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.

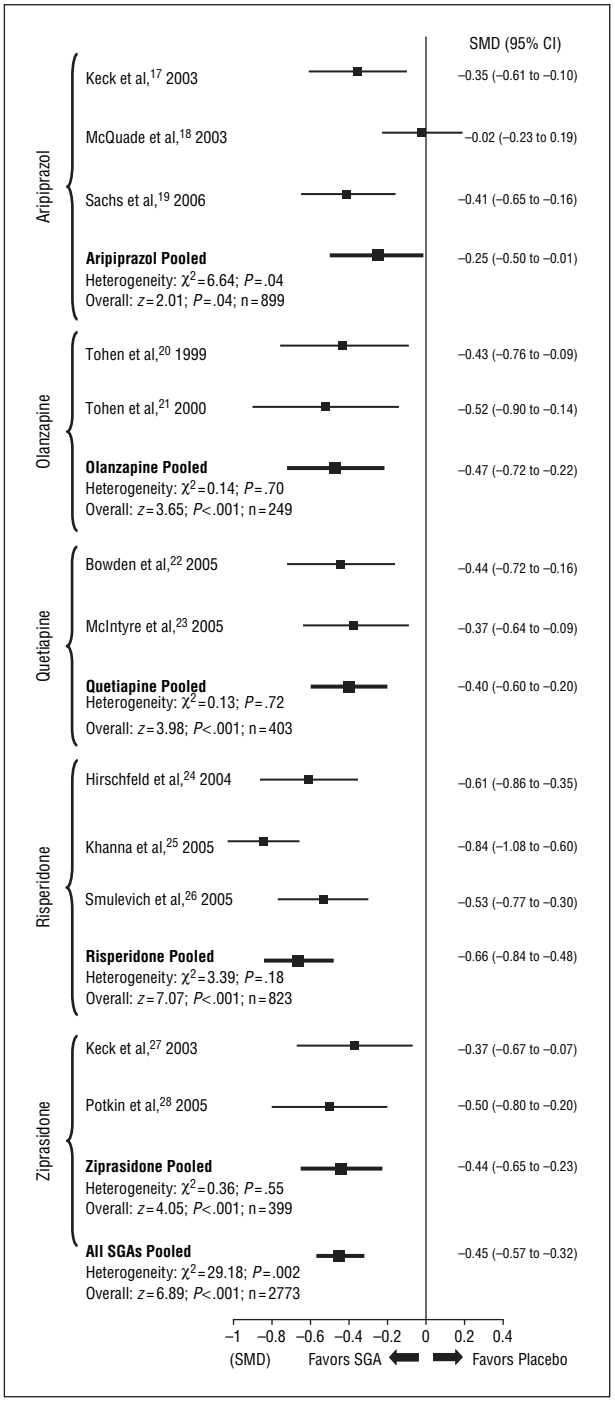

Figure 1. Mean Young Mania Rating Scale score changes: second-generation antipsychotics (SGAs) vs placebo. CI indicates confidence interval; SMD, standardized mean difference.

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.

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