Second-Generation Antipsychotic Agents in the Treatment of Acute Mania

A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Context: Recommendations of treatment guidelines concerning the use of second-generation antipsychotic (SGA) agents for acute mania vary substantially across committees or working groups. Meta-analyses addressing the use of SGAs in the treatment of acute mania are lacking.

Objective: To conduct a meta-analysis of the efficacy and safety of SGAs in the treatment of acute mania.

Data Sources: Randomized controlled trials comparing SGAs with placebo, first-generation antipsychotic drugs, or mood stabilizers (MSs) in the treatment of acute mania were searched for in the PsiTri and MEDLINE databases (last search: May 2006).

Study Selection: The abstracts, titles, and index terms of studies were searched using the following key words: *aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, ziprasidone,* and *zotepine* in conjunction with *mania, manic,* and *bipolar*.

Data Extraction: Data on efficacy, global dropout, dropout due to adverse events, dropout due to inefficacy, weight gain, rate of somnolence, and extrapyramidal symptoms were extracted and combined in a meta-analysis.

Data Synthesis: A total of 24 studies with 6187 patients were included. The SGAs were significantly more efficacious than placebo. The analysis demonstrated that adding antipsychotic agents to MS treatment was significantly more effective than treatment with MSs alone. The SGAs displayed efficacy comparable with that of MSs. Some SGAs seemed to induce more extrapyramidal symptoms than placebo. The SGAs were also associated with higher rates of somnolence than placebo.

Conclusion: Currently available data suggest that combining SGAs and MSs is the most efficacious treatment of acute mania.

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MOOD STABILIZERS (MSs) and first-generation antipsychotic agents have long been the mainstay of treatment of acute mania with and without psychotic features. However, there are reports of first-generation antipsychotics inducing or worsening depressive symptoms in patients with bipolar disorder.[1] Furthermore, patients with bipolar disorder are more susceptible to extrapyramidal symptoms (EPSs) than those with schizophrenia.[2,3] Therefore, first-generation antipsychotics are of limited applicability in the treatment of bipolar disorders.

In recent years, second-generation antipsychotic (SGA) agents have been developed and have proved to be effective in the treatment of bipolar mania. The SGAs do not seem to induce depressive episodes, and recent studies[4,5] revealed that some SGAs may have antidepressant effects.

Fountoulakis et al[6] recently reviewed treatment guidelines for bipolar disorder. Their investigation revealed that guidelines for the treatment of bipolar disorder vary significantly across committees or specialist groups. In particular for the treatment of acute mania, some guidelines recommend monotherapy with an MS or an SGA drug as first-line treatment, whereas others recommend a combination of an MS and an antipsychotic agent. However, meta-analyses addressing the efficacy and effectiveness of SGAs in the treatment of acute mania are lacking.[7-9]

Thus, the aim of this study is to compare the efficacy and safety of (1) SGAs vs placebo, (2) SGAs vs MSs, (3) combination therapy with SGAs plus MSs vs MSs alone, and (4) SGAs vs haloperidol.

METHODS

SEARCH

All published and unpublished randomized controlled trials that assessed the efficacy of SGAs (aripiprazole, amisulpride, clozapine, olanza-

pine, quetiapine, risperidone, ziprasidone, and zotepine) in the treatment of mania were searched for in the PsiTri database (http://psitri.stakes.fi) (last search: May 2006). PsiTri is a register of controlled trials that compiles the registers of all Cochrane review groups in the field of mental health. The registers of the single Cochrane review groups are compiled by means of regular searches of numerous electronic databases and conference abstract books and hand searches of major journals (the exact search strategies of the individual review groups are listed in The Cochrane Library[10]). We also searched MEDLINE. The abstracts, titles, and index terms of studies were searched using the following key words: *aripiprazole, amisulpride, clozapine, olanzapine, quetiapine, risperidone, ziprasidone,* and *zotepine* in conjunction with *mania, manic,* and *bipolar*. In addition, the reference sections of included articles and key reviews were screened, and the first and last authors (Michael Berk, Charles Bowden, William Carson, Marielle Erdekens, Robert Hirschfeld, Paul Keck, Sumant Khanna, Roger McIntyre, Steven Potkin, Gary Sachs, Mauricio Tohen, Lakshmi Yatham, and John Zajecka) of the included studies and the pharmaceutical companies (AstraZeneca, Eli Lilly, Janssen-Cilag, Bristol-Myers Squibb, and Pfizer) were asked by e-mail between October 1, 2005, and March 31, 2006, whether they were aware of further trials. They were also contacted for the provision of missing data necessary for the meta-analysis. We thank Tohen et al, Yatham et al, McIntyre et al, Smulevich et al, and Bowden et al for sending us additional data. A rating based on the 3 quality categories described in The Cochrane Collaboration Handbook[11] was given for each trial: A indicates low risk of bias (adequate allocation concealment); B, moderate risk of bias (some doubt about the results, mainly studies said to be randomized but without an explanation of the method); and C, high risk of bias (clearly inadequate allocation concealment, eg, alternate randomization). Only trials belonging to categories A and B were included. Two of us (H.S. and S.L.) independently extracted data from the trials. Any disagreement was discussed, and the decisions were documented.

OUTCOME PARAMETERS

The primary outcome of interest was the mean change in the Young Mania Rating Scale (YMRS) score or similar scale scores from baseline to the end point. Further outcome parameters were the rate of response and effectiveness criteria, such as the number of participants leaving the study early (dropouts) for any reason, dropouts due to adverse events, dropouts due to inefficacy, mean weight gain, rate of somnolence, and EPSs. For response, the definition used by the authors of the original studies was adopted by the reviewers. This was generally a reduction of at least 50% on an efficacy scale such as the YMRS.[12]

In a once randomized–analyzed approach (last observation carried forward method) we assumed in the case of dichotomous data that participants who dropped out before completion had no change in their condition unless otherwise stated. Continuous data had to be reported as presented in the original studies without any assumptions about those lost to follow-up.

META-ANALYTIC CALCULATIONS

The outcome data were combined in a meta-analysis. For continuous data the standardized mean difference based on the Hedges adjusted g (a slightly modified version of the Cohen D for correction in the case of small participant numbers below 10)[13] and its 95% confidence interval (CI) were calculated. When standard deviations were not indicated we either derived them from *P* values or used the mean standard deviations of the other studies. For dichotomous data, the relative risk (RR), which is defined as the ratio of the risk of an unfavorable outcome among treatment-allocated participants to the corresponding risk of an unfavorable outcome among those in the control group, was estimated again along with its 95% CI. Whereas many meta-analysts preferred to use odds ratios some years ago, it has been shown that the RR is more intuitive[14] and that odds ratios tend to be interpreted as RRs by physicians.[15] This misinterpretation then leads to an overestimated impression of the effect. The random-effects model of DerSimonian and Laird[16] was used in all cases. Random-effects models are, in general, more conservative than fixed-effects models because they take heterogeneity among studies into account, even if this heterogeneity is not statistically significant. Study heterogeneity was sought for by visual inspection of the forest plots and by using a χ^2 test, which contrasts the RRs of the individual trials with the pooled RR. Significance levels of $P<.1$ were set a priori to assume the presence of heterogeneity. Results of the pooled analyses, which were statistically significantly heterogeneous, were noted in the results. In the case of significant differences between groups, the number of participants needed to treat (NNT) and the number of participants needed to harm (NNH) were calculated. For this purpose we calculated risk differences (RDs) in addition to RRs. Then, NNT/NNH was derived from the RD by the formula NNT/NNH = 1/RD, with the 95% CIs of NNT/NNH being the inverse of the upper and lower limits of the 95% CI of the RD. Studies with negative results are less likely to be published than studies with significant results. The possibility of such publication bias was examined using the funnel plot method described by Egger and colleagues.[11] Owing to the small number of studies, we also tentatively analyzed the antipsychotics as a single group compared with placebo or MSs in the secondary analyses. All the calculations were performed using MetaView, meta-analytic standard software used by The Cochrane Collaboration (Review Manager Version 4.2.8, The Cochrane Collaboration, Oxford, England). The exact formulas were reported there. A $P<.05$ was considered significant. We conducted 4 comparisons: (1) SGAs vs placebo, (2) SGAs vs MSs, (3) SGAs vs placebo as add-on medication to MSs, and (4) SGAs vs haloperidol. In addition, in each comparison SGAs were entered in an exploratory pooled analysis. The latter results are detailed only in cases in which they were not heterogeneous.

RESULTS

INCLUDED STUDIES

A total of 24 studies dealing with all the SGAs except zotepine and amisulpride were included (eTables; available at: http://www.archgenpsychiatry.com). These studies could be classified according to 4 different comparisons (**Table 1**): (1) SGAs vs placebo,[17-28] (2) SGAs vs MSs,[22,29-32] (3) SGAs vs placebo as add-on to MSs,[33-38] and (4) SGAs vs haloperidol.[23,26,32,39,40] Four studies[22,23,26,32] conducted 3-branch examinations and could be used in 2 comparisons each. Assessment of manic symptoms was performed using the YMRS (18 trials), the Mania Rating Scale (3 trials), and the Mania Scale (1 trial).

The baseline mania scores were similar in all the trials except 2 studies with more[25] or less[33] severely manic patients. The duration of most studies was 3 weeks; however, 3 studies investigated a 4-week period[21,31,32] and 2 a 6-week period.[33,40] Four trials[23,26,30,37] investigated a 12-week period but also evaluated treatment outcomes after 3 weeks. The 3-week data were used for the analysis.

Four trials[22-24,35] investigated purely manic patients, 4 studies[26,31,32,34] did not report the types of manic episodes, and all the other trials examined patients with

Table 1. Characteristics of the 24 Included Studies

Intervention	Dose, Mean (SD), Range, mg/d, or [Blood Level, Mean (SD)]	MS Blood Level, Mean (SD)	Duration, wk	Randomized, No.	LOCF, No.	Age, Mean (SD), y	YMRS Score, Mean (SD)	Episode Type, %		Completers, %	Source
								Manic	Mixed		
Comparison 1: Second-Generation Antipsychotics vs Placebo											
Aripiprazole	27.9 (NA), 15-30	NA	3	130	123	40.5 (12.7)	28.2	72	28	42	Keck et al,[17] 2003
Placebo		NA		132	122	40.5 (11.8)	29.7	63	37	21	
Aripiprazole	NA, 15-30	NA	3	NA	256	NA	27.9	61	39	NA	McQuade et al,[18] 2003
Placebo		NA		NA	130	NA	28.3	61	39	NA	
Aripiprazole	27.7 (NA), 15-30	NA	3	137	136	37.3 (0.9)	NA	60	40	16	Sachs et al,[19] 2006
Placebo				135	132	40.4 (0.9)	NA	57	43	26	
Olanzapine	14.9 (5.0), 5-20	NA	3	70	70	39.5 (11.0)	28.7 (6.7)	83	17	61	Tohen et al,[20] 1999
Placebo				69	66	39.5 (11.0)	27.6 (6.5)	83	17	35	
Olanzapine	16.4 (4.2), 5-20	NA	4	55	54	38.3 (10.7)	28.76 (6.7)	56	44	62	Tohen et al,[21] 2000
Placebo				60	56	39.0 (10.1)	29.4 (6.8)	58	42	42	
Quetiapine	586 (NA), 400-800	NA	3	107	107	38.0	32.7	100	0	91	Bowden et al,[22] 2005
Lithium	0.8 (NA), 0.6-1.4*	NA		98	98	38.8	33.3	100	0	86	
Placebo				97	95	41.3	34.0	100	0	69	
Quetiapine	NA, 400-800	NA	3	102	101	42.8	34.0	100	0	65	McIntyre et al,[23] 2005
Haloperidol	NA, 2-8	NA		99	98	45.1	32.3	100	0	78	
Placebo				101	100	40.6	33.1	100	0	60	
Risperidone	4.1 (1.4), 1-6	NA	3	127	127	38.1 (11.9)	29.1 (5.1)	100	0	59	Hirschfeld et al,[24] 2004
Placebo				119	119	39.5 (12.2)	29.2 (5.5)	100	0	44	
Risperidone	5.6 (NA), 1-6	NA	3	146	144	34.7 (12.0)	36.9 (8.0)	97	3	89	Khanna et al,[25] 2005
Placebo				144	142	35.5 (12.3)	37.4 (7.9)	94	6	71	
Risperidone	4.2 (1.7), 1-6	NA	3	154	153	41.3 (13.1)	32.1 (6.9)	NA	NA	89	Smulevich et al,[26] 2005
Haloperidol	8.0 (3.6), 2-12	NA	3	144	144	38.5 (12.2)	31.3 (6.5)	NA	NA	90	
Placebo				140	138	39.4 (13.0)	31.5 (6.7)	NA	NA	85	
Ziprasidone	130.1 (34.5), 80-160	NA	3	140	131	39 (10.6)	27.0 (3.8)†	65	35	54	Keck et al,[27] 2003
Placebo				70	66	37 (10.3)	26.7 (7.0)†	63	37	44	
Ziprasidone	112.0 (NA), 80-160	NA	3	140	137	38.9 (11.6)	26.2 (7.2)†	59	41	61	Potkin et al,[28] 2005
Placebo				66	65	39.0 (11.5)	26.4 (7.5)†	61	39	55	

(continued)

purely manic symptoms (45%-97%) and patients with mixed symptoms (3%-55%). Each of these trials was matched for episode type. Seven studies[22,23,25,26,34,35,39] excluded patients with rapid cycling, 12 studies* did not report data on this aspect, and 5 trials[19-21,29,30] included 16% to 61% of patients with a rapid cycling course.

Given the small number of studies, the use of funnel plots (a method based on symmetry) was appropriate only for SGAs vs placebo. The plots on the primary efficacy outcomes did not suggest publication bias. The plot on dropouts regardless of reason was the only

References 17, 18, 24, 27, 28, 31-33, 36-38, 40.

Table 1. Characteristics of the 24 Included Studies (cont)

Intervention	Dose, Mean (SD), Range, mg/d, or [Blood Level, Mean (SD)]	MS Blood Level, Mean (SD)	Duration, wk	Randomized, No.	LOCF, No.	Age, Mean (SD), y	YMRS Score, Mean (SD)	Episode Type, %		Completers, %	Source
								Manic	Mixed		
Comparison 2: Second-Generation Antipsychotics vs Mood Stabilizers											
Olanzapine	17.4 (NA), 5-20	NA	3	125	125	40.0 (12.1)	27.4 (5.2)	56	45	69	Tohen et al,[29] 2002
Valproate	[83.9 (32.1)]‡	NA		126	123	41.1 (12.3)	27.9 (6.6)	59	41	64	
Olanzapine	14.7 (NA), 5-25	NA	3	57	57	38.1 (12.2)	32.3	54	46	68	Zajecka et al,[30] 2002
Valproate	[84.6 (36.8)]‡	NA		63	63	38.9 (12.1)	30.8	51	49	62	
Olanzapine	10 (NA)	NA	4	15	15	29.4	31.7§	NA	NA	93	Berk et al,[31] 1999
Lithium	[0.74 (NA)]*	NA		15	15	31.9	31.6§	NA	NA	87	
Risperidone	6 (NA)	NA	4	15	15	34.3	28.6†	NA	NA	87	Segal et al,[32] 1998
Haloperidol	10 (NA)	NA		15	15	29.5	24.8†	NA	NA	80	
Lithium	[0.72 (NA)]*	NA		15	15	37.1	28.4†	NA	NA	93	
Comparison 3: Second-Generation Antipsychotics vs Placebo as Add-on Medication to Mood Stabilizers											
Olanzapine	10.4 (4.9), 5-20	Lithium: 0.76 (0.16)* valproate sodium: 63.6 (18.4)‡	6	229	220	40.7 (11.2)	22.3 (5.4)	45	55	70	Tohen et al,[33] 2002
Placebo		Lithium: 0.82 (0.19)* valproate: 74.7 (18.6)‡		115	114	40.4 (10.8)	22.7 (9.4)	53	47	71	
Quetiapine	504 (NA), 200-800	Lithium: 0.78 (NA)* valproate: 65 (NA)‡	3	91	81	39.6	31.5	NA	NA	62	Sachs et al,[34] 2004
Placebo		Lithium: 0.71 (NA)* valproate: 65 (NA)‡		100	89	41.3	31.1	NA	NA	49	
Quetiapine	492 (204), 400-800	Lithium: 0.76 (0.22)* valproate: 69.5 (20.2)‡	3	197	185	39.2	32.0	100	0	68	Yatham et al,[35] 2004
Placebo		Lithium: 0.73 (0.2)* valproate: 73.6 (18.8)‡		205	185	40.7	31.9	100	0	56	
Risperidone	3.8 (1.8), 1-6	Lithium: 0.7 (0.3)* valproate: 65.4 (27.1)‡	3	52	51	41	28.0 (5.5)	81	19	73	Sachs et al,[36] 2002
Placebo		Lithium: 0.8 (0.3)* valproate: 77.3 (27.3)‡		51	47	43	28.0 (6.1)	78	22	49	
Risperidone	4.0 (NA), 1-6	Lithium/valproate/ carbamazepine: NA	3	75	68	37	29.3 (0.7)	93	7	64	Yatham et al,[37] 2003
Placebo				75	72	42	28.3 (0.7)	91	9	48	
Ziprasidone	NA, 80-160	NA	3	102	101	36.5 (11.5)	NA	61	39	69	Weisler et al,[38] 2003
Placebo		NA		103	103	36.6 (12.4)	NA	68	32	72	
Comparison 4: Second-Generation Antipsychotics vs Haloperidol											
Aripiprazole	22.6 (NA), 15-30	NA	3	175	174	42.6	31.1	92	8	50	Vieta et al,[39] 2005
Haloperidol	11.6 (NA), 10-15	NA		172	162	41.0	31.5	86	14	29	
Olanzapine	15.0 (5.1), 5-20	NA	6	234	231	41.0 (13)	31.1 (7.6)	94	6	71	Tohen et al,[40] 2003
Haloperidol	7.1 (4.3), 3-15	NA		219	213	40.0 (13)	30.6 (7.7)	95	5	64	

Abbreviations: LOCF, last observation carried forward; MS, mood stabilizer; NA, not available; YMRS, Young Mania Rating Scale.
*Given in milliequivalents per liter.
†Mania Rating Scale.
‡Given in micrograms per liter.
§Mania Scale.

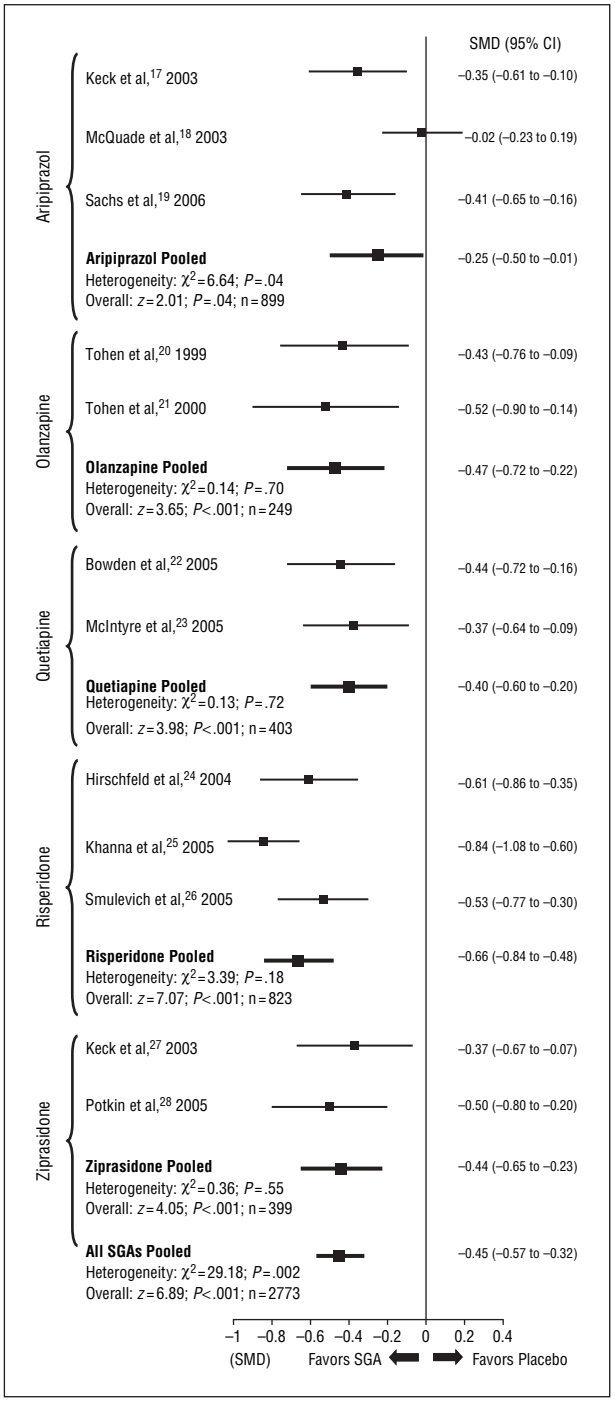

Figure 1. Mean Young Mania Rating Scale score changes: second-generation antipsychotics (SGAs) vs placebo. CI indicates confidence interval; SMD, standardized mean difference.

asymmetrical one, but it remains unclear whether a study was unpublished in case an SGA failed to prove superiority in terms of dropout rate.

COMPARISON 1: SGAs vs PLACEBO

Twelve trials compared the effects of aripiprazole,[17-19] olanzapine,[20,21] quetiapine,[22,23] risperidone,[24-26] and ziprasidone[27,28] vs placebo in the treatment of acute mania (Table 1). **Figure 1** displays the results of the primary outcome (YMRS score changes), and **Table 2** gives the pooled results of the secondary outcome parameters.

Reduction in Manic Symptoms and Response Rates

Each individual SGA agent was significantly superior to placebo in treating acute manic symptoms (Figure 1). Response rates were significantly higher in the aripiprazole, olanzapine, risperidone, and ziprasidone trials but not in the quetiapine trials.

Dropout Rates

The analysis revealed a significantly lower global dropout rate in patients treated with olanzapine and risperidone but not with aripiprazole, quetiapine, and ziprasidone. Dropout due to adverse events did not differ between treatments.

Except for aripiprazole, the dropout rate due to inefficacy was lower for SGAs and for the pooled data compared with placebo.

Weight Change and Somnolence

Weight gain was significantly greater in patients treated with olanzapine and quetiapine but not with the other SGAs.

All the SGAs exhibited significantly higher rates of somnolence (**Figure 2**).

Extrapyramidal Symptoms

The incidence of EPSs was significantly higher in the aripiprazole (NNH, 13; 95% CI, 9-20) and risperidone trials and in the pooled analysis of all SGAs (**Figure 3**). In addition, increased EPS rates were found for ziprasidone. Although this difference was not significant ($P=.06$), the RD was (NNH, 11; 95% CI, 7-33). The results were heterogeneous in the risperidone trials and in the pooled analysis ($\chi^2=4.98$; $P=.03$).

There were no overall differences in the symptom severity of EPS measures using the Simpson Angus Scale or the Extrapyramidal Symptom Rating Scale in the aripiprazole, olanzapine, risperidone, and ziprasidone trials. Akathisia, however, assessed using the Barnes Akathisia Scale, proved to be significantly more pronounced in patients treated with aripiprazole and ziprasidone.

COMPARISON 2: SGAs vs MSs

Five studies investigated olanzapine, quetiapine, and risperidone vs the MSs valproate sodium[29,30] or lithium[22,31,32] (Table 1). **Figure 4** displays the results of the primary outcome (YMRS score changes), and **Table 3** gives the pooled results of the secondary outcome parameters.

Reduction in Manic Symptoms and Response and Dropout Rates

Olanzapine compared with valproate showed greater symptom improvement (Figure 4). In no other trials were differences between the comparative treatments found.

Table 2. Comparison 1: SGAs vs Placebo

	Trials, No.	Participants, No.	RR or SMD (95% CI)	*P* Value	NNT (95% CI)
Response					
Aripiprazole	2	534	1.82 (1.43 to 2.32)*	<.001	5 (3-8)
Olanzapine	2	254	1.76 (1.31 to 2.36)*	<.001	4 (3-8)
Quetiapine	2	407	1.46 (0.81 to 2.64)*	.20	NA
Risperidone	3	844	1.75 (1.41 to 2.18)*	<.001	4 (3-11)
Ziprasidone	2	416	1.49 (1.13 to 1.98)*	.005	7 (4-17)
Combined	11	2455	1.67 (1.48 to 1.89)*	<.001	5 (4-7)
Global dropout					
Aripiprazole	2	534	0.82 (0.65 to 1.04)†	.10	NA
Olanzapine	2	254	0.62 (0.48 to 0.80)†	<.001	4 (3-8)
Quetiapine	2	407	0.54 (0.18 to 1.59)†	.26	NA
Risperidone	3	844	0.61 (0.38 to 0.95)†	.03	8 (5-50)
Ziprasidone	2	416	0.85 (0.68 to 1.05)†	.12	NA
Combined	11	2455	0.72 (0.62 to 0.83)†	<.001	8 (6-13)
Dropout due to adverse event					
Aripiprazole	2	534	1.13 (0.66 to 1.93)†	.65	NA
Olanzapine	2	254	0.79 (0.08 to 8.27)†	.84	NA
Quetiapine	2	407	1.13 (0.49 to 2.60)†	.77	NA
Risperidone	3	844	1.15 (0.62 to 2.17)†	.66	NA
Ziprasidone	2	416	3.09 (0.70 to 13.57)†	.13	NA
Combined	11	2455	1.19 (0.84 to 1.69)†	.32	NA
Dropout due to inefficacy					
Aripiprazole	2	534	0.58 (0.30 to 1.12)†	.11	NA
Olanzapine	2	254	0.64 (0.46 to 0.90)†	.01	7 (4-25)
Quetiapine	2	407	0.50 (0.31 to 0.81)†	.005	5 (3-8)
Risperidone	3	844	0.39 (0.27 to 0.58)†	<.001	7 (4-33)
Ziprasidone	2	416	0.50 (0.35 to 0.72)†	<.001	6 (4-14)
Combined	11	2455	0.52 (0.44 to 0.61)†	<.001	8 (8-13)
Weight gain					
Aripiprazole	2	514	0.16 (−0.02 to 0.33)‡	.06	NA
Olanzapine	2	246	0.75 (0.49 to 1.01)‡	<.001	NA
Quetiapine	1	203	0.44 (0.17 to 0.72)‡	.002	NA
Risperidone	3	824	0.29 (−0.19 to 0.78)‡	.23	NA
Ziprasidone	1	203	0.0 (−0.29 to 0.29)‡	>.99	NA
Combined	9	1990	0.33 (0.12 to 0.55)‡	.002	NA
SAS/ESRS					
Aripiprazole	2	507	0.17 (0.0 to 0.35)‡	.05	NA
Olanzapine	2	246	−0.18 (−0.43 to 0.07)‡	.15	NA
Quetiapine	NA	NA	NA	NA	NA
Risperidone	1	247	0.24 (−0.01 to 0.49)‡	.06	NA
Ziprasidone	2	395	0.13 (−0.08 to 0.34)‡	.24	NA
Combined	7	1395	0.10 (−0.03 to 0.23)‡	.13	NA
BAS					
Aripiprazole	2	507	0.34 (0.12 to 0.56)‡	.002	NA
Olanzapine	2	251	−0.18 (−0.43 to 0.07)‡	.15	NA
Quetiapine	NA	NA	NA	NA	NA
Risperidone	NA	NA	NA	NA	NA
Ziprasidone	2	395	0.22 (0.01 to 0.43)‡	.04	NA
Combined	6	1595	0.15 (−0.06 to 0.35)‡	.16	NA

Abbreviations: BAS, Barnes Akathisia Scale; CI, confidence interval; ESRS, Extrapyramidal Symptom Rating Scale; NA, not available; NNT, number of participants needed to treat; RR, relative risk; SAS, Simpson Angus Scale; SGAs, second-generation antipsychotics; SMD, standardized mean difference.

*RR>1 favors SGA; RR<1 favors placebo.

†RR<1 favors SGA; RR>1 favors placebo.

‡Negative SMD values favor SGA; positive SMD values favor placebo.

All the trials together indicated a trend for superiority of SGAs compared with MSs. Response rates were reported in 2 trials only.[22,24] In the olanzapine vs valproate comparison, patients treated with olanzapine showed a higher response rate. In the quetiapine vs lithium comparison, no difference was observed. As to the global dropout rate and the dropout rates due to adverse events or inefficacy, no differences between SGAs and MSs could be discerned.

Weight Change, Somnolence, and EPSs

Patients treated with olanzapine and quetiapine had greater weight gain and a greater rate of somnolence than

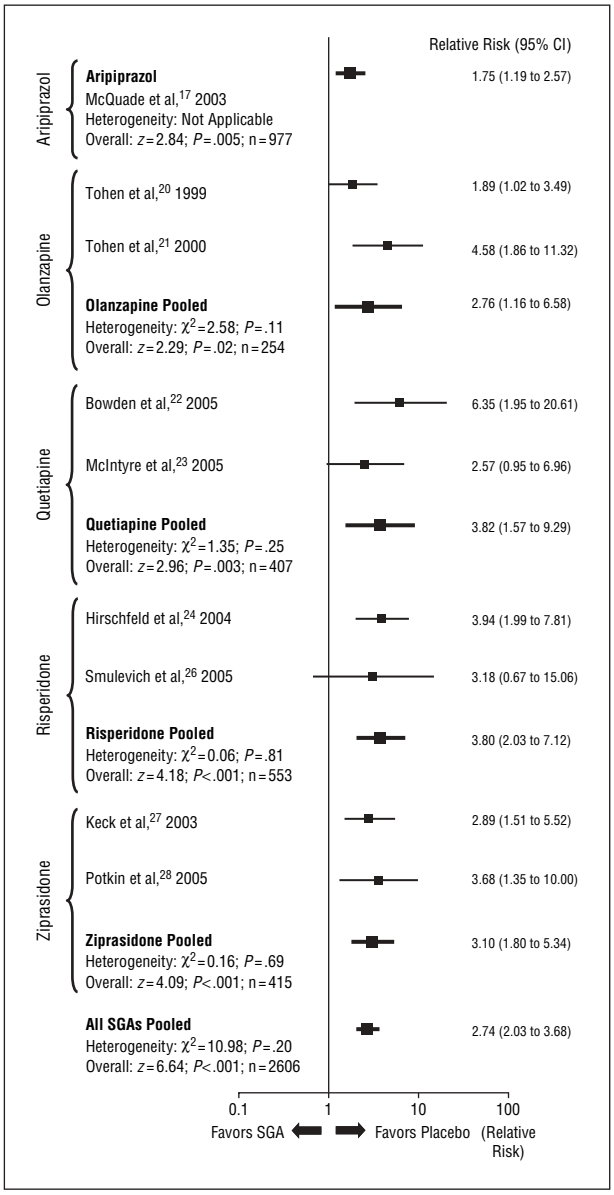

Figure 2. Mean rates of somnolence: second-generation antipsychotics (SGAs) vs placebo. CI indicates confidence interval.

those treated with lithium or valproate (data for risperidone were not available). In these studies, the rates of EPS were not reported.

COMPARISON 3: SGAs vs PLACEBO AS ADD-ON MEDICATION TO MSs

The 6 studies included in this analysis investigated olanzapine,[33] quetiapine,[34,35] risperidone,[36,37] and ziprasidone[38] vs placebo as add-on medication to the MSs lithium,[33-38] valproate,[33-37] and carbamazepine[37] (Table 1). Three of these studies[33-35] investigated patients who did not fully respond to MS monotherapy after 7, 14, or 28 days. Two more studies[36,37] included 43% and 64% of patients, respectively, with partial response to monotherapy with MSs. One trial[38] did not report previous treatment. **Figure 5** displays the results of the primary outcome (YMRS score changes), and **Table 4** gives the pooled results of the secondary outcome parameters.

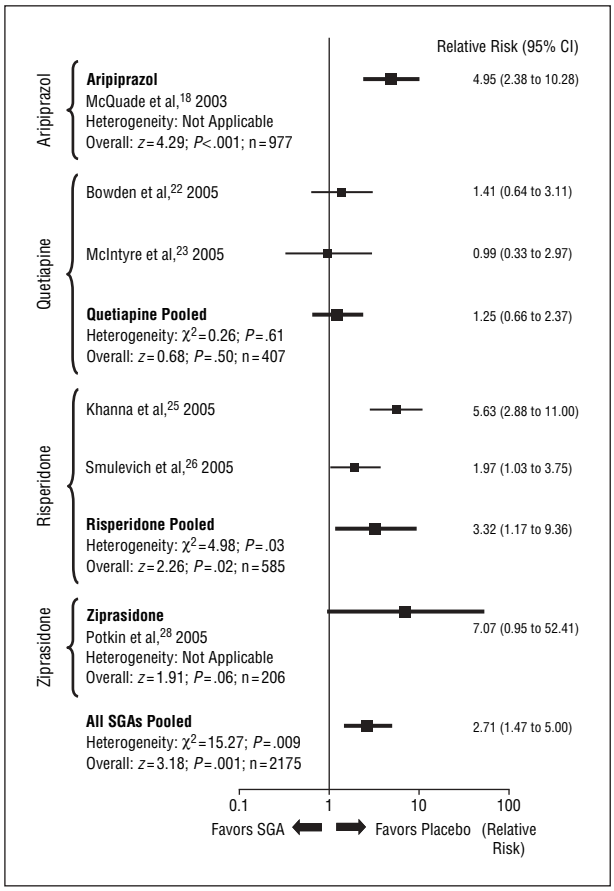

Figure 3. Mean rates of extrapyramidal adverse effects: second-generation antipsychotics (SGAs) vs placebo. CI indicates confidence interval.

Reduction in Manic Symptoms and Response Rates

Compared with placebo as add-on medication to MSs, statistically significant superiority in improving manic symptoms was found for olanzapine, quetiapine, and risperidone but not for ziprasidone (Figure 5). Considered as a group, the SGAs were significantly superior.

The percentage of patients with a response was much higher in groups of patients who received add-on treatment with olanzapine and quetiapine but not with risperidone (data for ziprasidone were not available). Analysis of all the trials showed a significant advantage for combination therapy.

Dropout Rates

The global dropout rate was significantly lower in patients treated with MSs plus quetiapine or risperidone than in those treated with MSs plus placebo. No difference was found for olanzapine and ziprasidone. Analysis of all the trials showed a significantly reduced global dropout rate in patients treated with combination therapy.

In studies with quetiapine, risperidone, and ziprasidone, adverse event dropout rates were not different; they were, however, higher for olanzapine than for placebo add-on treatment. There was no overall difference between the active treatment and placebo groups.

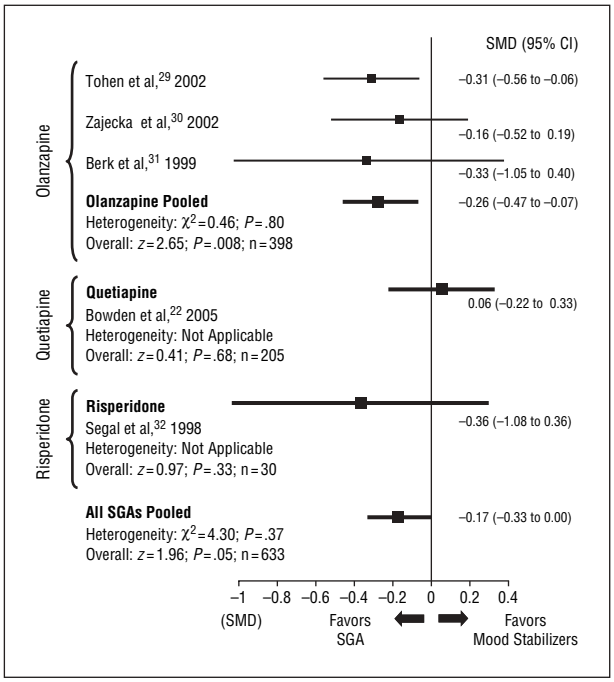

Figure 4. Mean Young Mania Rating Scale score changes: second-generation antipsychotics (SGAs) vs mood stabilizers. CI indicates confidence interval; SMD, standardized mean difference.

Regarding the dropout rate due to inefficacy, a significant advantage for combination therapy was shown in the olanzapine study but not for quetiapine and risperidone (data for ziprasidone were not available). The combined dropout rate due to inefficacy was significantly lower in patients treated with combination therapy.

Weight Change, Somnolence, and EPS

Mean weight change was increased in patients treated with olanzapine, risperidone, and quetiapine (data for ziprasidone were not available). The rate of somnolence was significantly higher in patients treated with olanzapine, quetiapine, and ziprasidone but not with risperidone. The pooled analysis revealed a significantly higher rate of somnolence in patients treated with MSs plus SGAs.

Data on EPS rates were reported only in the risperidone and ziprasidone trials. The incidence of EPSs was higher with ziprasidone than with placebo but not with risperidone vs placebo.

COMPARISON 4: SGAs vs HALOPERIDOL

We included 2 studies investigating aripiprazole[39] and olanzapine[40] vs haloperidol and the branches of 3 further studies analyzing quetiapine[23] and risperidone[26,32] vs haloperidol (Table 1). **Figure 6** displays the results of the primary outcome (YMRS score changes), and

Table 3. Comparison 2: SGAs vs Mood Stabilizers

	Trials, No.	Participants, No.	RR or SMD (95% CI)	*P* Value	NNT (95% CI)
Response					
Olanzapine vs valproate	1	251	1.32 (1.01-1.71)*	.04	8 (4-100)
Quetiapine vs lithium	1	201	1.0 (0.78-1.30)*	.98	NA
Combined	2	456	1.15 (0.88-1.50)*	.25	NA
Weight gain					
Olanzapine vs valproate	1	246	0.63 (0.37-0.88)†	<.001	NA
Quetiapine vs lithium	1	164	0.92 (0.59-1.24)†	<.001	NA
Combined	2	410	0.75 (0.47-1.03)†	<.001	NA
Somnolence					
Olanzapine vs valproate	2	371	1.79 (1.32-2.44)‡	<.001	5 (4-11)
Quetiapine vs lithium	1	205	2.14 (1.03-4.4)‡	.04	10 (5-100)
Combined	3	576	1.84 (1.39-2.45)‡	<.001	NA
Global dropout					
Olanzapine vs valproate	2	371	0.86 (0.64-1.14)‡	.30	NA
Olanzapine vs lithium	1	30	0.33 (0.04-2.85)‡	.32	NA
Quetiapine vs lithium	1	205	0.65 (0.30-1.40)‡	.28	NA
Combined	4	666	0.82 (0.63-1.07)‡	.14	NA
Dropout due to adverse event					
Olanzapine vs valproate	2	371	1.11 (0.57-2.14)‡	.76	NA
Olanzapine vs lithium	1	30	1.0 (0.07-14.55)‡	>.99	NA
Quetiapine vs lithium	1	205	0.07 (0.00-1.24)‡	.07	NA
Combined	4	666	0.85 (0.36-2.01)‡	.71	NA
Dropout due to inefficacy					
Olanzapine vs valproate	2	371	0.82 (0.48-1.40)‡	.47	NA
Olanzapine vs lithium	NA	NA	NA	NA	NA
Quetiapine vs lithium	1	205	1.22 (0.61-2.45)‡	.57	NA
Combined	3	576	0.95 (0.62-1.45)‡	.82	NA

Abbreviations: CI, confidence interval; NA, not available; NNT, number of participants needed to treat; RR, relative risk; SGAs, second-generation antipsychotics; SMD, standardized mean difference.
*RR>1 favors SGA; RR<1 favors mood stabilizers.
†Negative SMD values favor SGA; positive SMD values favor mood stabilizers.
‡RR<1 favors SGA, RR>1 favors mood stabilizers.

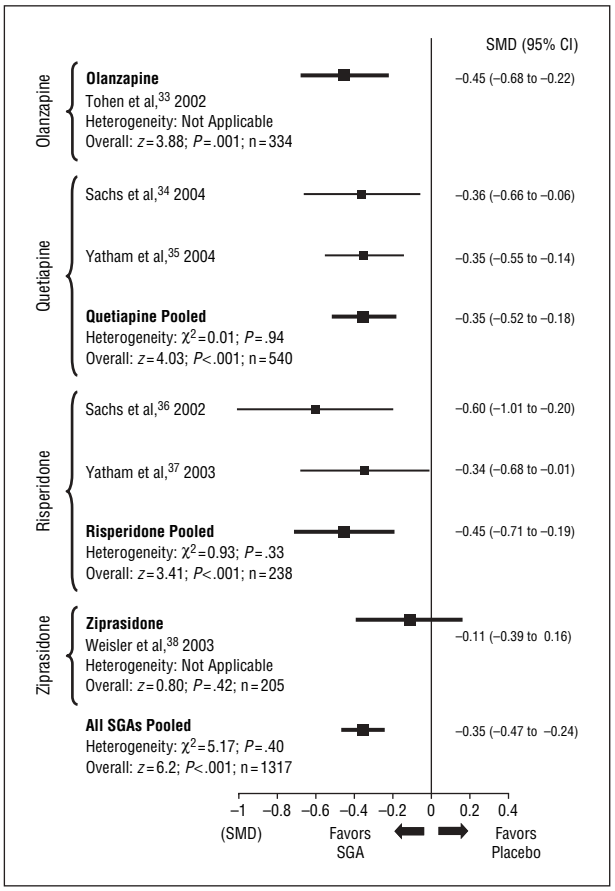

Figure 5. Mean Young Mania Rating Scale score changes: mood stabilizers plus second-generation antipsychotics (SGAs) vs mood stabilizers plus placebo. CI indicates confidence interval; SMD, standardized mean difference.

Table 5 gives the pooled results of the secondary outcome parameters.

Reduction in Manic Symptoms and Response Rates

Reduction in manic symptoms was similar for aripiprazole and risperidone compared with haloperidol. However, olanzapine and quetiapine showed a significantly lower improvement in YMRS scores (Figure 6). Overall there were no significant differences in mean YMRS score changes between patients treated with an SGA or haloperidol. However, the overall analysis was significantly heterogeneous (χ^2=13.0; P=.01) owing to the different results between the individual SGAs. The response rates did not differ between SGAs and haloperidol.

Dropout Rates

The analysis revealed a significantly lower global dropout rate in patients treated with aripiprazole and a trend toward a higher rate in patients treated with quetiapine. For olanzapine and risperidone, no difference was observed.

The dropout rate due to adverse events was significantly lower for aripiprazole. No differences were found in the other trials.

No differences in the dropout rate due to inefficacy were revealed for olanzapine, quetiapine, or risperidone compared with haloperidol. The dropout rate due to inefficacy was higher with aripiprazole.

Weight Change and Somnolence

Only 3 studies[26,39,40] reported data on weight change. In olanzapine-treated patients, the mean weight change was significantly greater than in haloperidol-treated patients but not for aripiprazole or risperidone (data on quetiapine were not available).

Regarding olanzapine, the rate of somnolence was significantly higher compared with that of haloperidol. It did not differ in the quetiapine and risperidone trials (data for aripiprazole were not available). The pooled analysis revealed that the rate of somnolence was significantly higher in patients treated with SGAs.

Extrapyramidal Symptoms

Four trials[27-30] reported the number of patients with at least 1 EPS. The analysis revealed a significantly higher incidence of EPSs in patients treated with haloperidol compared with all SGAs, taken either singly or as a group. Depressive symptoms improved more with aripiprazole treatment compared with haloperidol but not with olanzapine, quetiapine, or risperidone. In the pooled analysis, however, depressive symptoms improved more with SGAs.

COMMENT

To our knowledge, this is the first broad meta-analysis of efficacy, effectiveness, and adverse effects of SGAs in the treatment of acute mania. Its results deserve careful reflection. To draw firm conclusions concerning the overall benefits of SGAs, it is not enough simply to consider efficacy data, such as a reduction in symptoms in mania rating scales. Effectiveness criteria, which include dropout rates for any reason and due to adverse events, probably reflect the most valuable outcome parameters for clinical practice.

The SGAs are significantly more efficacious than placebo in the treatment of acute mania, as indicated by greater reductions in mania rating scores. Except for quetiapine, the superiority of SGAs is emphasized by higher response rates and, except for aripiprazole, lower dropout rates due to inefficacy.

The comparison of SGAs as a group with MSs as a group showed a certain trend toward the superiority of SGAs. This result was mainly due to the significant superiority of olanzapine in reducing manic symptoms. No differences were found for any other drugs or in any secondary outcome criteria.

Adding SGAs to MSs clearly increased the efficacy compared with monotherapy with MSs alone. Results of each single SGA drug, however, have to be discussed in detail. Olanzapine, for example, showed higher response rates and lower rates of dropout due to inefficacy but higher rates of dropout due to adverse events. Thus, the potential advantages of olanzapine in higher efficacy are

Table 4. Comparison 3: SGAs vs Placebo as Add-on Medication to Mood Stabilizers

	Trials, No.	Participants, No.	RR or SMD (95% CI)	*P* Value	NNT or NNH (95% CI)
Response					
Olanzapine	1	344	1.47 (1.17-1.84)*	<.001	5 (3-10)†
Quetiapine	2	593	1.46 (1.21-1.76)*	<.001	6 (4-13)†
Risperidone	1	151	1.38 (0.97-1.97)*	.08	NA
Combined	4	1088	1.45 (1.27-1.66)*	<.001	6 (4-9)†
Global dropout					
Olanzapine	1	344	1.05 (0.74-1.49)‡	.78	NA
Quetiapine	2	593	0.74 (0.61-0.90)‡	.003	8 (5-25)†
Risperidone	2	254	0.69 (0.52-0.93)‡	.01	6 (4-25)†
Ziprasidone	1	205	1.04 (0.69-1.57)‡	.84	NA
Combined	6	1396	0.77 (0.67-0.90)‡	<.001	11 (6-50)†
Dropout due to adverse event					
Olanzapine	1	344	6.28 (1.51-26.04)‡	.01	11 (7-25)§
Quetiapine	2	593	0.84 (0.39-1.82)‡	.65	NA
Risperidone	2	254	0.62 (0.15-2.69)‡	.53	NA
Ziprasidone	1	205	1.51 (0.44-5.21)‡	.51	NA
Combined	6	1396	1.17 (0.47-2.93)‡	.73	NA
Dropout due to inefficacy					
Olanzapine	1	344	0.25 (0.10-0.60)‡	.002	11 (7-33)†
Quetiapine	2	593	0.63 (0.37-1.07)‡	.09	NA
Risperidone	2	254	0.80 (0.24-2.65)‡	.72	NA
Ziprasidone	1	205	NA	NA	NA
Combined	6	1396	0.53 (0.31-0.89)‡	.02	NA
Weight gain					
Olanzapine	1	332	0.99 (0.75-1.23)‖	<.001	NA
Quetiapine	2	562	0.53 (0.36-0.69)‖	<.001	NA
Risperidone	2	203	0.51 (0.23-0.79)‖	<.001	NA
Ziprasidone	NA	NA	NA	NA	NA
Combined	5	1097	0.63 (0.41-0.86)‖	<.001	NA
Somnolence					
Olanzapine	1	344	1.91 (1.38-2.65)‡	<.001	NA
Quetiapine	2	589	3.73 (2.56-5.46)‡	<.001	NA
Risperidone	1	103	2.13 (0.88-5.16)‡	.10	NA
Ziprasidone	1	205	2.86 (1.57-5.21)‡	<.001	NA
Combined	5	1241	2.72 (1.97-3.78)‡	<.001	NA
EPSs					
Olanzapine	NA	NA	NA	NA	NA
Quetiapine	NA	NA	NA	NA	NA
Risperidone	2	253	1.88 (0.56-6.32)‡	.31	NA
Ziprasidone	1	205	5.55 (1.98-15.55)‡	.001	NA
Combined	3	458	3.04 (1.13-8.18)‡	.03	NA

Abbreviations: CI, confidence interval; EPSs, extrapyramidal symptoms; NA, not available; NNH, number of participants needed to harm; NNT, number of participants needed to treat; RR, relative risk; SGAs, second-generation antipsychotics; SMD, standardized mean difference.

*RR>1 favors combination treatment; RR<1 favors mood stabilizers alone.

†NNT.

‡RR<1 favors combination treatment; RR>1 favors mood stabilizers alone.

§NNH.

‖Negative SMD values favor combination treatment; positive SMD values favor mood stabilizers alone.

counteracted by a higher rate of adverse effects, which limits clinical effectiveness. For ziprasidone, in contrast, there is no proof of higher efficacy as an add-on treatment to MSs. These results are disputable because in 5 trials[33-37] patients with partial responses to monotherapy were included. These studies addressed more the question of whether an add-on treatment of an SGA to an MS in patients who were partial responders or nonresponders is more helpful than continuing them on their first medication rather than the efficacy of combination treatment. Therefore, we are reluctant to generalize the results of this comparison. However, these results are, in a way, remarkable because they are not in accordance with many clinical guidelines.[6] Some guidelines recommend as first-choice treatment monotherapy with an MS[41-47] or an SGA,[45-48] whereas others recommend combination treatment with MSs and SGAs,[49,50] especially in the case of severe manic episodes. Before any definitive recommendation of a combination therapy, pharmacoeconomic cost-benefit analyses are required. The selected studies do not provide any information on this question. In a recently published review[51] the researchers were unable to draw any firm conclusions because of the limited availability of meaningful data.

The SGAs showed no superiority in improving manic symptoms compared with haloperidol. Results for the individual SGAs were diverse. Olanzapine and quetiapine reduced manic symptoms less effectively

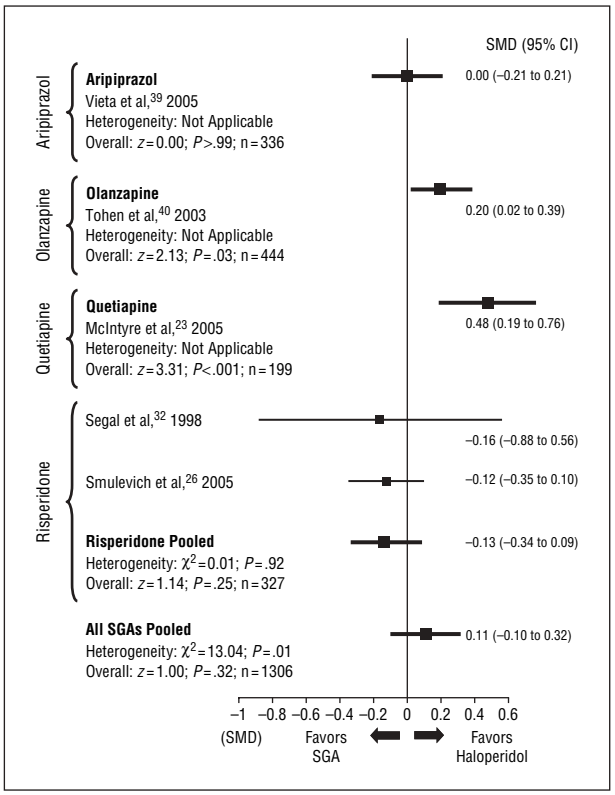

Figure 6. Mean Young Mania Rating Scale score changes: second-generation antipsychotics (SGAs) vs haloperidol. CI indicates confidence interval; SMD, standardized mean difference.

than haloperidol. In addition, quetiapine showed a lower rate of response and a higher rate of global dropout. Aripiprazole was less efficacious in terms of a higher rate of dropouts due to inefficacy, but effectiveness criteria such as rates of global dropout and dropout due to adverse events were superior compared with haloperidol. These findings are surprising because in meta-analyses in schizophrenia olanzapine has been consistently shown to be more effective than haloperidol, and quetiapine proved to be as effective as haloperidol.[52-54] Haloperidol-treated patients, however, showed a higher rate of dropout due to adverse events and higher rates of EPSs, which limits its use. Depressive symptoms improve less with haloperidol than with SGAs. Depressive symptoms were reported only as mean reductions in depression rating scale scores, and no study reported the number of patients who switched to depression. Therefore, we could not clarify whether SGAs improve depressive symptoms more than haloperidol or whether haloperidol more frequently leads to a switch into a full episode of major depression.

Adverse effects might hamper the clinical effectiveness of an antipsychotic agent despite its efficacy. As far as the data of the included studies have been reported, we analyzed the 3 important adverse events of antipsychotic drug treatment: weight gain, somnolence, and EPSs. In many studies, however, data on the rate of adverse events were reported incompletely. The SGAs are not alike, and this "class" of drugs is heterogeneous within itself.[55] The results require a balanced evaluation.

Mean weight gain was significantly greater in olanzapine- and quetiapine-treated patients, as is known from trials in schizophrenia. In contrast to the treatment of schizophrenia, however, very few data are available for bipolar disorder concerning metabolic effects.[56,57]

Rates of somnolence were increased with SGA treatment. It was not only higher in olanzapine- and quetiapine-treated patients but also in aripiprazole-, risperidone-, and ziprasidone-treated patients compared with placebo. The severity of sedation was not indicated in the included studies, which limits the interpretation of the present results. In the treatment of acute mania, somnolence can be a welcome effect that can calm agitated patients.

Findings concerning EPS rates are difficult to interpret, and EPS data were inconsistently reported, particularly in comparisons between SGAs and MSs alone or in combination. Only olanzapine and quetiapine had no evidence of increased EPS rates. In the placebo-controlled trials, a higher incidence of EPSs was observed for aripiprazole, risperidone, and ziprasidone; however, increases in EPS rating scales marginally failed to reach statistical significance. In the 2 trials in which risperidone was used in addition to an MS, no higher incidence of EPS was found compared with a treatment of MSs plus placebo. Aripiprazole-treated patients additionally showed significantly higher akathisia scores compared with placebo. No further data on aripiprazole were available compared with MSs. Treatment with ziprasidone also revealed increased scores on akathisia rating scales compared with placebo and a higher incidence of EPSs in combination with an MS compared with an MS plus placebo.

These results may open the discussion on whether some SGAs might be more prone to induce EPSs in patients with bipolar disorder. We conclude that at least some SGAs are more likely to generate EPSs compared with placebo. These results become more evident when looking at the incidence rates rather than the changes in rating scale scores. It seems to us that the incidence rate is of more clinical relevance.

In this regard, patients with bipolar disorder may differ from those with schizophrenia. For all SGAs investigated in schizophrenia trials, Leucht et al[52,58] did not find evidence of EPS rates higher than for placebo. A recent study[6] reanalyzed data on EPSs in olanzapine trials in patients with schizophrenia and bipolar disorder. This study revealed a higher incidence of EPSs in haloperidol-treated patients with bipolar disorder compared with haloperidol-treated patients with schizophrenia. They did not find a difference between olanzapine-treated patients with bipolar disorder and schizophrenia.

The rate of completers varied among different studies and trial arms. Furthermore, data on person-days of exposure were usually lacking. Thus, an unbalanced exposure of treatments cannot be excluded. In all the trials, antipsychotic agents and MSs were prescribed in commonly used dose ranges. The effect of psychotic features on efficacy were reported in 14 studies. Treatment efficacy was not different in patients with vs without psychotic symptoms in all but 2 studies.[23,29] Only 2 placebo-controlled studies reported outcome of treatment in patients with rapid cycling course. The studies concluded that aripiprazole[19]

Table 5. Comparison 4: SGAs vs Haloperidol

	Trials, No.	Participants, No.	RR or SMD (95% CI)	*P* Value	NNT or NNH (95% CI)
Response					
Aripiprazole	1	347	1.20 (0.95 to 1.50)*	.12	NA
Olanzapine	1	453	0.99 (0.88 to 1.11)*	.85	NA
Quetiapine	1	201	0.76 (0.57 to 1.01)*	.06	NA
Risperidone	1	298	1.00 (0.79 to 1.28)*	.98	NA
Combined	4	1299	0.99 (0.86 to 1.15)*	.90	NA
Global dropout					
Aripiprazole	1	347	0.69 (0.58 to 0.83)†	<.001	5 (3-8)‡
Olanzapine	1	453	0.82 (0.62 to 1.07)†	.14	NA
Quetiapine	1	201	1.59 (1.01 to 2.50)†	.05	NA
Risperidone	2	328	1.14 (0.58 to 2.22)†	.71	NA
Combined	5	1329	0.94 (0.67 to 1.34)†	.75	NA
Dropout due to adverse event					
Aripiprazole	1	347	0.37 (0.26 to 0.53)†	<.001	3 (2.5-5)‡
Olanzapine	1	453	0.71 (0.40 to 1.25)†	.24	NA
Quetiapine	1	201	0.49 (0.17 to 1.37)†	.17	NA
Risperidone	2	328	1.40 (0.40 to 4.87)†	.59	NA
Combined	5	1329	0.56 (0.34 to 0.94)†	.03	NA
Dropout due to inefficacy					
Aripiprazole	1	347	2.95 (1.49 to 5.84)†	.002	9 (6-20)§
Olanzapine	1	453	0.99 (0.64 to 1.54)†	.97	NA
Quetiapine	1	201	1.05 (0.66 to 1.67)†	.84	NA
Risperidone	1	298	2.34 (0.46 to 11.86)†	.31	NA
Combined	4	1299	1.43 (0.84 to 2.46)†	.19	NA
Weight change					
Aripiprazole	1	337	−0.02 (−0.23 to 0.19)‖	.86	NA
Olanzapine	1	440	0.58 (0.39 to 0.77)‖	<.001	NA
Quetiapine	NA	NA	NA	NA	NA
Risperidone	1	297	−0.03 (−0.26 to 0.20)‖	.79	NA
Combined	NA	NA	NA	NA	NA
Somnolence					
Aripiprazole	NA	NA	NA	NA	NA
Olanzapine	1	453	1.72 (1.02 to 2.92)†	.04	17 (8-100)§
Quetiapine	1	201	1.40 (0.63 to 3.13)†	.41	NA
Risperidone	1	298	1.31 (0.43 to 4.03)†	.64	NA
Combined	3	952	1.57 (1.04 to 2.37)†	.03	NA
EPSs					
Aripiprazole	1	347	0.26 (0.16 to 0.44)†	<.001	4 (3-6)‡
Olanzapine	1	453	0.09 (0.04 to 0.22)†	<.001	5 (4-6)‡
Quetiapine	1	201	0.17 (0.07 to 0.38)†	<.001	3 (2.5-5)‡
Risperidone	1	298	0.42 (0.28 to 0.63)†	<.001	4 (3-8)‡
Combined	4	1299	0.22 (0.12 to 0.41)†	<.001	4 (3-5)‡
Depressive symptoms					
Aripiprazole	1	347	−0.24 (−0.45 to −0.03)‖	.03	NA
Olanzapine	1	453	−0.16 (−0.34 to 0.02)‖	.09	NA
Quetiapine	1	201	−0.09 (−0.36 to 0.19)‖	.54	NA
Risperidone	1	298	−0.10 (−0.32 to 0.13)‖	.41	NA
Combined	4	1299	−0.15 (−0.26 to −0.05)‖	.005	NA

Abbreviations: CI, confidence interval; EPSs, extrapyramidal symptoms; NA, not available; NNH, number of participants needed to harm; NNT, number of participants needed to treat; RR, relative risk, SGAs, second-generation antipsychotics; SMD, standardized mean difference.

*RR>1 favors SGA; RR<1 favors haloperidol.

†RR<1 favors SGA; RR>1 favors haloperidol.

‡NNT.

§NNH.

‖Negative SMD values favor of SGA; positive SMD values favor haloperidol.

and olanzapine[20] are more efficacious than placebo. The effect of pure manic or mixed episode type on the outcome was also only marginally reported. Placebo-controlled trials showed that antipsychotic drugs are efficacious in manic and mixed episode types. One study reported that a combination of olanzapine with MSs was more efficacious than MSs alone in patients with mixed episodes.[33] Other studies found no difference in efficacy between episode types.[34,36] Only 1 study[33] reported the time to respond. In this study, median response time was significantly shorter in patients treated with a combination of olanzapine and MSs (18 days) compared with patients treated with MSs alone (28 days).

A limitation of this review is that most of the trials were sponsored by the pharmaceutical industry and were conducted to gain regulatory approval for the

treatment of acute mania. We found only 2 studies lacking industry support.[31,32] Therefore, the possibility of a sponsor bias induced in favor of their product cannot be excluded.[59]

Furthermore, the statistical power varied among the 4 categories of comparisons. The greatest number of studies (n=12) and patients (n=2827) was available for the first comparison (SGAs vs placebo). Five studies with 636 patients were included in the second comparison (SGAs vs MSs), 6 studies with 1395 patients in the third comparison (SGAs vs placebo as add-on medication to MSs), and 5 studies with 1329 patients in the last comparison (SGAs vs haloperidol). Owing to the low number of patients and trials in 3 comparisons, we also tentatively analyzed the SGAs as a single group vs the comparison treatments. The exploratory pooling procedure seems justified because efficacy results were rather homogenous, in particular in comparisons 2 and 4. Concerning all investigated adverse events, results were much more heterogeneous, indicating that SGAs differed substantially in tolerability.[55]

In conclusion, this meta-analysis found that SGA agents as add-on medication to MSs are highly superior to MSs alone in improving acute manic symptoms, as indicated by greater reductions in mania scores, higher response rates, and fewer dropouts due to inefficacy. However, effectiveness criteria should also be included in treatment decisions. Adverse effects such as somnolence, weight gain, and EPS have an impact on treatment adherence. Based on the results reported herein, combination treatment with an SGA and an MS should be the treatment of choice, in particular for severe manic episodes.

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Additional Information: The online-only eTables are available at http://www.archgenpsychiatry.com.

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eTable 1. Clinical Characteristics in the Available Data of Trials Included in the Meta-analysis

Source	Drug	RC	RC and Outcome	ME	ME and Outcome	PF	PF and Outcome	Time to Respond
				Comparison 1				
Keck et al,[17] 2003	Aripiprazole	NA	NA	NA	NA	NA	NA	NA
McQuade et al,[18] 2003	Aripiprazole	NA	NA	NA	NA	NA	NA	NA
Sachs et al,[19] 2006	Aripiprazole	Yes	Yes	Yes	Yes	NA	NA	NA
Tohen et al,[20] 1999	Olanzapine	Yes	Yes	Yes	Yes	Yes	Yes	NA
Tohen et al,[21] 2000	Olanzapine	Yes	NA	Yes	Yes	Yes	Yes	NA
Bowden et al,[22] 2005	Quetiapine	Excl	NA	Excl	NA	NA	NA	NA
	Lithium	Excl	NA	Excl	NA	NA	NA	NA
McIntyre et al,[23] 2005	Quetiapine	Excl	NA	Excl	NA	Yes	Yes	NA
	Haloperidol	Excl	NA	Excl	NA	Yes	Yes	NA
Hirschfeld et al,[24] 2004	Risperidone	NA	NA	Excl	NA	Yes	Yes	NA
Khanna et al,[25] 2005	Risperidone	Excl	NA	Yes	Yes	Yes	Yes	NA
Smulevich et al,[26] 2005	Risperidone	Excl	NA	Yes	NA	Yes	Yes	NA
	Haloperidol	Excl	NA	Yes	NA	Yes	Yes	NA
Keck et al,[27] 2003	Ziprasidone	NA	NA	Yes	Yes	NA	NA	NA
Potkin et al,[28] 2005	Ziprasidone	NA	NA	Yes	NA	NA	NA	NA
				Comparison 2				
Tohen et al,[29] 2002	Olanzapine	Yes	NA	Yes	NA	Yes	Yes	NA
	Valproate	Yes	NA	Yes	NA	Yes	Yes	NA
Zajecka et al,[30] 2002	Olanzapine	Yes	NA	Yes	NA	Yes	Yes	NA
	Valproate	Yes	NA	Yes	NA	Yes	Yes	NA
Berk et al,[31] 1999	Olanzapine	NA	NA	NA	NA	NA	NA	NA
	Lithium	NA	NA	NA	NA	NA	NA	NA
Segal et al,[32] 1998	Risperidone	NA	NA	NA	NA	NA	NA	NA
	Haloperidol	NA	NA	NA	NA	NA	NA	NA
	Lithium	NA	NA	NA	NA	NA	NA	NA
				Comparison 3				
Tohen et al,[33] 2002	Olanzapine	NA	NA	Yes	Yes	Yes	Yes	Yes
Sachs et al,[34] 2004	Quetiapine	Excl	NA	NA	Yes	Yes	Yes	NA
Yatham et al,[35] 2004	Quetiapine	Excl	NA	Excl	NA	Yes	Yes	NA
Sachs et al,[36] 2002	Risperidone	NA	NA	Yes	Yes	Yes	Yes	NA
Yatham et al,[37] 2003	Risperidone	NA	NA	Yes	NA	Yes	Yes	NA
Weisler et al,[38] 2003	Ziprasidone	NA	NA	Yes	NA	NA	NA	NA
				Comparison 4				
Vieta et al,[39] 2005	Aripiprazole	Excl	NA	Yes	NA	NA	NA	NA
Tohen et al,[40] 2003	Olanzapine	NA	NA	Yes	Yes	Yes	Yes	NA

Abbreviations: Excl, exclusion criterion for the study; ME, mixed episode type; ME and outcome, data on the effect of ME on outcome criteria reported; NA, not available; PF, data on the existence of psychotic features; PF and outcome, data on the effect of PF on outcome criteria reported; RC indicates rapid cycling course of illness; RC and outcome, data on the effect of RC on outcome criteria reported; yes, data were reported.

eTable 2. Outcome Criteria in the Available Data of Trials Included in the Meta-analysis*

Source	Drug	YMRS	Response	Dropout: Any Reason	Dropout: Adverse Events	Dropout: Inefficacy	SAS	BAS	AIMS	ESRS	MADRS	HAMD
					Comparison 1							
Keck et al,[17] 2003	Aripiprazole	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA
McQuade et al,[18] 2003	Aripiprazole	NA	NA	NA	Yes	NA	Yes	Yes	NA	NA	NA	NA
Sachs et al,[19] 2006	Aripiprazole	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA
Tohen et al,[20] 1999	Olanzapine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA
Tohen et al.[21] 2000	Olanzapine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	Yes
Bowden et al,[22] 2005	Quetiapine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	NA
	Lithium	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	NA
McIntyre et al,[23] 2005	Quetiapine	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	Yes	NA
	Haloperidol	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA	Yes	NA
Hirschfeld et al,[24] 2004	Risperidone	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	Yes	NA	NA
Khanna et al,[25] 2005	Risperidone	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	Yes	Yes	NA
Smulevich et al,[26] 2005	Risperidone	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	Yes	Yes	NA
	Haloperidol	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	Yes	Yes	NA
Keck et al,[27] 2003	Ziprasidone	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	NA
Potkin et al,[28] 2005	Ziprasidone	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	Yes
					Comparison 2							
Tohen et al,[29] 2002	Olanzapine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes
	Valproate	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes
Zajecka et al,[30] 2002	Olanzapine	Yes	NA	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes
	Valproate	Yes	NA	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes
Berk et al,[31] 1999	Olanzapine	Yes	NA	Yes	Yes	NA	Yes	NA	NA	NA	NA	NA
	Lithium	Yes	NA	Yes	Yes	NA	Yes	NA	NA	NA	NA	NA
Segal et al,[32] 1998	Risperidone	Yes	NA	NA	NA	NA	Yes	NA	NA	NA	NA	NA
	Haloperidol	Yes	NA	NA	NA	NA	Yes	NA	NA	NA	NA	NA
	Lithium	Yes	NA	NA	NA	NA	Yes	NA	NA	NA	NA	NA
					Comparison 3							
Tohen et al,[33] 2002	Olanzapine	Yes	Yes	Yes	Yes	Yes	NA†	NA†	NA†	NA	NA	Yes
Sachs et al,[34] 2004	Quetiapine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	NA
Yatham et al,[35] 2004	Quetiapine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes	NA
Sachs et al,[36] 2002	Risperidone	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	Yes	NA	NA
Yatham et al,[37] 2003	Risperidone	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	Yes	NA	Yes
Weisler et al,[38] 2003	Ziprasidone	Yes	NA	Yes	Yes	NA	NA	NA	NA	NA	NA	NA
					Comparison 4							
Vieta et al,[39] 2005	Aripiprazole	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Yes	NA
Tohen et al,[40] 2003	Olanzapine	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	Yes

Abbreviations: AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Scale; EPS, extrapyramidal symptoms; ESRS, Extrapyramidal Symptom Rating Scale; HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Asberg Depression Rating Scale; NA, not available; SAS, Simpson Angus Scale; yes, data were reported; YMRS, Young Mania Rating Scale.

*Data on the incidence of somnolence were reported for all studies except those by Khanna et al,[25] Berk et al,[31] Segal et al,[32] Yatham et al,[37] and Vieta et al.[39] Data on the incidence of weight gain were reported for all studies except those by Keck et al,[27] Potkin et al,[28] Berk et al,[31] Segal et al,[32] and Weisler et al.[38] Data on the incidence of EPS were reported for McQuade et al,[18] McIntyre et al,[23] Khanna et al,[25] Smulevich et al,[26] Potkin et al,[28] Sachs et al,[36] Yatham et al,[37] Weisler et al,[38] Vieta et al,[39] and Tohen et al.[40] Data on the incidence of akathisia were reported for Keck et al,[17] McQuade et al,[18] Sachs et al,[19] McIntyre et al,[23] Keck et al,[27] Potkin et al,[28] Weisler et al,[38] Vieta et al,[39] and Tohen et al.[40] Data on hyperkinesias were reported but not included in this analysis.

†Results are reported in the text, but no data were presented.