Antipsychotic Drug Treatment in First-Episode Mania: A 6-Month Longitudinal Study

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Objective: To determine the use of antipsychotics during and following inpatient treatment of patients with a first-episode of mania.

Method: The 198 subjects available for analysis were 129 consecutively hospitalized first-episode manic patients and 69 nonaffective psychotic patients assessed at admission and at 6-month follow-up postdischarge. Comparisons between the groups were made on frequency, type, and doses of antipsychotics prescribed during and after hospitalization in relation to clinical status.

Results: First-episode manic patients were given lower mean ± SD daily doses of antipsychotics than nonaffective psychotic patients at discharge (163 ± 132 mg chlorpromazine equivalents [CPZe] vs. 224 ± 167 mg CPZe, p = .0102), at 6-month follow-up (109 ± 167 mg CPZe vs. 260 ± 178 mg CPZe; p = .0001), and if recovered (110 ± 174 mg CPZe vs. 265 ± 207 mg CPZe, p = .0014). At 6-month follow-up, 31 (24%) of 129 manic and 24 (35%) of 69 nonaffective psychotic patients continued to receive antipsychotics (NS). There was no difference between the groups in the time to discontinuation of antipsychotic agents. The mean time to drug discontinuation in manic patients was 98 days.

Conclusion: (1) Antipsychotic doses at discharge and at 6-month follow-up were much lower in manic than in nonaffective psychotic patients, although there was no significant difference in the proportion of patients who continued to receive them 6 months after discharge. (2) The time to discontinuation was independent of clinical outcome. In those who discontinued the antipsychotic agent, the time to discontinuation was more rapid in the manic group than in the nonaffective psychotic patients.

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Antipsychotic medications are commonly used as adjuncts to mood stabilizers in the treatment of acute and recurring mania.[1–8] Antipsychotics given as adjuncts for the maintenance therapy of patients with bipolar disorder may contribute to the manifestation of symptoms that mimic depression, negative symptoms of psychosis, extrapyramidal side effects, tardive dyskinesia, and impaired functioning.[1,9,10] It is generally recommended that neuroleptic drugs be discontinued as soon as possible in bipolar patients in order to avoid these complications.[10] However, in the 2 studies that systematically examined the use of antipsychotics in multiepisode bipolar disorder patients following discharge, high rates of antipsychotic use were found 6 months postdischarge, averaging 76.9% (90/117).[4,8] One possible explanation for these high rates of antipsychotic use is that these cohorts included a large fraction of multiepisode manic patients for whom neuroleptics are used empirically with mood stabilizers to minimize relapse. This phenomenon may be specific to multiepisode manic patients. However, little is known about how antipsychotic drugs are prescribed in first-episode manic patients, in what doses they are given, and for how long patients remain on antipsychotic therapy after recovering or failing to recover from their manic episode. Since data are not available for first-episode manic patients, the present study was designed to examine the prescribing patterns of antipsychotic agents during hospitalization and at 6 months postdischarge in patients with first-episode acute mania. A smaller group of nonaffective first-episode psychotic patients was used for comparison purposes.

METHOD

Consecutive patients experiencing either a first manic or first psychotic episode were recruited from the inpatient units of McLean Hospital, Belmont, Mass., between July 1, 1989, and August 1, 1996. Patients were included in the present study if they met the following criteria: (1) age ≥ 16 years; (2) presence of DSM-III-R/IV mania or a psychosis syndrome (including formal thought disorder, hallucinations, delusions, or grossly disorganized behavior at the time of admission); and (3) provision of written informed consent, based on approval of the study by the McLean Hospital Institutional Review Board. Exclusion criteria included (1) presence of delirium or acute in-

toxication or withdrawal from drugs or alcohol, (2) previous psychiatric hospitalizations, or (3) prior treatment with an antipsychotic agent for > 3 days or with a mood stabilizer for > 3 months.

Psychiatric diagnoses were based on the Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P).[11] Initial diagnoses followed DSM-III-R (1989–1994) or DSM-IV criteria (1994–1996). DSM-III-R diagnoses were updated to meet DSM-IV criteria (American Psychiatric Association, 1994) for this report. All subjects were reevaluated at 6 months postdischarge. The study followed a naturalistic design. Treatment was determined clinically rather than by the investigators.

Clinical and demographic variables recorded at baseline included age, sex, race, years of education, employment status, and living situation; at discharge, the duration of initial hospital stay was also recorded. Comorbidity factors assessed for this report included current and lifetime comorbid alcohol or other substance use disorders. This information was obtained by research assistants trained to obtain such data reliably from medical records, SCID-P examination, and the patients, relatives, and treating clinicians. Patients were evaluated within 72 hours of admission and weekly thereafter until discharge.

Primary assessment scales used in the present study included an expanded (McLean) 36-item version of the Brief Psychiatric Rating Scale (BPRS)[12] (rated for severity, 0–7) and Global Assessment of Functioning[13] (GAF; 0–100) scales.

Patients were systematically evaluated at 6 months after hospital admission by an experienced professional rater blinded to the baseline information. Follow-up information was obtained by face-to-face or telephone interview, as reported previously,[14] and supplemented by information obtained with the patient's consent from a close relative, another household member, or treating physicians. Of the reported follow-up assessments, 90% were conducted by telephone and 10% were face-to-face. Sixty percent of the follow-up assessments were with the subject only, 30% of the assessments were with the subject and relatives or friends, and 10% of the assessments involved relatives or friends without the subject. In addition, we were able to contact 80% of the treating clinicians to verify the follow-up information. Follow-up rates have been excellent: of the cohort recruited during the time period of this study (July 1989–August 1996), 87% have been successfully followed for at least 6 months postdischarge.

In follow-up interviews, information elicited included sociodemographic changes, the course of the primary and comorbid alcohol and drug use, psychosocial status (GAF), symptomatic status to define syndromal recovery, and estimated time of such recovery (days since hospital admission). Follow-up interviews also included the Longitudinal Interval Follow-up Evaluation[15] to clarify psychosocial status, as well as the GAF.[13] Compliance with pharmacotherapy was assessed prospectively at the 6-month follow-up visit by using a structured clinician-administered questionnaire.

Data on medication use (agents, dose, and timing) were collected from medical records during hospitalization and by telephone interviews at 6 months.

Comparisons of antipsychotic drug use were made between first-episode manic patients and first-episode nonaffective psychotic patients (patients with schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, and psychosis not otherwise specified). The comparisons included frequency of antipsychotic use, type of drug prescribed, time to first dose, and doses during hospitalization (initial, average, peak, and discharge dose) and, at 6 months, time to discontinuation and clinical status at 6 months postdischarge. Doses of typical antipsychotics were converted to chlorpromazine-equivalent (CPZe) mg/day doses.[16] For persons exposed to more than one neuroleptic, the drug used on a majority of days was taken as the index agent and the reported dose in the total CPZe for all antipsychotics calculated. Clinical status determinations included an assessment of whether the patient had syndromically recovered. The definition of syndromic recovery used in this report has been described previously.[14] Time to discontinuation of antipsychotics was determined as days following an initial dose, whether the discontinuation occurred during hospitalization or after discharge. Clinical and demographic factors associated with discontinuation of antipsychotics were examined.

Interrater reliability was evaluated for the SCID-P for primary (intraclass correlation coefficient [ICC] = 0.92) and secondary (ICC = 0.90) diagnoses.[14] High interrater reliability was also obtained for the 36-item BPRS (ICC = 0.96),[14] as well as for agreement between telephone and in-person interviews (ICC = 0.96 and 0.90, respectively).[14,17]

All statistical analyses were performed with Statview-4.5 (Abacus Corp., Berkley, Calif.) and Stata (Stata Corp., College Station, Tex.) statistical analysis software systems. Categorical variables were compared by using the chi-square test or 2-tailed Fisher exact test when expected cell sizes were fewer than 5. Continuous variables were compared by using the Wilcoxon rank sum test or unpaired t test as appropriate. The relative influence of statistically independent variables was assessed by logistic regression. Antipsychotic discontinuation times were compared using Kaplan-Meier survival analysis, with risk-factor adjusted Kaplan-Meier survival functions determined with Cox regression methods.

RESULTS

Of an initial total of 182 recruited subjects, 158 (86.8%) were successfully followed up and included for

Table 1. Antipsychotic Use by First-Episode Manic and Nonaffective Psychotic Patients During Hospitalization and at 6 Months Postdischarge*

Measure	Manic Group (N = 129) Mean	Manic Group (N = 129) SD	Nonaffective Psychosis Group (N = 69) Mean	Nonaffective Psychosis Group (N = 69) SD
Age at admission, y	30.6	11.2	30.6	13.0
Length of hospitalization, d	27.4	16.6	30.7	28.1
Antipsychotic medication				
Total time taking antipsychotic in hospital, d	22.3	15.3	28.9	28.3
% Hospital days used	77.9	28.6	84.8	23.7
Time between admission and starting antipsychotic, d	3.1	5.2	2.6	4.7
Amount used, mg/d CPZe				
Initial	169.4	148.6	175.6	165.0
Peak	252.4	174.4	290.5	189.1
Average	191.1	107.5	228.7	136.0
Discharge	162.5	132.4[a]	224.3	166.8
At 6 months postdischarge	108.8	167.0[b]	259.5	177.5
Dose based on recovery status at 6 months				
Recovered	110.0	174.1[c]	264.6	206.9
Not recovered	102.2	127.1	234.0	107.6
Mean time to discontinuation of antipsychotic agent, d	98.0	74.3	114.0	114.0

Measure	Manic Group (N = 129) N	Manic Group (N = 129) %	Nonaffective Psychosis Group (N = 69) N	Nonaffective Psychosis Group (N = 69) %
Gender female	56	43.4	27	39.1
Recovered at 6 months	108	83.7[d]	41	59.4
Treatment				
Antipsychotic				
At discharge	99	76.7	52	75.4
At 6 months[e]	31	24.0	24	34.8
Lithium salts				
At discharge	100	77.5[f]	26	37.7
At 6 months	74	57.4[g]	6	8.7
Valproate				
At discharge	27	20.9	9	13.0
At 6 months	24	18.6[h]	4	5.8
Carbamazepine				
At discharge	4	3.1	4	5.8
At 6 months	4	3.1	0	0
One mood stabilizer				
At discharge	125	96.9[i]	39	56.5
At 6 months	101	78.3[j]	10	14.5
> 1 mood stabilizer				
At discharge	4	3.1	0	0
At 6 months	1	0.8	0	0
Benzodiazepines				
At discharge	26	20.2	12	17.4
At 6 months	18	14.0	9	13.0
Risperidone				
At discharge	4	3.1	2	2.9
At 6 months	3	2.3	2	2.9
Clozapine				
At discharge	1	0.8	1	1.5
At 6 months	1	0.8	2	2.9
Antipsychotic type				
High potency	15	11.6	12	17.4
Intermediate potency	87	67.4	44	63.8
Low potency	6	4.7	4	5.8

*Abbreviation: CPZe = chlorpromazine equivalents. In no case was an atypical antipsychotic (risperidone or clozapine) given as the primary antipsychotic agent during the hospitalization. Thus, the term antipsychotic agent refers to a typical antipsychotic unless otherwise specified.
[a]Significant difference between groups (z = 2.57, p = .0102).
[b]Significant difference between groups (z = 3.99, p = .0001).
[c]Significant difference between groups (z = 3.20, p = .0014).
[d]Significant difference between groups (χ^2 = 6.9, df = 1, p = .008).
[e]Percentage is calculated on patients discharged with typical antipsychotics.
[f]Significant difference between groups (χ^2 = 31.0, df = 1, p = .0001).
[g]Significant difference between groups (χ^2 = 44.0, df = 1, p = .0001).
[h]Significant difference between groups (Fisher exact test = 0.024).
[i]Significant difference between groups (χ^2 = 52.0, df = 1, p = .0001).
[j]Significant difference between groups (χ^2 = 74.0, df = 1, p = .0001).

analysis. Six who refused to be interviewed, 16 who could not be located at the 6-month follow-up, and 7 who were exposed to antipsychotics > 3 days prior to admission were excluded. Thus, 129 consecutive patients with a first episode of mania were followed up and met inclusion criteria. Of these, 108 (83.7%) presented with mania and 21 (16.3%) with mixed states; 103 (79.8%) patients had psychotic features, and 26 (20.2%) did not. The comparison group (nonaffective psychotic group) consisted of 69 patients with a diagnosis of schizophrenia (N = 18) or another nonaffective psychosis (schizoaffective disorder [N = 18], psychosis not otherwise specified [N = 11], delusional disorder [N = 11], and schizophreniform disorder [N = 11]). For the purposes of this report, the comparison group will be referred to as the nonaffective psychosis group.

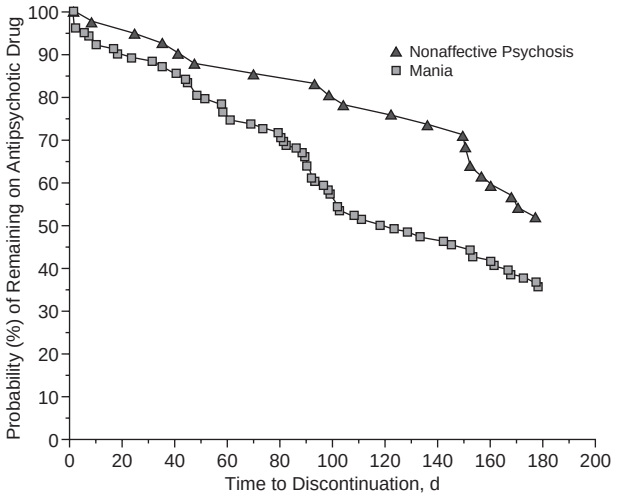
There were no differences in age, gender, length of hospitalization, total days of antipsychotic exposure, time between admission and starting antipsychotic, initial and peak antipsychotic doses, and antipsychotic potency between the manic and nonaffective psychotic groups (Table 1). There was a statistically significant difference in the proportion of manic and nonaffective psychotic patients meeting recovery criteria at 6 months (manic, N = 108, 83.7%, vs. nonaffective psychotic patients, N = 41, 59.4%; χ^2 = 6.94, df = 1, p = .008). The manic patients were more likely than the nonaffective psychotic patients to receive lower mean ± SD doses of antipsy-

Table 2. Demographic and Clinical Characteristics of First-Episode Manic Patients Who Did or Did Not Discontinue Antipsychotic Medication by 6 Months Postdischarge*

	Continued (N = 31)		Discontinued (N = 68)	
Variable	Mean	SD	Mean	SD
Age at admission, y	28.8	9.5	30.4	12.4
Admission GAF score	57.3	17.8	61.0	20.8
BPRS total score	95.2	22.8[a]	82.9	24.8
BPRS manic symptoms subscale score	26.8	12.4	25.3	11.5
BPRS depressive symptoms subscale score	19.9	9.7	17.6	7.7
% days taking antipsychotic during hospital stay	84.5	23.8	76.1	29.6
GAF at 6 months postdischarge	68.0	16.7	71.9	17.4
	N	%	N	%
Male	16	51.6	15	22.1
Married	6	19.4	20	29.4
White	30	96.8[b]	53	77.9
College graduate	9	29.0	22	32.4
Unemployed	5	16.1	7	10.3
Psychotic symptoms at admission	27	87.1	58	85.3
Alcohol use, previous 6 months	18	58.1	49	72.1
Drug use, previous 6 months	20	64.5	49	72.1
Alcohol use, at 6 months postdischarge	18	58.1	49	72.1
Drug use, at 6 months postdischarge	20	64.5	49	72.1
Taking lithium at discharge	27	87.1	50	73.5

*Abbreviations: BPRS = Brief Psychiatric Rating Scale, GAF = Global Assessment of Functioning scale. In no case was an atypical antipsychotic (risperidone or clozapine) given as the primary antipsychotic agent during the hospitalization. Thus, the term antipsychotic agent refers to a typical antipsychotic unless otherwise specified.
[a]Significant difference between groups (z = 2.64, p = .008).
[b]Significant difference between groups (z = 2.29, p = .022).

Figure 1. Time to Discontinuation of Antipsychotic Medication



chotic at discharge (163 ± 132 mg/day CPZe vs. 224 ± 167 mg/day CPZe; z = 2.57, p = .0102), at 6-month follow-up (109 ± 167 mg/day CPZe vs. 260 ± 178 mg/day CPZe; z = 3.99, p = .0001), and when recovered (110 ± 174 mg/day CPZe vs. 265 ± 207 mg/day CPZe; z = 3.20, p = .0014). There were, however, no differences in the frequency of antipsychotic use at discharge (N = 99, 76.7% vs. N = 52, 75.4%; $\chi^2 = 0.18$, df = 1, NS) or at 6-month follow-up (N = 31, 24.0% vs. N = 24, 34.8%; $\chi^2 = 0.009$, df = 1, NS) between the 2 groups.

Not surprisingly, manic patients were more likely than nonaffective psychotic patients to receive at least one mood stabilizer at discharge (N = 125, 96.9% vs. N = 39, 56.5%; $\chi^2 = 52.0$, df = 1, p = .0001) and at 6-month follow-up (N = 101, 78.3% vs. N = 10, 14.5%; $\chi^2 = 74.0$, df = 1, p = .0001). There were no differences in the use of benzodiazepines, risperidone, and clozapine between the 2 groups at discharge and at 6-month follow-up. In no case was risperidone or clozapine used as the primary antipsychotic drug (i.e., given as the index agent for the majority of the hospital days).

The manic group was also examined to determine if there were any differences in antipsychotic exposure associated with the presence or absence of psychotic features at admission and by the subtype of acute bipolar illness (manic vs. mixed). Psychotic manic patients were more likely to receive higher mean ± SD peak antipsychotic doses (265 ± 182 mg/day CPZe vs. 170 ± 78 mg/day CPZe; z = 2.02, p = .04) than nonpsychotic manic patients. Compared with mixed bipolar patients, manic patients were much more likely to continue antipsychotic use at discharge (74.1% [80/108] vs. 52.4% [11/21]; $\chi^2 = 12.0$, df = 1, p = .0004), but not at 6-month follow-up (25.0% [27/108] vs. 19.0% [4/21]; $\chi^2 = 1.0$, df = 1, NS). Except for mean ± SD age (manic: 29.9 ± 11.5 vs. mixed: 34.1 ± 11.2 years), there were no differences in the demographic and clinical variables tabulated in Table 2 between manic and mixed patients.

The mean ± SD time to antipsychotic discontinuation in manic patients was 98 ± 74 days. Among nonaffective psychotic patients, the mean ± SD time to discontinuation was 114 ± 114 days. The associated difference in survival curves is statistically significant by log-rank test ($\chi^2 = 4.16$, df = 1, p < .04). There was no difference in the mean ± SD time to antipsychotic discontinuation between manic patients who recovered and those who did not recover by 6 months (87.9 ± 52.9 vs. 93.8 ± 66.4 days, respectively). Time to discontinuation was graphed (Kaplan-Meier) for the manic vs. nonaffective groups in Figure 1. A second graph plotting time to discontinuation for recovered versus nonrecovered manic patients is not included here.

The only demographic and clinical predictors of antipsychotic discontinuation in manic patients by 6 months postdischarge were nonwhite race (z = 2.64, p = .008) and a lower (indicating less severe symptoms) BPRS total score at admission (z = 2.29, p = .022) (see Table 2).

DISCUSSION

To our knowledge, this is the first study to examine antipsychotic drug use in first-episode manic and nonaffective psychotic patients. Antipsychotic medication exposure at discharge and at 6-month follow-up among manic patients was substantially lower than in nonaffective psychotic subjects.

Manic patients were more likely than nonaffective psychotic patients to receive lower doses of antipsychotic drugs at discharge, at 6-month follow-up, and if recovered. Similar data comparing antipsychotic dosages in first-episode manic versus first-episode nonaffective psychotic patients are not available. We also found that the manic patients in the present study were more likely to receive lower doses of antipsychotics if they had recovered compared with those manic patients who had not recovered by 6 months. This latter finding suggests that clinicians are hesitant to lower doses of antipsychotics in manic patients until recovery occurs.

In terms of frequency of antipsychotic medication use, there were no significant differences between manic and nonaffective psychotic patients at discharge (77% vs. 75%, respectively) or at 6-month follow-up (24% vs. 35%, respectively).

Reasons for such differences in antipsychotic exposure between the manic and nonaffective psychotic patients are not known but may possibly be explained by a number of factors: first, clinicians treating patients with affective disorders may be more likely to use concomitant psychotropic drugs such as a mood stabilizer in order to minimize short- and long-term exposure to neuroleptics. In the present study, as expected, manic patients were more likely to receive mood stabilizer therapy than were nonaffective psychotic patients. Second, manic patients appear to have a higher vulnerability to extrapyramidal symptoms than patients with schizophrenia, and as a result may be prescribed lower doses of these agents.[18] The reason for the relatively low rates of antipsychotic use at 6 months postdischarge in the nonaffective psychosis group is unclear. One possible explanation is that this first-episode psychosis group was somewhat heterogeneous, so that some of these patients may have been maintained on treatment with mood stabilizers, antidepressants, or anxiolytics. Another possibility is that this group of patients was highly noncompliant to treatment. We were able to confirm the prescribed medications in 80% of the patients by contacting the treating clinician. However, unless blood levels are obtained to assure compliance, noncompliance remains an explanation for the low rates of antipsychotic drugs used at follow-up.

An interesting finding in this study is that there was no difference in antipsychotic exposure in manic patients whether or not they presented with psychotic features. This finding may be explained, in part, by a tendency for some psychiatrists to prescribe antipsychotics early in the hospital course because of the delay in onset of action of lithium.[19] Another possible reason for the frequent use of neuroleptics in nonpsychotic manic patients may be that this is simply due to habituation and tradition among the prescribers.[20]

Factors previously reported to be associated with maintenance antipsychotic treatment in bipolar patients include male gender, early age at onset, low educational level, medication noncompliance in the month prior to index hospitalization, severity of manic symptoms, receiving an antipsychotic at discharge, and a history of psychotic features.[8,21,22] These associations were not found in the present study; the reasons are unclear. In the present study, only ethnicity and high BPRS total scores at admission predicted antipsychotic maintenance treatment.

Strengths of this study include the use of a diagnostic semistructured interview, the collection of data prospectively, and a high follow-up rate (87%).

Potential limitations of the study include the possibility of noncompliance and the risk that rates of antipsychotic use may have been either underestimated or overestimated, especially when determined via telephone interview at 6-month follow-up, because of possible patient concerns about reporting noncompliance. However, we have found high rates of agreement between live and telephone interviews. Also, in the majority of cases, data on the clinical status and medications being prescribed were verified with 80% of the treating clinicians. Although compliance at 6 months was assessed prospectively, these reports could not always be verified by plasma concentrations of psychotropic agents. However, previous studies of medication compliance in patients with bipolar disorder have not found measures of plasma concentrations of medications to be more reliable than patient report.[23] Another potential limitation is that the results of the present study may not necessarily be generalizable to other treatment settings.

In conclusion, the present study finds that, for about 70% of patients recovering from their first-episode of psychotic mania, antipsychotic drugs were discontinued by 6 months following discharge. Among manic patients, a majority were discontinued by 3 months. Still, approximately a quarter of manic patients remained on such pharmacotherapy at 6 months. For these bipolar patients, future studies must determine when and how antipsychotic drugs should be discontinued following hospitalization for a manic episode. Such studies will suggest how to minimize complications that may occur with antipsychotic use and abrupt discontinuation.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), risperidone (Risperdal).

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