Article

Combination of a Mood Stabilizer With Risperidone or Haloperidol for Treatment of Acute Mania: A Double-Blind, Placebo-Controlled Comparison of Efficacy and Safety

Gary S. Sachs, M.D.

Fred Grossman, D.O.

S. Nassir Ghaemi, M.D.

Akiko Okamoto, Sc.D.

Charles L. Bowden, M.D.

Objective: The study assessed the efficacy and safety of risperidone as an adjunctive agent to mood stabilizers in the treatment of acute mania.

Method: This 3-week randomized, double-blind, placebo-controlled study included 156 bipolar disorder patients with a current manic or mixed episode who received a mood stabilizer (lithium or divalproex) and placebo, risperidone, or haloperidol. The primary efficacy measure was the Young Mania Rating Scale. Other assessments used the Brief Psychiatric Rating Scale, the Clinical Global Impression scale, and safety measures.

Results: The trial was discontinued by 25 (49%) of the 51 placebo group patients, 18 (35%) of the 52 risperidone group patients, and 28 (53%) of the 53 haloperidol group patients. Mean modal doses were 3.8 mg/day (SD=1.8) of risperidone and 6.2 mg/day (SD=2.9) of haloperidol. Significantly greater reductions in Young Mania Rating Scale scores at endpoint and over time were seen in the risperidone group and in the haloperidol group, compared with the placebo group. Young Mania Rating Scale total scores improved with risperidone and with haloperidol both in patients with psychotic features and in those without psychotic features at baseline. Extrapyramidal Symptom Rating Scale total scores at endpoint were significantly higher in the haloperidol patients than in the placebo patients. Antiparkinsonian medications were received by 8%, 17%, and 38% of patients in the placebo, risperidone, and haloperidol groups, respectively.

Conclusions: Risperidone plus a mood stabilizer was more efficacious than a mood stabilizer alone, and as efficacious as haloperidol plus a mood stabilizer, for the rapid control of manic symptoms and was well tolerated.

(Am J Psychiatry 2002; 159:1146–1154)

Acute manic episodes can have devastating consequences (1; DSM-IV). Management of acute mania is directed at rapidly controlling the irritability, agitation, impulsivity, aggression, and psychotic symptoms that characterize the hyperaroused state in manic and mixed episodes. The primary goal of treatment for mania is to restore behavioral control as quickly as possible so as to minimize dangerousness to self and others and limit the high economic, social, and personal costs of manic episodes. Although many experts agree that combination therapy may offer an advantage over monotherapy (2), few controlled studies offering evidence for the advantages of this approach have been performed.

In the United States, mood stabilizers, principally lithium and divalproex, are standard treatment choices for the management of bipolar disorder (2–4). Double-blind studies have demonstrated the superior efficacy of these agents compared with placebo as monotherapy for mania (5). However, these studies have also indicated that many patients treated for up to 3 weeks with lithium or divalproex retain clinically significant manic symptoms. Higher serum levels of the mood stabilizers have been associated with greater efficacy but are complicated by more adverse effects and secondary noncompliance (5, 6).

Conventional antipsychotics have been used alone to achieve rapid control of acute manic symptoms (7), but their efficacy appears to be modest (8, 9). In addition, conventional antipsychotics are often poorly tolerated. Although atypical antipsychotics are generally better tolerated than the conventional agents (10), we are aware of only three controlled trials assessing the effects of atypical antipsychotics in patients with bipolar disorder. Risperidone, haloperidol, and lithium were equivalent in efficacy in a 28-day double-blind study involving 45 inpatients with mania (11). In a 3-week double-blind study, olanzapine was superior to placebo for treatment of symptoms of acute mania in 139 patients for whom treatment with mood stabilizers had failed (12). A 4-week replication study again found olanzapine monotherapy superior to placebo in 115 patients hospitalized for acute mania (13). These reports are encouraging and suggest that the efficacy of treatment with atypical antipsychotics as mono-

therapy appears to be of the same magnitude as that for mood stabilizer monotherapy.

Because rapid control of acute mania is desired, adjunctive agents, including combinations of two mood stabilizers or of a mood stabilizer with an antipsychotic agent, are widely used (14). Although this approach has been recommended in published treatment guidelines (2, 3), few well-controlled studies of combination therapies have been conducted. For patients with bipolar I disorder who were receiving lithium, adjunctive treatment with gabapentin was equivalent to placebo for treatment acute mania or hypomania (15). The combination of a mood stabilizer plus an antipsychotic agent has been widely used for rapid control of acute manic episodes (14, 16). Muller-Oerlinghausen et al. (17) reported that adjunctive valproate plus a conventional antipsychotic provided greater symptom reduction than placebo and at a lower mean dose of the antipsychotic agent. Concern about possible additive adverse effects (particularly extrapyramidal symptoms and tardive dyskinesia) with combination therapy has limited the use of conventional antipsychotics for patients with bipolar disorder (18).

Evidence from several small trials (19–22) and a survey of a hospital database (23) have suggested that risperidone may be useful in patients with bipolar and affective disorders. In a 3-week double-blind, placebo-controlled study involving manic patients, we evaluated the effects of risperidone and haloperidol in combination with a mood stabilizer. To our knowledge, this study also provides the first controlled comparison of a typical and atypical antipsychotic in the treatment of mania.

Method

Subjects

Subjects were patients aged 18–65 years with a history of bipolar disorder and at least one prior manic episode who were hospitalized for treatment of a manic episode in one of 20 centers. Inclusion criteria included a minimum score of 20 on the Young Mania Rating Scale (24) and a DSM-IV diagnosis of bipolar disorder, with the most recent episode manic or mixed (296.4x, 296.6x). Patients had to be medically stable according to a pretrial physical examination, medical history, and electrocardiography. After complete description of the study to the subjects, written informed consent was obtained.

Exclusion criteria included another DSM-IV axis I diagnosis that required psychopharmacologic treatment; use of disallowed concomitant therapy; history of drug or alcohol abuse or dependence within 1 month before study entry; seizure disorder requiring medication; participation in an investigational drug trial within 30 days before the start of the trial; known sensitivity to risperidone, lithium, divalproex, or carbamazepine; use of clozapine within 1 month before study entry; use of depot neuroleptics within one cycle before study entry; and laboratory values outside the normal range. Women of childbearing potential who were without adequate contraception were also excluded.

Procedure

Patients were randomly assigned to receive placebo, risperidone, or haloperidol under double-blind conditions in addition to a mood stabilizer (lithium or divalproex) for up to 3 weeks. Random assignment was stratified by mood stabilizer (lithium or divalproex) and was preceded by a washout period of up to 3 days for patients who had received any disallowed concomitant medications such as antipsychotics other than risperidone or haloperidol or mood stabilizers other than lithium or divalproex.

Patients who had completed either the 3-week double-blind study or at least 7 days of double-blind treatment but who terminated because of lack of efficacy or an adverse event were eligible to enter a 10-week open-label extension study. Data from the 10-week study will be reported elsewhere.

Assessments

All patients received a psychiatric evaluation to establish the diagnosis of bipolar disorder. During the double-blind phase, the Young Mania Rating Scale was completed at baseline screening and days 1, 8, 15, and 22. The Clinical Global Impression (CGI) scale (25) was completed on days 1, 8, 15, and 22. Severity of extrapyramidal symptoms was rated with the Extrapyramidal Symptom Rating Scale (26) on days 1, 8, 15, and 22. Information on adverse events was obtained on days 1, 3, 8, 15, and 22. Electrocardiography and standard laboratory tests were performed at screening and day 22. Vital signs were measured at screening and days 1, 8, 15, and 22. Serum levels of the mood stabilizer were measured at screening and days 1 and 22. Patients received a physical examination at screening and on day 22 and were weighed on days 1 and 22.

Dosing Schedule

The study employed a flexible dosing schedule for risperidone, haloperidol, and the mood stabilizers. In addition to receiving lithium or divalproex, on days 1 and 2 of the double-blind phase, patients received 2 mg/day of risperidone (2 tablets), 4 mg/day of haloperidol (2 tablets), or 2 tablets of placebo. On days 3 and 4, the doses could be maintained, reduced to 1 tablet, or increased to 4 mg/day of risperidone, 8 mg/day of haloperidol, or 4 tablets of placebo. On days 5 to 21, the doses could be increased to 6 mg/day of risperidone, 12 mg/day of haloperidol, or 6 tablets of placebo.

If a patient was not receiving lithium or divalproex at study entry, treatment with one or the other was started immediately after consent was provided. Mood stabilizers could not be switched for lack of efficacy. If a patient experienced an adverse event attributed to the mood stabilizer, the dose could be reduced. If the adverse event persisted, the mood stabilizer could be switched. For the data analyses, three patients who switched mood stabilizers remained in their original mood stabilizer group (mood stabilizer groups were used as strata).

Investigators were instructed to adjust doses of the mood stabilizers to obtain serum concentrations in the usual therapeutic range: for divalproex, 50–120 μg/ml (trough); for lithium, 0.6–1.4 meq/liter (12 hours after last dose).

Concomitant Medications

The following were not permitted during the trial: antipsychotics other than risperidone or haloperidol; mood stabilizers other than lithium or divalproex; benzodiazepines other than temazepam, oxazepam, or flurazepam for sleep; lorazepam for agitation after day 7 (however, up to 4 mg/day was permitted during days 1 to 7 for sleep); antiparkinsonian medication at baseline; and antidepressants at entry into the double-blind phase.

Efficacy Measures

Severity of the illness and psychopathology were measured with the Young Mania Rating Scale (range=0–60), the CGI severity scale (from 0, "not ill," to 7, "extremely severe"), and the CGI change scale (from 1, "very much better," to 7, "very much

TABLE 1. Characteristics of Patients in a 3-Week Randomized, Double-Blind, Placebo-Controlled Study of Combination Therapy With a Mood Stabilizer and an Adjunctive Agent for Treatment of Acute Mania

Characteristic	Patients Receiving Placebo Plus a Mood Stabilizer (N=51)[a]		Patients Receiving Risperidone Plus a Mood Stabilizer (N=52)[a]		Patients Receiving Haloperidol Plus a Mood Stabilizer (N=53)[a]	
	Median	Range	Median	Range	Median	Range
Age (years)	43	18–64	41	18–61	44	20–66
	N	%	N	%	N	%
Male	24	47	26	50	30	57
Female	27	53	26	50	23	43
Severity of current manic episode						
Mild	0	0	1	2	3	6
Moderate	22	43	22	42	23	43
Severe, with psychosis	22	43	21	40	18	34
Severe, without psychosis	7	14	8	15	9	17
Episode type						
Manic	40	78	42	81	41	77
Mixed	11	22	10	19	12	23
Receiving psychotropic medication[b] at baseline	31	61	27	52	30	57

[a] Patients received either lithium or divalproex as a mood stabilizer.
[b] Other than lorazepam.

worse"). The primary measure of efficacy was the change in the mean Young Mania Rating Scale total score from baseline to endpoint. Endpoint was the last available postbaseline assessment. Secondary measures included changes from baseline in severity of illness as reflected in CGI change scale scores.

Statistical Analysis

All patients who were randomly assigned to treatment groups and had at least one postbaseline assessment were included in the efficacy analysis. All patients who were randomly assigned to treatment groups were included in the safety analysis. The primary time point was the endpoint of the double-blind phase (i.e., the last available observation for each patient during the double-blind phase), and the primary comparison was between risperidone and placebo. Haloperidol was included as an active comparator to assess the sensitivity of the trial. An analysis of covariance model was used to test differences between treatments at endpoint. The model included factors for treatment, investigator, and type of mood stabilizer and baseline score on the Young Mania Rating Scale as a covariate. Young Mania Rating Scale total scores at all time points in the double-blind treatment phase were analyzed jointly by means of a repeated-measures model. Investigator, type of mood stabilizer, and treatment over time were used as factors in the model, with an assumption that observations of each subject were correlated with an autoregression variance and covariance structure. Gehan's generalized Wilcoxon test (27) was used to evaluate differences in time to discontinuation, and the Van Elteren test (28) (controlling for investigator) was used to evaluate differences in CGI change scores.

Results

Characteristics of the patients in the three treatment groups are summarized in Table 1. The groups included equivalent proportions of men and women, all of whom received a DSM-IV diagnosis of bipolar disorder, manic or mixed episode. The severity specifier for the diagnosis was moderate or severe for most patients, and psychotic features were present in more than one-third of the patients. Differences in demographic and clinical characteristics between the groups at baseline were not significant.

Of the 180 patients who were recruited, 158 were randomly assigned to a treatment group; 156 of these received at least one dose of study medication. The trial was discontinued by 25 (49%) of the 51 patients in the placebo plus mood stabilizer group, 18 (35%) of the 52 patients in the risperidone plus mood stabilizer group, and 28 (53%) of the 53 patients in the haloperidol plus mood stabilizer group (Figure 1). Reasons for early discontinuation are shown in Table 2. Time to premature discontinuation was significantly shorter for the patients who received placebo plus a mood stabilizer (25% had discontinued by day 9) than for the patients who received risperidone plus a mood stabilizer (25% had discontinued by day 15) (χ^2= 4.35, df=1, p<0.04; Wilcoxon test).

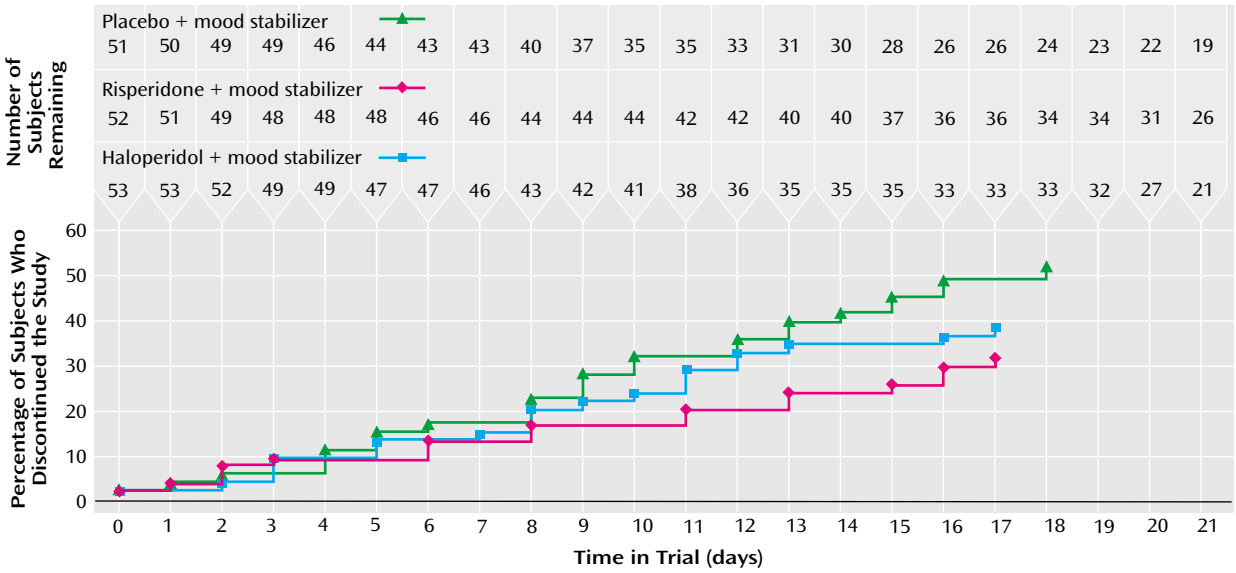
Medications

During the double-blind phase, the mean modal doses of medication were 3.8 mg/day (SD=1.8) of risperidone and 6.2 mg/day (SD=2.9) of haloperidol. The mean duration of exposure to medication was 17.1 days (SD=6.5) for the patients who received risperidone plus a mood stabilizer and 16.2 days (SD=6.6) for the patients who received haloperidol plus a mood stabilizer.

Before entering the trial, 63% of the patients (N=99 of 156) were receiving a mood stabilizer. At the start of the double-blind phase, 71% of the patients (N=111 of 156) received divalproex, and 29% (N=45 of 156) received lithium (Table 3). Blood levels of the medications at week 3 were within the targeted therapeutic range for all groups.

Lorazepam was received by 59% (N=30 of 51) of the patients in the placebo plus mood stabilizer group, 67% (N= 35 of 52) in the risperidone plus mood stabilizer group, and 64% (N=34 of 53) in the haloperidol plus mood stabilizer group. Antiparkinsonian medications were received by four (8%) patients in the placebo plus mood stabilizer group, nine (17%) patients in the risperidone plus mood

FIGURE 1. Time to Study Discontinuation in a 3-Week Randomized, Double-Blind, Placebo-Controlled Study of Combination Therapy With a Mood Stabilizer and an Adjunctive Agent for Treatment of Acute Mania[a]



[a] For patients who discontinued the double-blind study to enter the open-label study, discontinuation was the first date of open-label enrollment. For patients who discontinued and did not enter the open-label study, discontinuation was the last date medication was administered in the double-blind study. Patients who completed 19 days or more of the double-blind study were considered completers.

stabilizer group, and 20 (38%) patients in the haloperidol plus mood stabilizer group. The only significant between-group difference was in the use of antiparkinsonian medications between the placebo plus mood stabilizer group and the haloperidol plus mood stabilizer group (Cochran-Mantel-Haenszel χ^2=12.96, df=1, p<0.001).

Efficacy

The mean total scores on the Young Mania Rating Scale for the three groups at baseline were comparable (Table 4). Significantly greater improvement in the mean total score on the Young Mania Rating Scale was seen in the risperidone plus mood stabilizer group than in the placebo plus mood stabilizer group at endpoint (–14.3 versus –8.2) (Table 4, Figure 2). In the haloperidol plus mood stabilizer group also, improvement in the mean total score on the Young Mania Rating Scale was significantly greater than in the placebo plus mood stabilizer group at endpoint (–13.4 versus –8.2). Significantly greater improvements in Young Mania Rating Scale total scores over time were seen in the risperidone plus mood stabilizer group and in the haloperidol plus mood stabilizer group than in the placebo plus mood stabilizer group (Figure 2).

An additional analysis compared treatment effects in the 99 patients (63%) who were receiving mood stabilizers when they entered the trial (patients with a "breakthrough episode") and the 57 patients (37%) who started treatment with mood stabilizers on entering the trial. Among patients who were receiving mood stabilizers at the start of the trial ("breakthrough" patients), the mean total score on the Young Mania Rating Scale (higher scores indicate more severe symptoms) decreased by 7.4 (SD=10.8) in those who received placebo plus a mood stabilizer (N=28), 15.7 (SD=10.6) in those who received risperidone plus a mood stabilizer (N=34), and 14.9 (SD=9.5) in those who received haloperidol plus a mood stabilizer (N=33). Among patients who did not receive mood stabilizers until the start of the trial, the mean total score on the Young Mania Rating Scale decreased by 9.4 (SD=10.1) in the patients who received placebo plus a mood stabilizer (N=19), 11.3 (SD=6.9) in the patients who received risperidone plus a mood stabilizer (N=17), and 10.1 (SD=10.4) in the patients who received haloperidol plus a mood stabilizer (N=17).

A comparison was also made of patients with and without psychotic features at baseline. Of the 156 patients re-

TABLE 2. Reasons for Early Discontinuation From a 3-Week Randomized, Double-Blind, Placebo-Controlled Study of Combination Therapy With a Mood Stabilizer and an Adjunctive Agent for Treatment of Acute Mania

	Patients Receiving Placebo Plus a Mood Stabilizer (N=51)[a]		Patients Receiving Risperidone Plus a Mood Stabilizer (N=52)[a]		Patients Receiving Haloperidol Plus a Mood Stabilizer (N=53)[a]	
Reason for Discontinuation	N	%	N	%	N	%
Withdrew consent	10	20	9	17	15	28
Insufficient response	5	10	3	6	3	6
Noncompliance	1	2	3	6	1	2
Ineligible	2	4	1	2	3	6
Lost to follow-up	3	6	0	0	5	9
Adverse event	2	4	2	4	1	2
Other[b]	2	4	0	0	0	0
All reasons	25	49	18	35	28	53

[a] Patients received either lithium or divalproex as a mood stabilizer.
[b] Including moved to a distant location, subject felt well.

TABLE 3. Doses and Serum Levels of Mood Stabilizers in a 3-Week Randomized, Double-Blind, Placebo-Controlled Study of Combination Therapy With a Mood Stabilizer and an Adjunctive Agent for Treatment of Acute Mania

	Patients Receiving Placebo Plus a Mood Stabilizer			Patients Receiving Risperidone Plus a Mood Stabilizer			Patients Receiving Haloperidol Plus a Mood Stabilizer		
Mood Stabilizer and Characteristic	N at Baseline	Mean	SD	N at Baseline	Mean	SD	N at Baseline	Mean	SD
Divalproex	37			38			36		
Dose at start of double-blind phase (mg/day)		1312	410		1418	433		1436	686
Serum level (µg/ml) at week 3 of double-blind phase		77.3	27.3		65.4	27.1		76.2	25.6
Lithium	14			14			17		
Dose at start of double-blind phase (mg/day)		1077	285		1052	431		1041	337
Serum level (meq/liter) at week 3 of double-blind phase		0.8	0.3		0.7	0.3		0.7	0.2

TABLE 4. Scores on the Young Mania Rating Scale at Baseline and Change in Scores From Baseline in a 3-Week Randomized, Double-Blind, Placebo-Controlled Study of Combination Therapy With a Mood Stabilizer and an Adjunctive Agent for Treatment of Acute Mania

	Patients Receiving Placebo Plus a Mood Stabilizer[a]			Patients Receiving Risperidone Plus a Mood Stabilizer[a]			Patients Receiving Haloperidol Plus a Mood Stabilizer[a]		
Young Mania Rating Scale Variable	N	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline score	50	28.0	6.1	52	28.0	5.5	53	27.3	6.1
Change in score from baseline									
Week 1	46	–6.1	8.6	49	–9.7	7.8	47	–9.4	7.2
Week 2	36	–8.4	9.8	43	–13.7	8.5	39	–11.5	10.2
Week 3	25	–13.4	8.7	38	–16.6	7.9	33	–15.4	8.9
Endpoint[b]	47	–8.2	10.4	51	–14.3	9.7	50	–13.4	10.0

[a] Patients received either lithium or divalproex as a mood stabilizer.
[b] Significant differences between the risperidone plus mood stabilizer and the placebo plus mood stabilizer groups (t=2.65, df=128, p=0.009) and between the haloperidol plus mood stabilizer and the placebo plus mood stabilizer groups (t=2.34, df=128, p<0.03) but not between the risperidone plus mood stabilizer and the haloperidol plus mood stabilizer groups (t=0.31, df=128, p=0.76) in analyses of covariance with treatment, baseline score, type of mood stabilizer, and investigator as factors.

ceiving at least one dose of study medication, 61 had psychotic features at baseline and 95 did not. The mean total score on the Young Mania Rating Scale had improved at endpoint with risperidone plus a mood stabilizer and with haloperidol plus a mood stabilizer both in patients with psychotic features (mean change=–15.4, SD=11.2, N=20; and mean change=–16.8, SD=10.1, N=18, respectively) and in patients without psychotic features (mean change=–13.5, SD=8.7, N=31; and mean change=–11.3, SD=9.5, N=32). For the patients who received placebo plus a mood stabilizer, the mean changes in score were –9.3 (SD=11.5) and –7.5 (SD=9.7) in patients with (N=20) and without (N=27) psychotic features, respectively.

The results were also analyzed in subgroups of patients with a manic or a mixed episode. In patients with pure mania, the improvement in the mean total score on the Young Mania Rating Scale was greater with risperidone plus a mood stabilizer (mean change=–14.4, SD=9.4, N=42) or haloperidol plus a mood stabilizer (mean change=–13.7, SD=10.9, N=38) than with placebo plus a mood stabilizer (mean change=–6.6, SD=10.2, N=37). Patients with a mixed episode showed similar improvements with risperidone plus a mood stabilizer (mean change=–13.6, SD=11.3, N=9), haloperidol plus a mood stabilizer (mean change=–12.1, SD=6.3, N=12), and placebo plus a mood stabilizer (mean change=–14.2, SD=9.5, N=10).

CGI severity scores were similar in the treatment groups at baseline, with severity of manic symptoms being rated as marked to moderate in most patients. At endpoint, significant between-group differences were noted on the CGI change scale: ratings of much or very much improved were reported in 30% (N=14 of 47) of the patients who received placebo plus a mood stabilizer, 53% (N=27 of 51) of those who received risperidone plus a mood stabilizer, and 50% (N=25 of 50) of those who received haloperidol plus a mood stabilizer (risperidone plus mood stabilizer versus placebo plus mood stabilizer: Cochran-Mantel-Haenszel χ^2=9.7, df=1, p=0.002; and haloperidol plus mood stabilizer versus placebo plus mood stabilizer: Cochran-Mantel-Haenszel χ^2=8.9, df=1, p=0.003). An endpoint rating of very much improved was achieved by none of the patients who received placebo plus a mood stabilizer, 25% of the patients who received risperidone plus a mood stabilizer, and 16% of the patients who received haloperidol plus a mood stabilizer.

A comparison of results for patients receiving lithium versus divalproex showed that improvements in the mean total scores on the Young Mania Rating Scale at endpoint were similar in the risperidone plus mood stabilizer group and the haloperidol plus mood stabilizer group (range of mean changes in score: –11.9, SD=9.6, to –14.4, SD=9.9). However, improvement was greater in patients who received placebo plus lithium (mean change=–12.5, SD=

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.