Brief Report

Double-Blind Comparison of the Continued Use of Antipsychotic Treatment Versus Its Discontinuation in Remitted Manic Patients

Carlos A. Zarate, Jr., M.D.
Mauricio Tohen, M.D., Ph.D.

Objective: The goal of this study was to determine the benefits of the continued use of a typical antipsychotic agent following remission from an acute manic episode.

Method: Immediately following remission of a manic episode treated with the combination of a typical antipsychotic (perphenazine) and a mood stabilizer (lithium, carbamazepine, or valproate), 37 patients were randomly assigned to 6 months of double-blind treatment in which in addition to the mood stabilizer they received either continued perphenazine treatment or placebo.

Results: Patients randomly assigned to continue perphenazine treatment, relative to those who discontinued it, were more likely to have a shorter time to depressive relapse, discontinue the study, and have increased rates of dysphoria, depressive symptoms, and extrapyramidal symptoms.

Conclusions: There were no short-term benefits with the continued use of a typical antipsychotic after achieving remission from an episode of acute mania. In fact, its continued use was associated with detrimental effects.

(Am J Psychiatry 2004; 161:169–171)

Typical antipsychotic drugs have a prominent role in the treatment of acute mania. However, it remains unclear whether additional benefits are gained with their continued use following remission from mania. Naturalistic and maintenance treatment studies with typical antipsychotics have found that they are associated with high rates of extrapyramidal symptoms, neuroleptic dysphoria, depressive relapses, and percent time ill in depression (1–4). Despite these risks, between 68% and 95% of bipolar disorder patients continue receiving typical antipsychotics for lengthy periods of time following a manic episode (5–8). The short-term benefits of continued typical antipsychotic treatment following remission from acute mania have not been systematically studied.

The objective of this study was to determine the outcome of patients for whom typical antipsychotic treatment was continued versus those for whom it was discontinued after remission from a manic episode.

Method

Subjects of investigation were 37 patients (nine men and 28 women) in a manic or mixed episode of bipolar disorder, with or without psychotic features, as determined with the Structured Clinical Interview for Axis I DSM-IV Disorders—Patient Version (9). Patients had been free of comorbid substance abuse for at least 4 weeks and substance dependence for 6 months at the time of recruitment. Patients had no other axis I disorder diagnoses in the preceding 12 months and were free of acute medical illness, rapid cycling, and tardive dyskinesia. Written informed consent was obtained from all subjects after the procedures had been fully explained. Participants were treated openly with the combination of a typical antipsychotic (all were required to take perphenazine [4–64 mg/day] as the typical antipsychotic) and one or more mood stabilizers (lithium, carbamazepine, or valproate), the blood serum levels of which were maintained within the following ranges: lithium=0.6–1.2 meq/liter; valproate=50–125 mg/liter; carbamazepine=4–12 mg/liter. Subjects were evaluated on a weekly basis until symptomatic remission was obtained. Those not achieving remission by week 10 were excluded from further study participation. Symptomatic remission was defined as achievement of total score ≤10 on both the Young Mania Rating Scale (10) and the 21-item Hamilton Depression Rating Scale (11) for 2 consecutive weeks. Remitted patients were then randomly assigned to either continue treatment with perphenazine or receive placebo (perphenazine was tapered off over the course of 1 week) administered in a double-blind fashion for 6 months in combination with one or two mood stabilizers (open label). If serum blood levels of the mood stabilizer deviated, the dose was adjusted to reestablish blood levels within the specified range. The dose of perphenazine that was effective in achieving remission during the open treatment phase was kept constant during the double-blind phase. Mood symptoms were then rated monthly by using the Young Mania Rating Scale and Hamilton depression scale. Scales for assessment of extrapyramidal symptoms included the Simpson–Angus Scale (12), Barnes Akathisia Scale (13), and Abnormal Involuntary Movement Scale (AIMS) (14). Adjunctive use of lorazepam, ≤2 mg/day, for no more than 10 consecutive days and benztropine mesylate, ≤2 mg/day, throughout the study for treatment of extrapyramidal symptoms (but not prophylaxis) was permitted.

As a primary estimation of relapse prevention, survival analyses were conducted to determine the time to syndromic relapse, defined as meeting DSM-IV criteria for a manic or depressive episode, following symptomatic remission. A secondary efficacy measure included the time to discontinuation from the study.

Results

Nineteen patients (four men and 15 women; mean age=32.5 years, SD=5.4) were randomly assigned to receive placebo (i.e., discontinued perphenazine), and 18 patients (five men and 13 women; mean age=36.2 years, SD=8.7) were randomly assigned to continue treatment with perphenazine. There were no between-group differences in terms of age, length of illness, time to remission, dose of perphenazine, blood serum levels of the mood stabilizers, sex, bipolar episode subtype, presence of psychotic fea-

TABLE 1. Characteristics of Bipolar Disorder Patients Treated With a Mood Stabilizer and Perphenazine Who Were Randomly Assigned After Acute Manic Episode Remission to Either Continue Perphenazine Treatment or Receive Placebo

Characteristic	Postremission Treatment: Mood Stabilizer and Perphenazine (N=19)		Mood Stabilizer and Placebo[a] (N=18)	
	Mean	SD	Mean	SD
Age (years)	33.7	8.1	38.1	9.7
Length of illness (years)	10.8	4.2	11.1	4.5
Time to symptomatic remission (weeks)	7.1	2.0	6.1	2.1
Perphenazine dose (mg/day)	28.2	11.7		
Mood stabilizer serum level at follow-up				
Carbamazepine (mg/liter)	9.3	1.5	5.0[b]	
Lithium (meq/liter)	0.70	0.07	0.71	0.06
Valproate (mg/liter)	62.6	10.2	64.2	12.8
	Mean	SE	Mean	SE
Time to relapse into depression (days)[c]	157	10		
Time to discontinuation (days)[d]	130	12	163	9
	N	%	N	%
Female	15	78.9	13	72.2
Bipolar episode subtype at study entry				
Manic	13	72.2	11	61.1
Mixed	5	27.8	7	38.9
Psychotic features present	14	77.8	15	83.3
History of substance use disorder	8	42.1	7	38.9
Mood stabilizer received during study[e]				
Carbamazepine	3	15.8	1	5.6
Lithium	8	42.1	10	55.6
Valproate	14	73.7	12	66.7
Discontinued before study end[f]	10	52.6	3	16.7
Relapse	5	26.3	2	11.1
Depression	4	21.1	0	0.0
Mania	1	5.3	2	11.1
Side effect	4	21.1	1	5.6
Other	1	5.3	0	0.0
Side effects				
Akathisia	3	15.8	0	0.0
Akinesia[f]	6	31.6	0	0.0
Dysphoria[f]	9	47.4	3	16.7
Parkinsonism[g]	9	47.4	1	5.6

[a] The perphenazine received during acute episode treatment was tapered off over the course of 1 week.
[b] There was only one subject receiving carbamazepine.
[c] No relapses in the group receiving placebo; significant difference between groups (log-rank test, $p<0.03$).
[d] Significant difference between groups (log-rank test, $p<0.03$).
[e] Twenty-six subjects were taking one and 11 subjects were taking two mood stabilizers.
[f] Significant difference between groups ($p<0.05$, Fisher's exact test).
[g] Significant difference between groups ($p<0.01$, Fisher's exact test).

tures, history of substance use disorder, or type of mood stabilizer used (Table 1).

As seen in Table 1, patients given placebo were more likely than those who continued receiving perphenazine to complete the study (83.3% versus 47.4%, respectively), have a longer time to depressive relapse, remain in the study for a longer duration of time, and experience akinesia, dysphoria, and parkinsonism less frequently. Patients who discontinued perphenazine treatment also had lower Hamilton depression scale total scores at follow-up (mean=6.1 [SD=2.7]) than did those who continued perphenazine treatment (mean=9.2 [SD=2.7]) (Mann-Whitney U=27.5, N=25, p=0.007). There were no differences in manic relapses between the groups. Young Mania Rating Scale total scores at endpoint did not differ between the groups. None of the covariates examined in Table 1 indicated a significant ($p<0.05$) relationship to failure time (survival time) by the product limit nor by the Cox proportional hazards method.

Discussion

The continued use of a typical antipsychotic following remission from acute mania was associated with a shorter time to depressive relapse, more depressive symptoms, higher rates of dysphoria and parkinsonism, and greater discontinuation rates. These findings imply that the continued use of a typical antipsychotic following remission from mania is detrimental for a subgroup of patients, some of whom may benefit from taper of the typical antipsychotic immediately following remission.

These preliminary results need to be interpreted with caution. First, the group size was small. Second, our results may not be generalized to patients with certain characteristics (e.g., rapid cycling course, noncompliance, presence of substance use disorders, or predominantly recurrent manic episodes). Third, these results may not apply to all typical antipsychotic drugs. Fourth, it is possible that some of the acutely manic patients may have improved with a mood stabilizer alone during the acute treatment phase and therefore may have not required a typical antipsychotic during the double-blind phase. However, all subjects recruited were already being prescribed a typical antipsychotic by their treating psychiatrist. Finally, it is possible that the high rates of neurological side effects and depression observed in the typical antipsychotic group may be because the dose of neuroleptics used was higher than needed and that some patients may have benefited from a dose reduction.

In conclusion, these results suggest that the continuation of a typical antipsychotic following remission from mania for extended periods of time may be detrimental for some patients. Larger controlled studies are needed to replicate the present findings.

Presented in part at the 58th annual meeting of the Society of Biological Psychiatry, San Francisco, May 15–17, 2003. Received Jan. 22, 2003; revision received June 11, 2003; accepted June 13, 2003. From the Bipolar and Psychotic Disorders Program, Consolidated Department of Psychiatry, McLean Hospital, Harvard Medical School, Belmont, Mass. Address reprint requests to Dr. Zarate, Mood and Anxiety Disorders Program, National Institute of Mental Health, 9000 Rockville Pike, Building 10, Unit 3 West, Room 3s250, Bethesda, MD 20892; zaratec@intra.nimh.nih.gov (e-mail).

Supported in part by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression.

The authors thank David Luckenbaugh for statistical assistance.

References

1. Kukopulos A, Reginaldi D, Laddomada P, Floris G, Serra G, Tondo L: Course of the manic-depressive cycle and changes caused by treatment. Pharmakopsychiatr Neuropsychopharmakol 1980; 13:156–167
2. Ahlfors UG, Baastrup PC, Dencker SJ, Elgen K, Lingjaerde O, Pedersen V, Schou M, Aaskoven O: Flupenthixol decanoate in recurrent manic-depressive illness: a comparison with lithium. Acta Psychiatr Scand 1981; 64:226–237
3. White E, Cheung P, Silverstone T: Depot antipsychotics in bipolar affective disorder. Int Clin Psychopharmacol 1993; 8:119–122
4. Esparon J, Kolloori J, Naylor GJ, McHarg AM, Smith AH, Hopwood SE: Comparison of the prophylactic action of flupenthixol with placebo in lithium treated manic-depressive patients. Br J Psychiatry 1986; 148:723–725
5. Keck PE Jr, McElroy SL, Strakowski SM, Balistreri TM, Kizer DI, West SA: Factors associated with maintenance antipsychotic treatment of patients with bipolar disorder. J Clin Psychiatry 1996; 57:147–151
6. Keck PE Jr, McElroy SL, Strakowski SM, Soutullo CA: Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. J Clin Psychiatry 2000; 61(suppl 4):33–38
7. Sernyak MJ, Griffin RA, Johnson RM, Pearsall HR, Wexler BE, Woods SW: Neuroleptic exposure following inpatient treatment of acute mania with lithium and neuroleptic. Am J Psychiatry 1994; 151:133–135
8. Zarate CA Jr, Tohen M: Antipsychotic drug treatment in first-episode mania: a 6-month longitudinal study. J Clin Psychiatry 2000; 61:33–38
9. First MB, Spitzer RL, Williams JBW, Gibbon M: Structured Clinical Interview for DSM-IV—Patient Edition (SCID-P). Washington, DC, American Psychiatric Press, 1997
10. Young RC, Biggs JT, Ziegler VE, Meyer DA: A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 133:429–435
11. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
12. Simpson GM, Angus JWS: A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970; 212:11–19
13. Barnes TRE: A rating scale for drug-induced akathisia. Br J Psychiatry 1989; 154:672–676
14. Guy W (ed): ECDEU Assessment Manual for Psychopharmacology: Publication ADM 76-338. Washington, DC, US Department of Health, Education, and Welfare, 1976, pp 534–537