Psychiatry, Depression Clinical and Research Program, 15 Parkman St., WAC 812, Boston, MA 02114 (e-mail: gpapakostas@partners.org).

Despite the progressive increase in the number of available antidepressants,[1] many patients suffering from depression continue to be symptomatic. For example, as many as half of all patients enrolled in 2 academic-based depression specialty clinics did not achieve remission despite receiving numerous adequate antidepressant trials.[2] To complicate matters further, residual symptoms among remitters are common and are associated with poorer psychosocial functioning[3] as well as increased relapse rates.[4] Yet, there is little consensus among psychiatrists regarding optimizing treatment for patients with incomplete response.

In light of the challenge that treatment-resistant major depressive disorder (TRD) poses to clinicians and patients alike, there is an urgent need to develop novel treatment strategies for resistant depression that are both safer and more effective than those currently employed. Judging by their complex receptor-binding profile as well as their effects on brain neurotransmitters, regional brain activity, and neuroplastic properties, the atypical antipsychotic agents offer a spectrum of activities suggestive of antidepressant utility.[5] Not surprisingly, although conventional antipsychotics have long been used to treat psychotic and delusional depression, the atypical antipsychotics, with their reduced side effect profiles, are emerging as beneficial adjunctive therapy for treatment-resistant, nonpsychotic depression.[5] In 1999, for example, almost 70% of prescriptions worldwide were written for off-label uses,[6] including their use as adjunctive treatment in TRD.

However, the efficacy of this popular off-label treatment strategy has yet to be firmly established. Although

numerous reports have been published examining the combination of atypical antipsychotic agents and antidepressants in TRD,[5] the vast majority of these studies consist of case reports/series or open-label clinical trials.[7–24] Until recently, there has been a paucity of double-blind, randomized, placebo-controlled trials, with a handful of published studies presenting conflicting results.[25–28] However, a number of studies of rigorous design focusing on the use of these agents as adjuncts in TRD have recently been conducted. In light of the widespread, off-label use of the atypical antipsychotic agents for TRD, there is an urgent need to examine whether such a popular treatment approach is, indeed, both safe and effective. The purpose of this work was to conduct a systematic review and meta-analysis of all double-blind, randomized, placebo-controlled clinical trials assessing adjunctive treatment of standard antidepressants with an atypical antipsychotic for TRD.

METHOD

Data Sources and Search Strategy

Studies were first identified using searches of MEDLINE/PubMed. Searches were conducted by cross-referencing the term depression with each of the 5 following terms: *risperidone*, *olanzapine*, *quetiapine*, *ziprasidone*, and *aripiprazole*. The search was limited to "randomized controlled trials." No language or year of publication limits were used. These searches were then repeated using EMBASE and the Cochrane database as well.

We also obtained the program syllabi and searched the abstracts of major psychiatric meetings held since 2000 (American Psychiatric Association; New Clinical Drug Evaluation Unit of the National Institute of Mental Health; American College of Neuropsychopharmacology; European College of Neuropsychopharmacology; Collegium Internationale Neuropsychopharmacologicum; Society of Biological Psychiatry, World Federation of Societies of Biological Psychiatry; World Psychiatric Association). Authors or study sponsors were contacted in order to obtain a copy of the presentation as well as any pertinent study details. Finally, the clinical trial registries of the makers of olanzapine (Eli Lilly: www.lillytrials.com), quetiapine (AstraZeneca: www.astrazenecaclinicaltrials.com), and aripiprazole (Bristol-Myers Squibb: ctr.bms.com/ctd/start.do) as well as the PhRMA clinical trial results registry (www.clinicalstudyresults.org) were searched for completed trials not published or presented at major psychiatric meetings. At this time, the makers of ziprasidone (Pfizer) and risperidone (Janssen) do not have clinical trial results registries. Therefore, these companies were directly contacted in order to solicit for completed studies not presented at major psychiatric meetings or published.

Study Selection

We selected randomized, double-blind, placebo-controlled clinical trials assessing adjunctive treatment of standard antidepressants with an atypical antipsychotic for major depressive disorder. We then selected for studies which also met all of the following inclusion criteria: (1) studies that used either the Hamilton Rating Scale for Depression (HAM-D)[29] or the Montgomery-Asberg Depression Rating Scale (MADRS)[30] as their primary outcome measure and (2) studies that exclusively focused on TRD.

Reports were excluded if they exclusively focused on the treatment of patients with bipolar disorder, dysthymic disorder, psychotic major depressive disorder, minor depressive disorder, or seasonal affective disorder or depressed patients with a specific medical condition or active alcohol or substance abuse disorders. Reports not describing original data (i.e., containing data published elsewhere) and those that were not focused on the acute phase of treatment (i.e., continuation, maintenance, or relapse prevention) were excluded.

Data Extraction

Data were extracted with the use of a precoded form. The following data were extracted from studies included in the meta-analysis: the criteria used to establish the diagnosis of major depressive disorder, the number of patients randomized to each treatment arm, the antidepressants and antipsychotic agents used as well as their doses, the duration of the trial, the primary outcome measure used (HAM-D or MADRS), response rates and remission rates for the primary outcome measure, overall discontinuation rates, the rate of discontinuation due to adverse events, and the rate of discontinuation due to inefficacy.

Quantitative Data Synthesis

The primary outcome of the meta-analysis was to compare remission rates between the adjunctive atypical antipsychotic–treated and placebo-treated groups using the primary outcome measure (i.e., HAM-D or MADRS) of the individual study. To accomplish this, we pooled the estimates of remission rates among studies after examining for homogeneity using the test statistic proposed by DerSimonian and Laird.[31] Examination of the pooled results was performed using both the fixed- and random-effects models to ascertain differences in pooled estimates by the 2 techniques.[31–33] We presented as our final estimate the findings of the random-effects model; this model is more conservative than the fixed-effects model and incorporates both within-study and between-study variance.

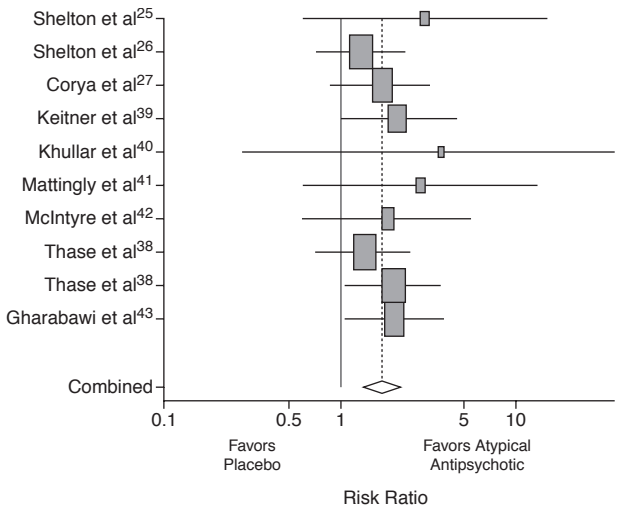
Secondary outcomes included comparing the rates of response, overall discontinuation, discontinuation due to inefficacy, and discontinuation due to adverse events. We also used a random-effects model to compare the 2 treatment groups on all secondary outcome measures. All

Table 1. Studies Included in the Meta-Analysis

Study	Atypical Antipsychotic	Antidepressant	Primary Outcome Measure	Duration, wk	N	Remission
Shelton et al[25]	Olanzapine	Fluoxetine	MADRS	8	20	MADRS score < 9
Shelton et al[26]	Olanzapine	Fluoxetine	MADRS	12	288	MADRS score < 9
Corya et al[27]	Olanzapine	Fluoxetine	MADRS	12	303	MADRS score < 9
Keitner et al[39]	Risperidone	Various	MADRS	4	100	MADRS score < 11
Khullar et al[40]	Quetiapine	SSRI or SNRI	HAM-D-17	8	15	HAM-D-17 score < 8
Mattingly et al[41]	Quetiapine	SSRI or SNRI	HAM-D-17	8	36	HAM-D-17 score < 8
McIntyre et al[42]	Quetiapine	SSRI or SNRI	HAM-D-17	8	58	HAM-D-17 score < 8
Thase et al[38]	Olanzapine	Fluoxetine	MADRS	8	206	MADRS score < 11
Thase et al[38]	Olanzapine	Fluoxetine	MADRS	8	200	MADRS score < 11
Gharabawi et al[43]	Risperidone	Various	HAM-D-17	6	274	HAM-D-17 score < 8

Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Primary Meta-Analytic Findings: Remission



analyses utilized the meta package of meta-analytic tools as implemented in Stata 8.0 (Stata, College Station, Tex.).

RESULTS

Initially 116 abstracts were identified with the use of MEDLINE/PubMed. Of these, 112 did not meet the inclusion criteria. The remaining 4 abstracts described double-blind, randomized clinical trials comparing adjunctive treatment with an atypical antipsychotic agent versus placebo for TRD. These 4 articles were obtained, and reviewed thoroughly. One of these articles was excluded because it did not focus on the acute phase of treatment (Rapaport et al.[28] was a relapse prevention study). The remaining 3 articles were included in the meta-analysis. No additional studies were identified with either EMBASE or the Cochrane database.

An additional 11 relevant reports were identified from the program syllabi of relevant scientific meetings. Two were excluded due to overlap of data: data presented in Dube et al.[34] and Corya et al.[35] were included in Shelton et al.[26] and Corya et al.[27]; 2 were excluded due to the lack of double-blinding,[10,36] and 1 was excluded because it did not involve an antidepressant-placebo treatment arm as a comparator.[37] The remaining 6 reports described 7 trials that were included in the meta-analysis (Thase et al.[38] described 2 clinical trials of identical design). No additional studies were identified with the use of clinical trial results registries or by contacting the makers of atypical antipsychotic agents who did not maintain such registries.

We were able to obtain response rates and remission rates based on those of each clinical trial using the primary outcome measure for all 10 trials (Table 1). Thus, the meta-analysis was all-inclusive, with studies pooled involving a total of 1500 TRD outpatients randomized to adjunctive treatment with either an atypical antipsychotic agent or placebo. All 10 studies reported response rates as a 50% decrease in scores of their primary outcome measure during the course of the trial. The definition of remission differed somewhat between trials (see Table 1 for details). We were able to obtain overall discontinuation rates, discontinuation rates due to adverse events, and discontinuation rates due to inefficacy for all 10 trials.

Analysis of Primary and Secondary Outcome Measures

Augmentation of standard antidepressants with typical antipsychotic agents resulted in greater remission and response rates than adjunctive placebo treatment in TRD. Specifically, across the trials, the pooled risk ratio (RR) for remission was 1.75 (95% CI = 1.36 to 2.24, $p < .0001$) and for response rates was 1.35 (95% CI = 1.13 to 1.63, $p = .001$) for the random-effects model (Figures 1 and 2). Pooled remission and response rates for the 2 treatment groups were 47.4% vs. 22.3% and 57.2% vs. 35.4%, respectively (Figure 3). A test for heterogeneity suggested no significant heterogeneity between the included studies for response rates ($Q = 6.326$, $df = 9$, $p = .707$) or remission rates ($Q = 3.310$, $df = 9$, $p = .951$). Although there was no difference in overall discontinuation rate (RR = 1.18, 95% CI = 0.93 to 1.49, $df = 9$, $p = .929$) or the rate of discontinuation due to inefficacy (RR = 0.66, 95% CI = 0.39 to 1.13, $df = 9$, $p = .133$) between the 2 treat-

Figure 2. Primary Meta-Analytic Findings: Response

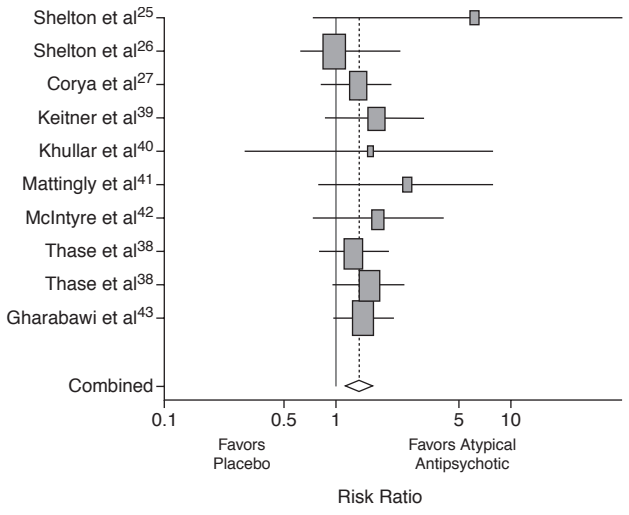
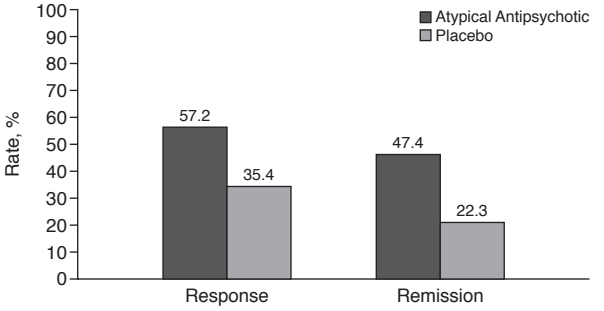


Figure 3. Pooled Response and Remission Rates (10 RCTs, N = 1500)



Abbreviation: RCT = randomized controlled trial.

ment groups, the rate of discontinuation due to adverse events was lower among placebo-treated patients (RR = 3.38, 95% CI = 1.98 to 5.76, df = 9, $p < .0001$).

DISCUSSION

In the present meta-analysis, we found evidence suggesting the efficacy of augmenting standard antidepressants with atypical antipsychotics for treatment-resistant major depressive disorder. Specifically, among patients who had failed to experience sufficient improvement following an adequate trial of antidepressants, the likelihood of achieving either a significant improvement of depressive symptoms or a full remission of their depressive episode was higher for patients who received adjunctive treatment with an atypical antipsychotic agent than for those who received placebo. Pooled remission and response rates for atypical antipsychotics and placebo were 47.4% vs. 22.3% and 57.2% vs. 35.4%, respectively. There was no difference in overall discontinuation rate or the rate of discontinuation due to inefficacy between the 2 treatment groups. However, the rate of discontinuation due to adverse events was more than 3-fold higher among patients treated with atypical antipsychotic agents than placebo.

Before the adjunctive use of atypical antipsychotics can be given an unqualified recommendation, several factors need to be considered. First, the side effect burden may be significant and can include extrapyramidal effects, sedation, hyperprolactinemia, weight gain, and the metabolic syndrome.[44] This was evidenced by the relatively higher rate of discontinuation due to adverse events in the present analysis. Moreover, although the rates of tardive dyskinesia appear to be low, it remains a significant risk.[45] Finally, the comparative efficacy against other combination therapies such as bupropion, mirtazapine, mianserin, buspirone, liothyronine, *S*-adenosylmethionine, folic acid, modafinil, lithium, or cognitive-behavioral therapy is unknown.

We note several important limitations of our work. First, the analysis involved pooling studies involving only risperidone, olanzapine, or quetiapine. Since studies involving the use of ziprasidone and aripiprazole were not included, conclusions drawn from this study cannot be generalized to all atypical antipsychotics. An additional limitation is that the present work involved pooling clinical trials, which involve a number of inclusion and exclusion criteria. Hence, it may not be possible to directly extend the findings of this study to groups of patients typically excluded from participating in randomized clinical trials (e.g., those with active substance abuse or certain comorbidities). Furthermore, pooled analyses and meta-analyses involve combining studies of heterogeneous design. For example, there were differences in some studies pooled in terms of their definition of remission. In general, a single clinical trial of equivalent statistical power can yield more accurate estimates of a treatment effect. However, it is important to point out that, in the present work, there was no statistical evidence for heterogeneity in the study results for remission. An additional limitation was that all studies included in the analysis were of 4 to 12 weeks in duration. Whether the present findings would extend beyond the acute phase of treatment remains to be determined. Finally, other limitations specifically pertain to the identification of studies to be included in pooled analyses or meta-analyses. Thus, it is possible that studies not identified by our search have been completed. However, an extensive search of a number of clinical trial results registries also did not reveal any additional completed studies.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), buspirone (BuSpar and others), fluoxetine (Prozac and others), lithium (Eskalith, Lithobid, and others), mirtazapine (Remeron and others), liothyronine (Triostat, Cytomel, and others), modafinil (Provigil),

olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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