Atypical Antipsychotics in the Treatment of Mania: A Meta-Analysis of Randomized, Placebo-Controlled Trials

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Background: Randomized, controlled trials have demonstrated efficacy for atypical antipsychotics in the treatment of mania in bipolar disorder, either as monotherapy or adjunctive treatment. However, there are no published comparisons of individual atypical antipsychotics for mania.

Data Sources and Study Selection: We conducted a systematic review and meta-analysis of randomized, placebo-controlled monotherapy and adjunctive therapy trials of atypical antipsychotics for acute bipolar mania. Studies published through 2004 were identified using searches of PubMed/MEDLINE with the search terms *mania*, *placebo*, and each of the atypical antipsychotics, limited to randomized, controlled clinical trials; review of abstracts from the 2003 meetings of the American College of Neuropsychiatry, American Psychiatric Association, and International Conference on Bipolar Disorder; and consultations with study investigators and representatives of pharmaceutical companies that market atypical antipsychotics.

Data Extraction: Analyses were performed on the changes in Young Mania Rating Scale or Mania Rating Scale total scores from baseline to endpoint, using last observation carried forward and computing the difference in change scores between each drug and its corresponding placebo arm. A random-effects model with fixed drug effects was used to combine the studies and make comparisons of the antipsychotics to each other and to placebo.

Data Synthesis: Data from 12 placebo-controlled monotherapy and 6 placebo-controlled adjunctive therapy trials involving a total of 4304 subjects (including 1750 placebo-treated subjects) with bipolar mania were obtained. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone all demonstrated significant efficacy in monotherapy (i.e., all confidence intervals exclude zero). However, after adjusting for multiple comparisons, pairwise comparisons of individual effects identified no significant differences in efficacy among antipsychotics. Magnitude of improvement was similar whether the antipsychotic was utilized as monotherapy or adjunctive therapy.

Conclusions: The 5 newer atypical antipsychotics were all superior to placebo in the treatment of bipolar mania. For monotherapy and add-on therapy, cross-trial comparisons suggest that differences in acute efficacy between the drugs, if any, are likely to be small.

(J Clin Psychiatry 2006;67:509–516)

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Supported by grant K23MH067060 from the National Institute of Mental Health, Bethesda, Md. (Dr. Perlis).

Presented in part at the 44th annual meeting of the New Clinical Drug Evaluation Unit (NCDEU), June 1–4, 2004, Phoenix, Ariz.

Financial disclosure is listed at the end of the article.

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Randomized, placebo-controlled trials have demonstrated efficacy for multiple atypical antipsychotics, either as monotherapy[1–12] or in combination with another antimanic agent such as lithium or valproate,[13–18] in the treatment of bipolar mania. Contemporary treatment guidelines include atypical antipsychotics as first-line treatments,[19,20] and in a relatively brief period of time, these agents have become among the most widely prescribed in the treatment of bipolar disorder.

Despite the abundance of clinical trial data, there are no published comparisons of the efficacy of individual atypical antipsychotics in mania, which might allow more evidence-based sequencing of treatment options. Although atypical antipsychotics are generally classified together because of their common effects at the dopamine D_2 receptor, they differ markedly in their affinity for other receptors[21,22] and degree of receptor agonism,[23] which might influence therapeutic effect. Even if overall efficacy is similar, differences in short-term tolerability might be reflected in comparative trial outcomes.

By pooling groups from multiple studies, and allowing comparison between studies, meta-analytic techniques enable questions about overall magnitude of effect, and relative effect, to be addressed with greater statistical power than individual trials allow. Therefore, we conducted a structured review and meta-analysis of randomized, placebo-controlled trials of atypical antipsychotics for the acute treatment of mania in bipolar disorder, com-

paring treatment efficacy among atypical antipsychotics applied as monotherapy or adjunctive therapy.

METHOD

Search Strategy

Studies were identified using searches of PubMed/MEDLINE with the search terms *mania, placebo*, and each of the atypical antipsychotics, limited to randomized, controlled clinical trials; review of abstracts from the 2003 meetings of the American College of Neuropsychiatry, American Psychiatric Association, and International Conference on Bipolar Disorder; and consultations with study investigators and representatives of pharmaceutical companies that market atypical antipsychotics.

Study Characteristics

We selected for inclusion randomized, controlled trials that prospectively compared one of the atypical antipsychotics approved for any indication by the U.S. Food and Drug Administration as of September 2004 (aripiprazole, clozapine, quetiapine, risperidone, ziprasidone, olanzapine) with a placebo control group. We attempted to include all studies where results have been analyzed and presented in any forum; thus, there was no requirement that papers be published in a peer-reviewed journal for inclusion. For all industry-supported studies, the sponsor was contacted and asked to confirm the values reported in publications or posters.

We allowed both monotherapy studies and studies in which the drug was added to lithium, valproate, or carbamazepine. Only studies for which results were available in the English language were included; this did not lead to the exclusion of any studies.

Data Analysis

The primary outcomes were change in Young Mania Rating Scale (YMRS)[24] score at day 21 or 28 and rates of response at endpoint (defined as 50% decrease in YMRS score). Analyses were performed on the change in YMRS total score from baseline to endpoint, which was typically day 21 except in 2 trials of olanzapine (days 28 and 42). The trials of ziprasidone utilized the Mania Rating Scale (MRS),[25] which is similar to the YMRS in scoring and apparent responsiveness to treatment effects[1] and was therefore considered equivalent to the YMRS for analytic purposes. The difference in change scores between each drug and its corresponding placebo arm was computed—that is, how much more improvement was observed in the drug arm compared to the placebo arm. Where standard deviations (SDs) for change scores were not available, the median SD from those trials where SD was reported was substituted.

We also examined outcomes by response rates, defined in all trials as the proportion of subjects achieving 50% or greater improvement. For analysis of response rates, the log-odds ratio for response in each drug arm versus the corresponding placebo arm was computed. Figure 2 displays the pooled odds ratios—that is, the odds of achieving response in the active treatment arm divided by the odds of achieving response in the placebo arm.

Since all sample sizes were reasonably large and response rates were not close to 0 or 1, the log-odds ratios were assumed to follow normal distributions with these variances. This approximation allows us to use similar computational techniques for meta-analysis of both mean change scores and categorical response rates.

Since it was considered likely a priori that not all trials would produce exactly equal underlying effect sizes (even after adjustment for sampling errors and differences among drugs), a random-effects model was considered preferable to a fixed-effects model. The fixed-effects model assumes that between-trial variation is completely attributable to sampling error and between-drug differences in effect. The random-effects model incorporates both within-study and between-study variance into the estimate of average treatment effects and is therefore usually more realistic than the fixed-effects model, as it assumes that factors other than measurement error and drug effect may account for between-trial differences. The model was implemented using restricted maximum likelihood (REML) using SAS PROC MIXED (SAS; Cary, N.C.). The inverse variances of the mean differences were specified as known within-trial parameters in a heterogeneous-variance structure (treating the within-trial variances as known, when they are actually estimated from the data, is standard meta-analytic practice[26,27]). Dummy variables representing the drugs tested were included as fixed effects. In addition, a random trial effect was specified to allow for additional heterogeneity among trials (i.e., variation beyond what could be explained by within-trial sampling error or systematic differences associated with particular drugs).

The magnitude of statistical heterogeneity is reported in terms of the 95% confidence interval for the between-study variance. The Tukey honestly significant difference (HSD) procedure was utilized for post hoc pairwise comparisons. Since graphical tools for publication bias (e.g., funnel plots) and statistical tests based on this plot are difficult to interpret unless there is no statistical heterogeneity,[28] we did not perform a formal assessment of publication bias. However, we performed a variety of sensitivity analyses to examine the effect of individual trials on the pooled results, as well as the impact of imputing missing change score SDs.

RESULTS

The MEDLINE search identified 17 studies; 7 of these met the inclusion criteria. An additional 11 studies were

Table 1. Atypical Antipsychotics in the Treatment of Mania: Placebo-Controlled, Randomized, Monotherapy, and Adjunctive Therapy Studies

Study	Duration (wk)	Comparators	Patients (N)[a]	Baseline YMRS Score	YMRS Change From Baseline	Patients With Rapid Cycling (%)	Patients With Mixed Episodes (%)
Monotherapy trials							
Keck et al[1]	3	Aripiprazole	123	28.2	–8.2	22	28
	3	Placebo	122	29.7	–3.4	25	37
Sachs et al[2]	3	Aripiprazole	136	28.45	–12.5	19	43
	3	Placebo	132	28.89	–7.2	16	40
McQuade et al[3]	3	Aripiprazole	129	27.8	–10.8	20[b]	39[b]
	3	Aripiprazole	127	27.9	–10.0	20[b]	39[b]
	3	Placebo	130	28.3	–10.1	20[b]	39[b]
Tohen et al[4]	3	Olanzapine	70	28.66	–10.3	27.1	17.1
	3	Placebo	66	27.65	–4.9	37.7	17.4
Tohen et al[5]	4	Olanzapine	54	28.76	–14.8	45.5	43.6
	4	Placebo	56	29.43	–8.1	33.3	41.7
Brecher and Huizar[6]	3	Quetiapine	101	34	–12.3	0	0
	3	Haloperidol	98	32.3	–15.7	0	0
	3	Placebo	100	33.1	–8.3	0	0
Paulsson and Huizar[7]	3	Quetiapine	107	32.7	–14.6	0	0
	3	Lithium	98	33.3	–15.2	0	0
	3	Placebo	95	34	–6.7	0	0
Hirschfeld et al[8]	3	Risperidone	127	29.1	–10.6	0	0
	3	Placebo	119	29.2	–4.8	0	0
Khanna et al[9]	3	Risperidone	146	37.1	–22.7	0	3
	3	Placebo	144	37.5	–10.5	0	6
Smulevich et al[10]	3	Risperidone	153	32.1	–15.1	0	0
	3	Haloperidol	144	31.3	–13.9	0	0
	3	Placebo	138	31.5	–9.4	0	0
Keck et al[11c]	3	Ziprasidone	131	27	–12.4	0	35
	3	Placebo	66	26.7	–7.8	0	37
Segal et al[12c]	3	Ziprasidone	137	26.19	–11.1	0	41
	3	Placebo	65	26.42	–5.6	0	39.4
Adjunctive therapy trials							
Tohen et al[13]	6	Olanzapine	220	22.31	–13.1	0	54.6
	6	Placebo	114	22.67	–9.1	0	47
Mullen et al[14]	3	Quetiapine	104	NA	–16.5	0	0
	3	Placebo	96	NA	–14.3	0	0
Sachs et al[15]	3	Quetiapine	81	31.5	–13.8	0	0
	3	Placebo	89	31.1	–9.9	0	0
Sachs et al[16]	3	Risperidone	51	28	–14.3	0	19
	3	Haloperidol	50	27.3	–13.4	0	23
	3	Placebo	47	28	–8.2	0	22
Yatham et al[17]	3	Risperidone	68	29.3	–14.5	0	7
	3	Placebo	72	28.3	–10.3	0	9
Weisler et al[18c]	3	Ziprasidone	99	NA	–0.7	0	38.6
	3	Placebo	99	NA	–0.7	0	32

[a]Number of patients used in efficacy analyses.
[b]Values reported for total patient sample; not available for comparator groups separately.
[c]Mania Rating Scale used in these trials.
Abbreviations: NA = not available, YMRS = Young Mania Rating Scale.

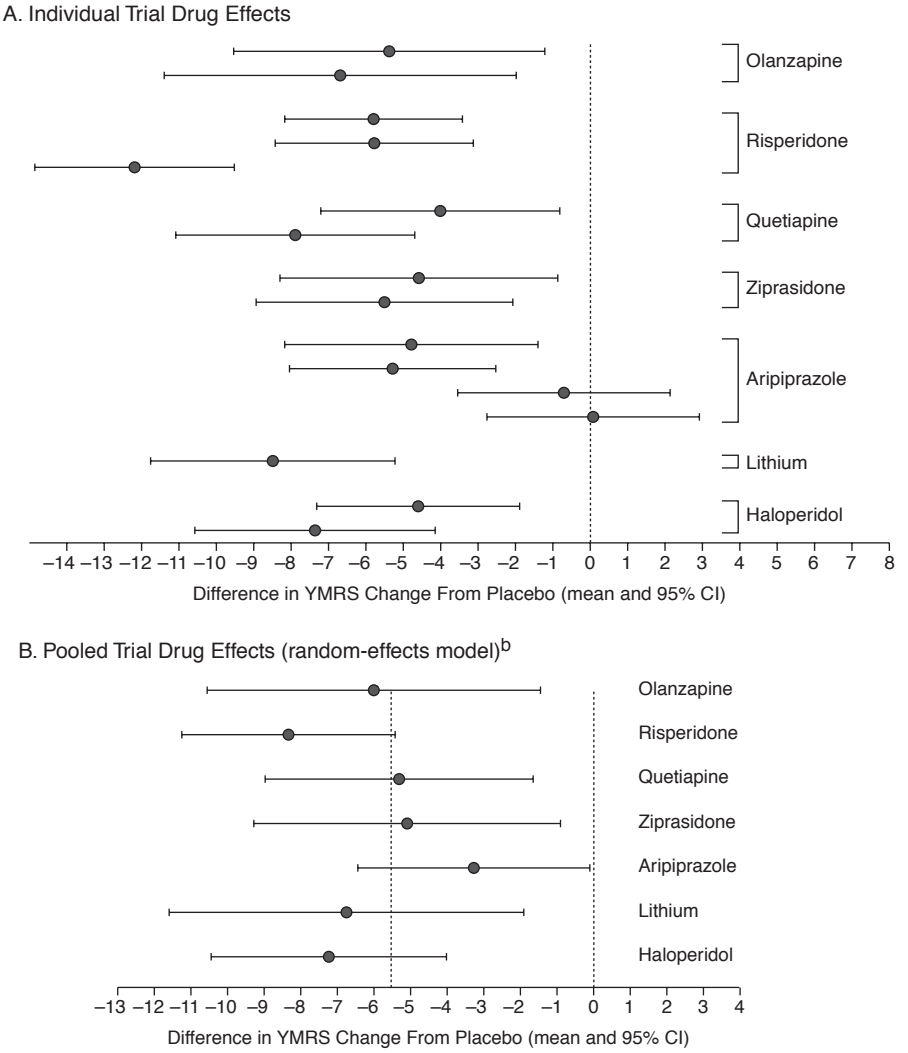
identified from review of meeting proceedings or consultation with study investigators. In total, data from 12 placebo-controlled monotherapy trials[1–12] were obtained, including 1881 drug-treated and 1233 placebo-treated subjects. Aripiprazole[1–3] and risperidone[8–10] were each tested in 3 trials. Each of the other 3 atypical antipsychotics was tested in 2 trials.[4–7,11,12] Three trials included an active comparator in addition to the placebo arm.[6,7,10] In addition, data from 6 placebo-controlled adjunctive or combination therapy trials[13–18] were obtained, including 673 drug-treated and 517 placebo-treated subjects. Risperidone[16,17] and quetiapine[14,15] were each tested in 2 trials, olanzapine[13] and ziprasidone[18] were each tested in 1 trial, and no trials of aripiprazole were identified. Haloperidol was used as a comparator in 1 adjunctive therapy trial.[16]

Monotherapy Studies

Monotherapy study characteristics are shown in Table 1. In general, studies were of similar size and design. One study[5] reported data at 28 days postbaseline for the primary analysis; all other studies reported data at 21 days postbaseline.

For the 16 individual nonplacebo arms in the 12 trials, Figure 1A shows the mean differences from placebo and the associated 95% confidence intervals for each inter-

Figure 1. Monotherapy Efficacy Relative to Placebo[a]



[a]Bars represent 95% confidence intervals.
[b]The dotted line on the left indicates the pooled difference from placebo among all monotherapy and combination trials.
Abbreviation: YMRS = Young Mania Rating Scale.

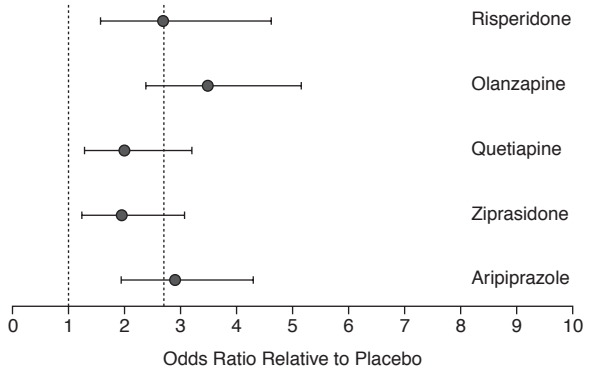
vention. Random-effects estimates of each drug effect (pooled across all monotherapy studies that included that drug) and associated 95% confidence intervals are in Figure 1B. All of the agents demonstrated significant efficacy (i.e., all confidence intervals in the pooled analysis exclude zero).

Treatment effects relative to placebo exhibited a moderate degree of residual heterogeneity (between-trial variance = 6.0 [95% CI = 2.3 to 40.8], p = .07), such that each drug's treatment effect tended to vary between trials by approximately 30% of its average effect.

No differences were detected among any of the atypical antipsychotics (i.e., the global F test for a main effect of drug was not significant [p = .38], and no pairwise significant differences among drugs were found at the .05 level after adjustment for multiple comparisons using the Tukey HSD procedure). Of note, although some information on the comparisons between risperidone and haloperidol, quetiapine and haloperidol, and quetiapine and lithium comes from within individual studies (the 3 aforementioned 3-arm studies), the comparisons among drugs are, in general, cross-trial contrasts.

Numbers of patients achieving a clinical response, defined as a 50% reduction in YMRS score from baseline to endpoint, were reported for 8 of the 12 monotherapy trials (2 trials each of risperidone, olanzapine, ziprasidone, and aripiprazole). These trials included 925 drug-treated patients and 776 placebo-treated patients. Overall rates of response were 53% for atypical antipsychotics and 30% for placebo. Figure 2 shows the odds

Figure 2. Monotherapy Efficacy in Terms of Drug Versus Placebo Odds Ratios of 50% Improvement (random-effects model)[a]



[a]Bars represent 95% confidence intervals. The dotted line on the right indicates the mean OR.

ratios in favor of treatment with each of these medications. All intervals exclude the null value (1.0), indicating significant treatment effects. There were no significant differences among these odds ratios, whose mean value was 2.7 (95% CI = 2.2 to 3.4). Between-trial heterogeneity was estimated at zero, but again the confidence interval was extremely wide, so substantial heterogeneity cannot be ruled out.

Add-On Therapy Studies

A total of 6 add-on therapy studies were also examined (see Table 1), with 7 active treatment arms. These studies exhibited somewhat greater heterogeneity in design, particularly in terms of nature, timing, and dose of primary mood stabilizer. For example, the risperidone trial[17] included carbamazepine, while other trials did not.

Figure 3A shows placebo-subtracted change in YMRS scores from each of the 6 nonplacebo combination therapy arms, and Figure 3B shows the random-effects estimates of each drug effect. Residual between-trial heterogeneity was estimated as zero, although this estimate is likely to be unreliable due to the small number of trials. Consequently, the random-effects analysis reduced to a fixed-effects analysis for this set of trials. No differences in efficacy were detected among any of the drugs: the global F test for a main effect of drug was not significant (p = .25), and no pairwise significant differences among drugs were found (minimum p = .21 prior to adjustment for multiple comparisons). While the confidence interval for the ziprasidone study is centered near zero, it overlaps with that of the other studies, accounting for the absence of statistically significant difference. Studies that used combination therapy reported a pooled difference of 4.1 (95% CI = 1.7 to 6.6) on the YMRS, versus 5.5 (95% CI = 4.0 to 7.1) for studies that used a monotherapy design. Importantly, these effect sizes are not directly comparable, since they are relative to different control groups (placebo for monotherapy studies, mood stabilizer plus placebo in combination trials).

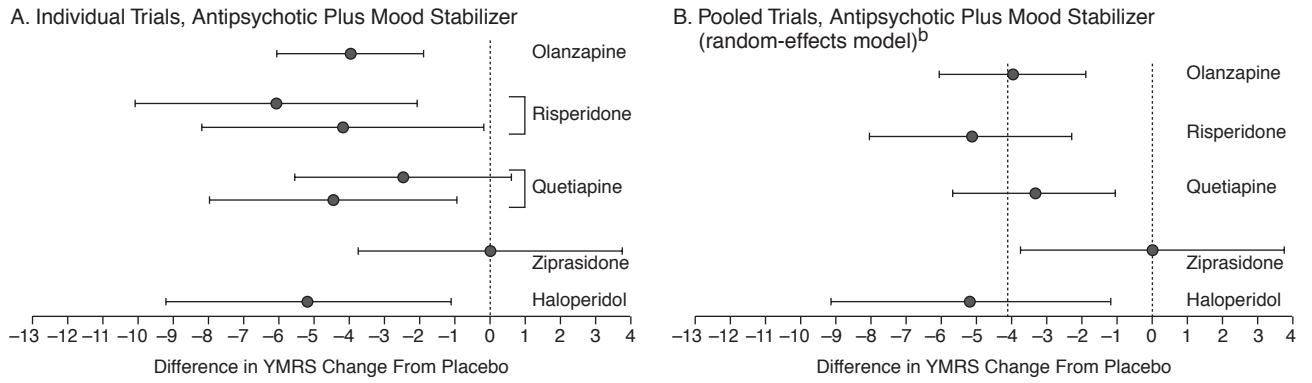
Only 3 trials (1 each of risperidone, olanzapine, and quetiapine) reported data on rates of 50% improvement. The REML algorithm failed to converge for such a small set of data, although the mean odds ratio for atypical antipsychotic treatment (i.e., ignoring any differential effects among the atypical antipsychotics) could be estimated as 2.4 (95% CI = 1.2 to 4.9), p = .03.

DISCUSSION

We found little difference overall in efficacy, measured as change in mania rating scale (YMRS or MRS) score versus placebo or in differential rates of response, among the individual atypical antipsychotics, whether used alone or in combination with another antimanic agent. Because of the large numbers of subjects included in these studies, it is likely that if such differences do exist, they are quite small. While only 3 studies utilizing active comparators were included, these analyses also suggested similar benefit for lithium and haloperidol in acute treatment. Therefore, efficacy alone may not be a useful factor in selecting from among the various acute treatment options available.

Our aggregate findings also confirm those of individual trials indicating that add-on therapy with atypical antipsychotics confers an additional benefit over monotherapy with a traditional mood stabilizer; it therefore appears that recommendations for the use of combination therapy with a traditional mood stabilizer and an atypical antipsychotic in manic patients, rather than a traditional mood stabilizer alone, are warranted.[19] Unfortunately, these studies do not allow us to directly examine the converse question: whether the addition of mood stabilizers confers additional benefit over atypical antipsychotic monotherapy alone. The one study to date examining combination therapy versus antipsychotic monotherapy[29] included primarily typical antipsychotics such as perazine and thus does not directly address atypical antipsychotic treatment. Our examination of improvement in monotherapy or adjunctive therapy trials, which suggests a similar degree of improvement, does not allow a conclusion to be drawn about initial combination therapy. Patients in add-on trials have already received some period of treatment with a mood stabilizer prior to beginning treatment with the atypical antipsychotic.[16] This would tend to bias results toward less benefit with the combination strategy, if patients have already experienced some improvement from the mood stabilizer. Unfortunately, initial (pre-randomization) improvement is not reported consistently. The important question of whether initial combination therapy is superior to mono-

Figure 3. Combination Therapy Efficacy Relative to Mood Stabilizer Monotherapy[a]



[a]Bars represent 95% confidence intervals.
[b]The dotted line on the left indicates the pooled difference from placebo among all monotherapy and combination trials.
Abbreviation: YMRS = Young Mania Rating Scale.

therapy with an atypical antipsychotic thus cannot be answered with the present data set.

We elected to compare drugs based upon their difference from placebo, rather than absolute change in mania rating scale score, as a means of controlling for study differences that could contribute to greater responses in all groups. While studies are often compared in terms of effect size,[30] this measure is somewhat more difficult to interpret in clinical terms. In addition, because nearly all of the studies examined used the same primary outcome measure, consideration of placebo-subtracted change allows a more direct reporting of effect: how many additional points of improvement were conferred by randomization to active drug? The most clinically useful endpoint would be remission, generally defined as near-complete absence of mood symptoms and often operationalized as YMRS score ≤ 12. However, as not all studies defined or reported remission consistently, and as short-term treatment is often insufficient for achieving remission, we elected to omit this endpoint.

We note several important limitations of these comparisons. First, despite the general similarity of studies, some sources of heterogeneity must be considered. For example, longer studies might be expected to demonstrate greater effects. Indeed, in those studies included here that reported 12-week outcomes, some additional improvement beyond 3 weeks was noted.[6,7] Importantly, however, the placebo groups also continued to improve, and the additional placebo-subtracted improvement was relatively small in trials reported to date.

The studies also differed in whether they included rapid-cycling patients or those in mixed states and in the proportion of patients with psychosis. However, the few subgroup analyses published to date suggest little or no difference in overall efficacy across these subgroups.[31] Likewise, severity of mania varied somewhat across studies, raising the possibility of a floor effect in studies with less severity. We cannot exclude the possible effects of study population on placebo response.[32] Rates of study completion highlighted the differences between studies; they varied considerably across studies, from less than 30% to greater than 80%.

A final important source of heterogeneity arises from differences in design among the add-on studies. Mean levels for the primary mood stabilizer (typically lithium or valproate) were not entirely consistent across studies and were often less than those advised by treatment guidelines. In the 1 study to include carbamazepine, drug-drug interactions may have influenced observed efficacy with risperidone.[17] Perhaps most importantly, the mean interval from initiation of primary mood stabilizer treatment to initiation of atypical antipsychotic treatment, and the proportion of patients beginning primary mood stabilizer treatment de novo, also varied between studies. Thus, some patients might be considered monotherapy failures (see, for example, the study by Tohen et al.[13]), while others had not yet had the opportunity to respond to monotherapy. All of these differences might be expected to impact absolute improvement, but, as they should exert similar effects in the placebo group, would be expected to have less impact on placebo-subtracted change. In the absence of statistical evidence of heterogeneity, we chose to examine and compare the studies with these important caveats in mind.

Our analysis required that all studies, including studies that report minimal benefit, be included. So-called publication bias, in which negative studies may be terminated prematurely or may be less likely to be published, has been raised as a major limitation in interpreting the psychiatric[33] and general medical literature.[34] It is impossible to rule out publication bias entirely without the mandated use of a clinical trial registry.[35] However, all study spon-

sors were contacted to confirm that no qualifying studies were extant.

In summary, our results suggest broad similarity across the atypical antipsychotics in efficacy for the treatment of bipolar mania, whether used in monotherapy or add-on therapy. In the face of substantial study heterogeneity, we cannot exclude modest differences. However, treatment selection among these agents may be better governed by factors other than short-term efficacy, such as maintenance efficacy, tolerability, safety, or cost.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, haloperidol and clozapine are not approved by the U.S. Food and Drug Administration for the treatment of mania.

Financial disclosure: In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME article were asked to complete a statement regarding all relevant financial relationships between themselves or their spouse/partner and any commercial interest (i.e., a proprietary entity producing health care goods or services) occurring within at least 12 months prior to joining this activity. The CME Institute has resolved any conflicts of interest that were identified. The disclosures are as follows: Dr. Perlis is a consultant for or member of the speakers/advisory boards of AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, and Pfizer. Dr. Hirschfeld is a consultant for or member of the advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Organon, Pfizer, Shire, UCB Pharma, and Wyeth-Ayerst and is a principal or coinvestigator on research studies sponsored by Wyeth-Ayerst. Dr. Keck is a consultant for or member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Ortho-McNeil, Pfizer, and Shire and is a principal or coinvestigator on research studies sponsored by Abbott, the American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Eli Lilly, Janssen, Merck, National Institute of Mental Health, National Institute on Drug Abuse, Organon, Ortho-McNeil, Pfizer, the Stanely Medical Research Institute, and UCB Pharma. Dr. Welge and Ms. Vornik have no significant commercial relationships to disclose relative to the presentation.

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