Psychosis in Mania: Specificity of Its Role in Severity and Treatment Response

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Background: Psychosis is a prominent characteristic of manic episodes. We investigated relationships between the presence of psychotic features, the severity of the manic syndrome, and syndrome severity's response to treatment.

Method: 179 subjects meeting Research Diagnostic Criteria for a manic episode of bipolar I disorder were hospitalized for acute manic episodes and treated in a randomized trial of lithium, divalproex sodium, or placebo. Factor and cluster analyses were carried out using the clinician-rated Schedule for Affective Disorders and Schizophrenia, Change version (SADS-C) and the nurse-rated Affective Disorder Rating Scale (ADRS).

Results: Subjects with psychotic features had significantly ($p < .005$) greater overall impairment (lower Global Assessment Scale [GAS] scores) but did not differ in severity of mania scores compared with those without psychotic features. Psychosis factor scores correlated significantly ($p < .000001$) with GAS scores but not with mania scores. Baseline psychosis factor scores did not correlate with subsequent treatment-associated change in mania scores, but change in mania scores during treatment correlated significantly ($p < .000001$) with change in the psychosis factor. Changes in psychosis factor scores correlated significantly with changes in mania rating scale scores regardless of treatment.

Conclusions: Psychotic features as a component of manic episodes contribute substantially to overall impairment. Treatments that successfully treat mania also reduce psychosis scores.

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About half of manic episodes have psychotic features.[1] Delusions and formal thought disorder in mania can be as severe as they are in schizophrenia, leading to potential misdiagnosis.[2,3] Psychosis could be a dimensional aspect of severe psychiatric illnesses, itself nondiagnostic, that is superimposed on other aspects of manic episodes and requires specific treatment. This possibility is supported by the work of Prien et al.[4] that showed poor response to lithium in psychotic manic episodes unless neuroleptics were also given.[4] Alternatively, psychotic features could be an integral part of a severe manic syndrome and may respond to any sufficiently vigorous antimanic treatment. This possibility is supported by reports by Small et al.[5] and McElroy et al.[6] showing that vigorous or combined treatment with drugs such as lithium, carbamazepine, or divalproex sodium could be as effective as neuroleptic treatment in psychotic mania.

We recently completed a multivariate analysis of the manifestations of manic episodes in hospitalized patients.[7] Factor analysis revealed 6 factors: psychosis, impulsivity, hyperactivity, anxious pessimism, distressed appearance, and hostility. These factors formed 4 clusters or subtypes of manic episodes: depressive, psychotic, classic, and irritable. The subtypes differed in course of illness[7] and treatment response.[8] The manic syndrome scores of patients in the psychotic subtype improved significantly during treat-

ment with divalproex or with lithium, but not with placebo. However, improvement in psychosis factor scores did not differ significantly across the 3 treatments. Delusion factor scores improved in subjects with significant antimanic response to any of the 3 treatments. Psychosis could therefore be a nonspecific manifestation of severe mania that improves if the underlying mania improves. In this article, we will investigate the relationships between baseline psychotic features and other aspects of manic episodes, and clinical correlates of change in psychotic features during treatment with lithium, divalproex, or placebo.

METHOD

Protocol

The study has been described in detail.[9] One hundred seventy-nine subjects meeting Research Diagnostic Criteria for a manic episode of bipolar I disorder were randomly assigned to receive lithium, divalproex, or placebo in a 1:2:2 ratio. One hundred fifty-eight subjects had complete pretreatment ratings, and 154 had complete pretreatment and posttreatment data. The protocol was approved by the institutional review board of each facility, and before participation in the study, subjects gave informed consent after full discussion of the study's risks, including those associated with placebo use. Behavioral evaluations, including the clinician-rated Change version of the Schedule for Affective Disorders and Schizophrenia (SADS-C)[10] and Global Assessment Scale (GAS) and the nurse-rated Affective Disorder Rating Scale (ADRS)[11] were carried out at baseline and weekly during 21 days of inpatient randomized treatment. These scales provide reliable indicators of severity of psychotic symptoms but have no items differentiating mood-congruent from mood-incongruent symptoms.[10,11]

Raters were trained using standard training materials and videotapes designed for these instruments and were periodically retrained throughout the study. To serve as raters, rating investigators were required to achieve an intraclass correlation of > 0.50 within the original group of raters for the SADS-C items; most were > 0.7 (0.40–0.74 represents "fair to good agreement"[12]). Midway through the study, correlations for the mania items were 0.86–0.91 within centers and 0.89 across centers.

Treatments started at 900 mg/day for lithium or 750 mg/day for divalproex and were adjusted by the blinded (treating) clinician, based on response and tolerability, to final average doses of 1900 mg/day for lithium and 2075 mg/day for divalproex. An unblinded clinician, not involved in patient treatment or associated with the treatment unit, was notified of lithium or valproate levels and instructed the treating clinician to make dose changes if indicated; random dose changes were also given for subjects randomly assigned to placebo. Patients were allowed chloral hydrate (maximum dose 4 g/day on days 1 through 4 and 2 g/day on days 5 through 8) or lorazepam (maximum dose 2 mg/day on days 1 through 4 and 1 mg/day on days 5 through 8) for the first 8 days of the study, but no rescue medicine after that; no antipsychotic drugs were given. Rescue medicine was not allowed during the 8 hours before the weekly behavioral assessments.

Patients were removed from the study and given optimal standard treatment if the treating clinician considered it clinically appropriate. Patients completing at least 8 days of randomized treatment were considered evaluable.

Data Analysis

The factor and cluster analyses have been described in detail.[7] Factor analysis entered all of the item scores from the SADS-C and ADRS scales in a principal components analysis with varimax rotation.[13] Six factors had eigenvalues greater than 2: impulsivity, hyperactivity, anxious pessimism, distressed appearance, delusions, and hostility. (See reference 7 for detailed descriptions of the item scores making up each factor.) These factors were used in tree clustering of the subjects in order to determine whether there were naturalistically occurring subgroups differing in patterns of factor scores. K-means cluster analysis was then conducted using 4 clusters, since beyond that number, many small clusters formed but the overall structure did not change, with clusters either preserved intact or fragmented.[14] Four subtypes resulted from the cluster analysis: depressed, psychotic, hostile, and classic. We have shown[7,8] that these subtypes differed in previous illness course and treatment response.

The statistical analyses in this paper used analysis of variance and Pearson correlation coefficients if appropriate assumptions were met, and corresponding nonparametric statistics otherwise. Comparisons were 2-tailed and required $p < .05$ to be statistically significant.

RESULTS

Pretreatment Psychotic Symptoms and Severity of Illness

Table 1 shows that subjects who definitely had hallucinations had significantly lower baseline GAS scores than did those who definitely did not have hallucinations, but those subjects did not differ in mania rating scores. Subjects with definite delusions also differed significantly in GAS scores from those without delusions; in this case the groups also had differences in manic syndrome scores that were significant statistically but not clinically, since the effect sizes were small. Baseline delusion factor scores did not correlate significantly with baseline SADS-C manic syndrome scores ($r = 0.134$) but correlated significantly with baseline GAS scores ($r = –0.473$, $p < 10^{-4}$).

The contribution of the 6 behavioral factors to baseline GAS scores was assessed using multiple linear regression

Table 1. Pretreatment Psychotic Symptoms and Severity of Mania[a]

	Hallucinations		Delusions	
Scale	Present (N = 32)	Absent (N = 126)	Present (N = 68)	Absent (N = 90)
GAS	32.0 ± 9.3	38.1 ± 9.8**	32.8 ± 9.4	39.0 ± 9.1**
Manic syndrome	18.6 ± 4.9	18.9 ± 4.3	19.7 ± 4.7	18.2 ± 4.1*
Behavior and ideation	15.8 ± 3.6	16.4 ± 3.4	16.2 ± 3.9	16.3 ± 3.1
Mania rating	38.4 ± 7.2	38.6 ± 7.0	40.0 ± 7.5	37.5 ± 6.4*

[a]All values are mean ± SD. Mania ratings are from the Schedule for Affective Disorders and Schizophrenia, Change version (SADS-C).
Significance of Student t test: *p < .05; **p < .005.
Abbreviation: GAS = Global Assessment Scale.

Table 2. Contribution of Behavioral Factors to Pretreatment Global Assessment Scale Scores[a]

Factor	Slope (mean ± SD)	Partial r	p Value
Impulsivity	0.107 ± 0.089		
Hyperactivity	–0.136 ± 0.081		.09
Anxious pessimism	–0.014 ± 0.072		
Distressed appearance	–0.142 ± 0.076	–0.156	.043
Hostility	–0.016 ± 0.082		
Delusions	–0.496 ± 0.080	–0.461	10^{-6}

[a]Variables were entered in one block. R = 0.5, R^2 = 0.25, F = 8.7, df = 6,157; p < 10^{-6}.

analysis. As shown in Table 2, the delusion factor was the only one that contributed substantially to the baseline GAS score.

These data show that psychotic symptoms are a component of severe manic episodes that, independently of the manic syndrome, contribute substantially to overall severity of illness.

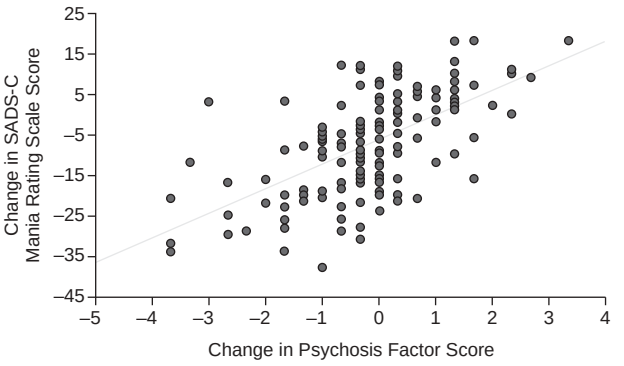
Effect of Baseline Psychosis Severity on Antimanic Treatment Outcome

Across the entire group, presence of hallucinations or delusions at baseline had no effect on subsequent change in SADS-C mania scores (t tests of mean differences, p > .2). Analysis of variance with respect to treatment drug and psychotic symptoms revealed no significant main effect of hallucinations or delusions on changes in SADS-C mania scores (for manic syndrome scale, F = 2.48, df = 1,152; p = .12 for hallucinations; F = 0.2, df = 1,152; p = .67 for delusions). Finally, there were no significant correlations between baseline delusion factor score and change in SADS-C mania scores or in changes for the 6 factors. Therefore, although baseline psychosis severity contributed substantially to impairment, it did not appear to alter the overall effectiveness of antimanic treatment.

Relationship Between Improvement in Psychosis and Antimanic Response

Despite the lack of correlation between baseline scores and subsequent change in mania ratings, change in the delusion factor correlated strongly with change in mania scores in all 4 subtypes and for the group as a whole, regardless of randomized treatment. Figure 1 shows the relationship between changes in mania rating and in psychosis factor scores for all patients. Table 3 shows that the correlation was similar for subjects treated with divalproex, lithium, or placebo.

Figure 1. Relationship Between Change in Psychosis Factor Score and Mania Rating Scale Score During Treatment for All Subjects[a,b]



[a]The scales have no common items. Spearman r = 0.583, N = 154, p < 10^{-6}.
[b]Some dots represent more than 1 patient.
Abbreviation: SADS-C = Schedule for Affective Disorders and Schizophrenia, Change version.

Table 3. Correlations Between Changes in Psychosis Factor Scores and Mania Ratings[a]

Rating	All Subjects (N = 154)	Placebo (N = 66)	Divalproex (N = 61)	Lithium (N = 27)
Manic syndrome	0.507**	0.515**	0.414*	0.459
Behavior and ideation	0.492**	0.485*	0.459*	0.435*
Mania rating scale	0.583**	0.619**	0.500*	0.550*

[a]The table shows Spearman correlation coefficients. All were significant at p < .05.
*p < .005, **p < 10^{-5}.

DISCUSSION

Mania scores improved in subjects treated with divalproex or lithium. There are previous reports that psychotic manic episodes responded similarly to haloperidol at 0.2 mg/kg/day or divalproex at 20 mg/kg/day[6] or to either carbamazepine or haloperidol combined with lithium,[5] and that treatment responses in acute exacerbations of manic and schizoaffective disorders were identical.[15] While baseline psychosis scores did not correlate significantly with baseline manic syndrome scores, changes in the 2 measures were strongly correlated. These findings suggest that, rather than independent treatment of mania and psychosis, vigorous treatment of the underlying mania may, at least in some patients, bring about resolution of psychosis

as well. Muller-Oerlinghausen et al.[16] recently reported that neuroleptic drugs and valproate had synergistic effects in manic episodes, independent of psychotic features. More information is needed about the specificity of treatment effects on manic versus psychotic symptoms.

Mechanisms of antipsychotic effects observed in this study may be analogous to those of antipsychotic drugs, or they may be synergistic.[16] In a recent double-blind trial in acutely psychotic subjects with schizophrenia, adjunctive divalproex enhanced the effect of an atypical antipsychotic.[17] Dopaminergic and GABA systems may have synergistic roles in psychosis[18,19] and its treatment.[20]

These and other results suggest that the pharmacologic specificity of psychosis in mania might be overvalued. Psychotic features are common in manic episodes. Drugs that are not considered to have antipsychotic features can effectively reduce psychotic symptoms in manic episodes.[5,6] Efficacy of olanzapine and divalproex was identical in patients with psychotic manic episodes.[21] Conversely, drugs that are considered to be antipsychotic, both conventional[22–24] and atypical,[25–27] are effective in nonpsychotic as well as psychotic manic episodes.

One potentially specific aspect of psychosis is the presence of mood-incongruent delusions or hallucinations. Mood-incongruent features are not uncommon in manic episodes, especially early ones.[28] They may be associated with worse long-term or psychosocial outcome,[28–30] perhaps because they are associated with worse overall severity of illness.[29] Most structured treatment studies in bipolar disorder, however, including this one, have not addressed the mood-incongruent/-congruent distinction. Therefore, it remains to be seen whether the presence of mood-incongruent psychotic features would influence treatment response more specifically.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), divalproex (Depakote), haloperidol (Haldol and others), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan), olanzapine (Zyprexa).

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REFERENCES

1. Coryell W, Leon AC, Turvey C, et al. The significance of psychotic features in manic episodes: a report from the NIMH collaborative study. J Affect Disord 2001;67:79–88
2. Abrams R, Taylor MA. Importance of schizophrenic symptoms in the diagnosis of mania. Am J Psychiatry 1981;138:658–661
3. Lipkin KM. The many faces of mania. Arch Gen Psychiatry 1970;22:262–267
4. Prien RF, Caffey EM Jr, Klett CJ. Comparison of lithium carbonate and chlorpromazine in the treatment of mania: report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. Arch Gen Psychiatry 1972;26:146–153
5. Small JG, Klapper MH, Marhenke JD, et al. Lithium combined with carbamazepine or haloperidol in the treatment of mania. Psychopharmacol Bull 1995;31:265–272
6. McElroy SL, Keck PE Jr, Stanton SP, et al. A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. J Clin Psychiatry 1996;57:142–146
7. Swann AC, Janicak PL, Calabrese JR, et al. Structure of mania: depressive, irritable, and psychotic clusters with different retrospectively-assessed course patterns of illness in randomized clinical trial participants. J Affect Disord 2001;67:123–132
8. Swann AC, Bowden CL, Calabrese JR, et al. Pattern of response to divalproex, lithium, or placebo in four naturalistic subtypes of mania. Neuropsychopharmacology 2002;26:530–536
9. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994;271: 918–924
10. Spitzer RL, Endicott J. Schedule for Affective Disorders and Schizophrenia: Change Version. 3 ed. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1978
11. Murphy DL, Pickar D, Alterman I. Methods for the quantitative assessment of depressive and manic behavior. In: Burdoch EI, Sudilovsky A, Gershon S, eds. Quantitative Techniques for the Evaluation of the Behavior of Psychiatric Patients. New York, NY: Marcel Dekker; 1982:355–393
12. Fleiss JL. Statistical Models for Rates and Proportions. 2nd ed. New York, NY: John Wiley & Sons Inc; 1981
13. Tabachnick BG, Fidell LS. Using Multivariate Statistics. New York, NY: Harper Collins Publishers; 1989
14. Hartigan JA. Clustering Algorithms. New York, NY: John Wiley & Sons Inc; 1975
15. Abrams R, Taylor MA. Mania and schizo-affective disorder, manic type: a comparison. Am J Psychiatry 1976;133:1445–1447
16. Muller-Oerlinghausen B, Retzow A, Henn FA, et al. Valproate as an adjunct to neuroleptic medication for the treatment of acute episodes of mania: a prospective, randomized, double-blind, placebo-controlled, multicenter study. J Clin Psychopharmacol 2000;20:195–203
17. Casey DE, Daniel DG, Wassef AA, et al. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 2003;28:182–192
18. Benes FM. The role of stress and dopamine-GABA interactions in the vulnerability for schizophrenia. J Psychiatr Res 1997;31:257–275
19. Wassef AA, Dott SG, Harris A, et al. Critical review of GABA-ergic drugs in the treatment of schizophrenia. J Clin Psychopharmacol 1999; 19:222–232
20. Wassef AA, Hafiz NG, Hampton D, et al. Divalproex sodium augmentation of haloperidol in hospitalized patients with schizophrenia: clinical and economic implications. J Clin Psychopharmacol 2001;21: 21–26
21. Tohen M, Baker RW, Altshuler LL, et al. Olanzapine versus divalproex in the treatment of acute mania. Am J Psychiatry 2002;159: 1011–1017
22. Garfinkel PE, Stancer HC, Persad E. A comparison of haloperidol,

lithium carbonate and their combination in the treatment of mania. J Affect Disord 1980;2:279–288
23. Janicak PG, Bresnahan DB, Sharma R, et al. A comparison of thiothixene with chlorpromazine in the treatment of mania. J Clin Psychopharmacol 1988;8:33–37
24. Cookson JC, Silverstone T, Wells B. A double-blind controlled study of pimozide vs chlorpromazine in mania. Neuropharmacology 1979;18: 1011–1013
25. Berk M, Ichim L, Brook S. Olanzapine compared to lithium in mania: a double-blind randomized controlled trial. Int Clin Psychopharmacol 1999;14:339–343
26. Tohen M, Jacobs TG, Grundy SL, et al, for the Olanzapine HGGW Study Group. Efficacy of olanzapine in acute bipolar mania: a double-blind, placebo-controlled study. Arch Gen Psychiatry 2000;57:841–849
27. Tohen M, Chengappa KN, Suppes T, et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002;59:62–69
28. Fennig S, Bromet EJ, Karant MT, et al. Mood-congruent versus mood-incongruent psychotic symptoms in first-admission patients with affective disorder. J Affect Disord 1996;37:23–29
29. Toni C, Perugi G, Mata B, et al. Is mood-incongruent manic psychosis a distinct subtype? Eur Arch Psychiatry Clin Neurosci 2001;251:12–17
30. Strakowski SM, Williams JR, Sax KW, et al. Is impaired outcome following a first manic episode due to mood-incongruent psychosis? J Affect Disord 2000;61:87–94