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Research report

# Adjunctive antipsychotic use in bipolar patients: an open 6-month prospective study following an acute episode

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**Abstract**

*Background*: We examined the use of adjunctive antipsychotics in the treatment of bipolar patients. *Methods*: A total of 88 bipolar type I patients (DSM-IV diagnosis) were included. The patterns of adjunctive antipsychotic use in the first 6 months after an index episode were examined. *Results*: A total of 34 patients (39%) received at least one antipsychotic during the follow-up period. At time 0, 23 subjects (26%) were on antipsychotics; at 3 months, 10 subjects (11%); and at the end of the 6 month period, 11 subjects (12%). Prolonged use of antipsychotics (more than 15 weeks) was found in eight patients (9%). No significant differences were found in demographic characteristics or baseline clinical variables between the patients who received or did not receive antipsychotics, except that the use of adjunct antipsychotics in the 6-month period was significantly more common after an index manic than depressive episode (68 versus 17%, respectively, $P = 0.001$; Fisher's exact test). *Limitations*: This report presents a secondary analysis of follow-up data from a prospective study, and therefore the hypotheses here examined were not originally part of the primary hypotheses that led to the design of the study. A larger sample size could eventually reveal small differences among the patient sub-groups not presently found. *Conclusions*: The use of adjunctive antipsychotics among bipolar patients was less extensive than previously reported, and mostly related to an index manic episode. Our findings suggest that in samples of carefully diagnosed bipolar type I patients the group that may need continued antipsychotic treatment is relatively small. 

*Keywords:* Bipolar disorder; Antipsychotics; Neuroleptics; Treatment; Follow-up

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## 1. Introduction

Substantial antipsychotic use has been reported in the pharmacological treatment of bipolar disorder patients (Sernyak and Woods, 1993; Sernyak et al., 1994; Gelenberg and Hopkins, 1996; Goldberg et al., 1996; Keck et al., 1996; Verdoux et al., 1996; Sernyak et al., 1997; Soares et al., 1997). These findings are a reason for concern, due to the higher risks associated with the use of antipsychotic medications in this patient population, particularly the risk of tardive dyskinesia (Yassa et al., 1984; Mukherjee et al., 1986; Waddington and Youssef, 1988; Hunt and Silverstone, 1991).

In the acute phase of treatment, extensive antipsychotic utilization has been reported. After 6 months of an inpatient hospitalization for an index episode of bipolar disorder, 68–95% of the bipolar patients who received antipsychotics were still on those medications (Keck et al., 1996; Sernyak et al., 1994). Among outpatients, high chronic antipsychotic utilization (as high as 67%) has been reported (Sernyak and Woods, 1993; Verdoux et al., 1996; Sernyak et al., 1997). However, the profile of the antipsychotic-requiring bipolar patients in the acute or maintenance phase of treatment has not been well-characterized (Soares et al., 1997). There are suggestions that younger males, elderly females, more severely ill manic patients, and patients with previous history of treatment non-compliance have a higher likelihood of receiving antipsychotics (D'Mello and McNeil, 1990; Keck et al., 1996). History of psychotic features, early age at onset of illness, and low educational level have also been correlated with increased rates of antipsychotic utilization (Verdoux et al., 1996). These preliminary findings require further examination and confirmation in additional studies.

We investigated the use of antipsychotics in bipolar type I patients during the first six months after an index episode of the disorder. Herein we report the extent and patterns of antipsychotic use, and attempt to characterize the sub-group of patients who required adjunctive antipsychotic medications.

## 2. Methods

### *2.1. Subjects*

All patients were seen at the Depression and Manic Depression Prevention Clinic (DMDPC), Western Psychiatric Institute and Clinic (WPIC), University of Pittsburgh Medical Center. They were being followed through the NIMH-funded Maintenance Therapies in Bipolar Disorder (MTBD) Study (Frank et al., 1997), conducted by Dr. Ellen Frank. All bipolar type I patients who enrolled in the MTBD protocol by October 1996 and continued in treatment at the DMDPC for at least 6 months were considered in the current analysis. All patients met DSM-IV criteria (American Psychiatric Association, 1994) for bipolar disorder, type I. The diagnosis was made on the basis of information collected by the staff of the clinic, through a SADS (Endicott and Spitzer, 1978) or a SCID interview (Spitzer et al., 1990), and it was later confirmed in a clinical evaluation with a staff psychiatrist. The diagnosis was reviewed in a consensus meeting with the clinician who completed the diagnostic interview, the clinic research coordinator, and a senior investigator. All patients gave informed consent to enroll in the protocol. The inclusion criteria for patients in the MTBD protocol were: (1) current episode is at least a third bipolar episode, or second if both episodes were manic, (2) at least one other episode within last 5 years, (3) remission period between current and most recent episode of at least 12 weeks, (4) age 21–65 years, (5) residence in the WPIC catchment area or within a reasonable commuting distance. Patients were excluded if they were rapid-cyclers, had other psychiatric disorders during the 5 years preceding the index episode (except for anxiety disorders), had a chronic drug or alcohol abuse within the past 5 years, diagnosis of organic affective syndrome, borderline or antisocial personality disorders, presence of significant physical illness, or current mood symptoms secondary to prescribed drugs. For females, being pregnant, or not using proper contraception were exclusion criteria.

### *2.2. Clinical procedures*

As per the MTBD protocol, all patients were initially seen for treatment of an acute episode of the disorder, and were randomly assigned to medication clinic or a psychosocial intervention especially designed for bipolar disorder patients – Interpersonal

and Social Rhythms Therapy (IP/SRT) (Frank et al., 1994). The pharmacological management did not differ in either group (psychosocial intervention or medication clinic groups). Patients were evaluated on each clinic visit with the Hamilton Depression Rating Scale (HDRS) – (17 and 25 items), and the Bech–Rafaelsen Mania Scale. These assessments were performed by a trained evaluator. When considered necessary, the psychiatrist in charge of the case had the choice of initiating antipsychotic medication as an adjunct to the primary mood stabilizer, which was lithium. The prescription of adjunctive antipsychotics was permitted only if the patients had significant psychotic symptoms; otherwise the adjunctive agent of choice was lorazepam. However, if the patient had prominent agitation not successfully managed with lorazepam, then a course of adjunctive antipsychotic was also allowed. Perphenazine was the recommended adjunctive antipsychotic in the protocol, but other choices were also permitted. According to the MTBD protocol guidelines, the adjunctive antipsychotics, when used, were to be discontinued as soon as clinical stabilization was achieved, by tapering at the rate of 25% of the treatment dose per week.

### *2.3. Statistical analyses*

Among the variables we considered in this analysis, only age and HDRS-17 items score conformed to a normal distribution, as determined by the Kolmogorov–Smirnov test with Lilliefors significance level. The variables which did not conform to a normal distribution were: age at first depressive episode, age at first manic episode, HDRS-25 items score, Bech–Rafaelsen mania score, duration of current depressive episode, duration of current manic episode, number of previous depressive episodes, and number of previous manic episodes. *T*-tests were used to compare the variables age and HDRS-17 between the patient groups; for the other variables, non-parametric tests (Mann–Whitney *U*-test or Kruskal Wallis test) were used. We used a descriptive statistical approach to examine the extent and course of antipsychotic use in this patient sample.

The MTBD study is a prospective follow-up study. However, our currently reported investigation on adjunctive antipsychotic use in the MTBD patients was not part of the primary study hypotheses at the time of its design and implementation, and therefore constitutes a secondary analysis of the primary MTBD study data.

## 3. Results

### *3.1. Sample demographics and baseline clinical information*

The patient cohort consisted of 34 men (39%) and 54 women (61%). The mean age of the patients was 36.8 years (S.D. = 9.2). At entry in the protocol, 38% ($n = 33$) of the subjects had been inpatients within the previous 2 months; the mean Beck–Rafaelson Mania Score was 10.7 (S.D. = 13.2; median = 3.0), the mean HDRS 17 item score was 15.7 (S.D. = 7.9; median = 16.0), and the mean HDRS-25 item score was 19.9 (S.D. = 10.2; median = 22.0). Please see Table 1 for a summary of the baseline clinical information.

At the time of entry into the research protocol, 30 patients had an index depressive episode (DD), and 19 had an index manic episode (MM). Nineteen others had initial mania at the time of screening but were in a depressive episode at the time of actual entry into the protocol (MD), and seven had initial

Table 1
Demographic and summary clinical information

| | Mean | S.D.[a] | Median |
|---|---|---|---|
| Age (years) | 36.8 | 9.2 | 37.0 |
| Age at first depression (years) | 22.9 | 7.9 | 20.0 |
| Number of previous depressive episodes | 6.4 | 7.3 | 4.0 |
| Age at first mania (years) | 26.3 | 8.9 | 24.5 |
| Number of previous manic episodes | 3.9 | 3.8 | 3.0 |
| Duration of current depressive episode (weeks) | 21.2 | 26.3 | 16.0 |
| Duration of current manic episode (weeks) | 9.2 | 8.4 | 6.0 |
| Bech–Rafaelsen baseline score | 10.7 | 13.2 | 3.0 |
| HDRS-17 item baseline score[b] | 15.7 | 7.9 | 16.0 |
| HDRS-25 item baseline score[b] | 19.9 | 10.2 | 22.0 |

[a] S.D., standard deviation.
[b] HDRS, Hamilton Depression Rating Scale.

depression but were in a manic episode at entry (DM). Other types of index episodes included six patients with initial depression and subsequent cycling (DC), two with initial depression and a mixed state at entry (DX), two with initial mania and cycling at the time of entry (MC), and three with initial mania but a mixed state at the time of entry (MX).

### 3.2. Antipsychotic usage

Thirty-four of 88 patients (39%) received at least one antipsychotic agent during the 6-month follow-up period. The antipsychotics used included: perphenazine, thioridazine, haloperidol, thiothixene, risperidone, chlorpromazine, pimozide, and loxapine. The two most utilized drugs were perphenazine (45% of the times when an antipsychotic was prescribed), and thioridazine (38% of the times). The group of 34 patients who received antipsychotics had a total of 56 episodes (periods) when antipsychotics were prescribed during the 6-month period. Twenty-one (62%) of these 34 patients had only one episode when antipsychotics were prescribed; nine patients (26%) had two episodes, and a small proportion of the patients (12%, $n = 4$) had three or more episodes when antipsychotics were prescribed. On average, the 34 patients who required antipsychotics were on those medications for 9.4 weeks (S.D. = 7.7; median = 6.8) in the 6-month follow-up period.

### 3.3. Antipsychotic use and index episode

When the type of index episode was considered, the use of antipsychotics was concentrated in two main groups: (1) the patients who presented in a manic index episode (MM), where 13 of 19 (68%) received antipsychotics within the 6 month period; (2) the patients who presented initially depressed at screening, but had cycled into mania at the time of entrance in protocol (DM), where six of seven (86%) received antipsychotics. In the group of patients who had a depressive index episode (DD), only five of 30 (17%) received antipsychotics within the 6-month period. In the group of patients who were manic at screening but depressed at the time of entrance in the protocol (MD), only six of 19 (32%) received antipsychotics. The use of adjunct antipsychotics in the 6-month period was significantly more common after an index manic (MM) than depressive (DD) episode (68 versus 17%, respectively, $P = 0.001$; Fisher's exact test). Please see Table 2 for detailed information on antipsychotic use in the 6-month period as a function of index episode.

### 3.4. Course of antipsychotic use

Please refer to Fig. 1 for a longitudinal view of the course of antipsychotic use in this patient population. At time 0 (entry in the protocol), 23 patients (26%) were on adjunctive antipsychotics, with a mean antipsychotic dose in equivalents of chlorpromazine of 117.0±97.2 mg. At 3 months, 10 patients (11%) were on adjunctive antipsychotics, with a mean dose in equivalents of chlorpromazine of 116.5±135.0 mg. At 6 months, 11 patients (12%) were on antipsychotics, with a mean dose of 174.8±251.1 mg in equivalents of chlorpromazine. Among the 23 patients who received antipsychotics at time 0, only eight (35%) were still on them at 6 months, but another three patients who were not on antipsychotics at time 0 were receiving them at 6 months.

Table 2
Antipsychotic use during the 6-month treatment period and type of index episode[a]

| Antipsychotic use | DD | DM | DC + DX | MD | MM | MC + MX | Total |
|---|---|---|---|---|---|---|---|
| Yes | 5 | 6 | 2 | 6 | 13 | 2 | 34 |
| No | 25 | 1 | 6 | 13 | 6 | 3 | 56 |
| Total | 30 | 7 | 8 | 19 | 19 | 5 | 88 |

[a] DD, depressive/depressive; DM, depressive/manic; DC, depressive/cycling; DX, depressive/mixed; MD, manic/depressive; MM, manic/manic; MC, manic/cycling; MX, manic/mixed. The first letter relates to time of screening, and the second letter relates to time of actual entry in the protocol.

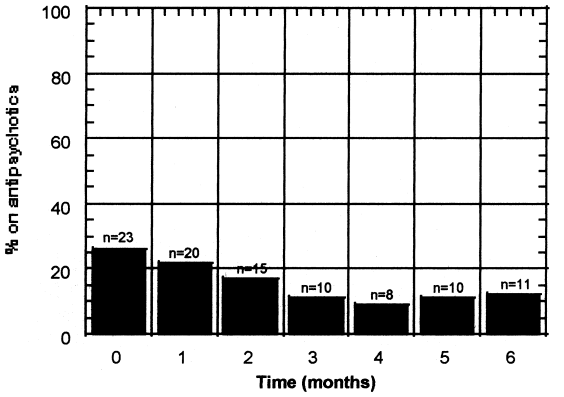


Fig. 1. Percentage of patients on adjunctive antipsychotics over the 6-month follow-up period. These are percentages in relation to the total sample of 88 bipolar type I subjects.

### 3.5. Patterns of antipsychotic usage

The patients who received antipsychotics ($n = 34$) were divided into three groups (Table 3), based on the extent of antipsychotic use during the 6 month follow-up period: (1) prolonged use – eight patients (9% of total sample) received antipsychotics for more than 15 weeks. Among these patients, only five (6% of total sample) received antipsychotics for the entire 6-month follow-up period. (2) Transient use – 11 patients (12% of total sample) received antipsychotics for up to 4 weeks. All patients had only a single and transient period of antipsychotic use. (3) Intermediate use – 15 patients (17% of total sample) received antipsychotics for more than 4, and less than 15 weeks. These three groups of patients did not differ significantly among themselves in any of the demographic or clinical measures obtained at entry into the study (HDRS 17 and 25 items, Beck–Rafaelson Mania Score, age, sex, age at first depressive episode, age at first manic episode, duration of current episode, number of previous depressive episodes, or number of previous manic episodes; Kruskal Wallis tests, $P > 0.05$). The group of prolonged antipsychotic users did not differ significantly from the group of patients who did not receive antipsychotics in any of the above variables (Mann–Whitney $U$-tests, $P > 0.05$).

### 3.6. Characteristics of patients who received antipsychotics

The patients who received antipsychotics ($n = 34$) during the 6-month treatment period had significantly lower depression scores on the HDRS-17 items (mean$\pm$S.D. $= 12.4 \pm 8.0$, median $= 11.0$ versus mean$\pm$S.D. $= 17.7 \pm 7.2$, median $= 17.0$, respectively; $Z = -3.3$, $P = 0.01$; Mann–Whitney $U$-test) and HDRS-25 items (mean$\pm$S.D. $= 15.8 \pm 10.9$, median $= 11.0$ versus mean$\pm$S.D. $= 22.5 \pm 8.9$, median $= 24.0$, $Z = -2.7$, $P = 0.007$; Mann–Whitney $U$-test), and significantly higher scores in the Bech–Rafaelson Mania Scale (mean$\pm$S.D $= 17.4 \pm 14.5$, median $= 17.5$ versus mean$\pm$S.D $= 6.4 \pm 10.5$, median $= 2.0$, respectively; $Z = -3.3$, $P = 0.001$; Mann–Whitney $U$-test) at entry into the protocol compared to subjects who did not receive antipsychotics. No significant differences in age, sex, age at first depressive episode, age at first manic episode, duration of current episode, number of previous depressive episodes, or number of previous manic episodes were found between the patients who received and those who did not receive antipsychotics.

Table 3
Patterns of antipsychotic use among bipolar I patients in the first 6 months after an index episode

| Antipsychotic use | *N* (%) | Median (weeks) | Range (weeks) |
|---|---|---|---|
| No antipsychotic use | 56 (62%) | – | – |
| Transient use[a] | 11 (12%) | 3.6 | 0.4–3.7 |
| Intermediate use[b] | 15 (17%) | 7.6 | 4.1–13.1 |
| Prolonged use[c] | 8 (9%) | 22.2 | 15.3–26.0 |

[a] Transient use: use of antipsychotics for up o 4 weeks of the total 6-month follow-up period.
[b] Intermediate use: for more than 4, and less than 15 weeks.
[c] Prolonged use: for more than 15 weeks.

## 4. Discussion

We found considerable rates of adjunctive antipsychotic use (39%) in the 6-month follow-up period after an index episode in bipolar type I patients. Nonetheless, these rates were substantially lower than those found in previous studies (Sernyak and Woods, 1993; Keck et al., 1996; Sernyak et al., 1994,1997; Verdoux et al., 1996). There are two main explanations for this discrepancy. First, our current findings are from a relatively homogeneous sample of carefully diagnosed bipolar type I subjects, without significant comorbidities. The role of diagnostic comorbidities, such as substance abuse, in worsening the course of bipolar disorder is well-recognized, as discussed elsewhere (Soares and Gershon, 1998). In addition, our inclusion criteria favored the enrollment of a less severe sample of bipolar type I subjects because rapid cyclers were excluded. Our sample only included subjects who had a period of remission of at least 12 weeks between current and previous episode, and that also probably contributed to select less severe cases. Also, it consisted mostly of outpatients (62% had not been inpatients in the 2-month period before entry in the protocol). Therefore, our sample probably included less severe cases of bipolar type I compared to previous reports (Sernyak and Woods, 1993; Keck et al., 1996; Sernyak et al., 1994,1997; Verdoux et al., 1996). Second, the patients received their pharmacological treatment in the context of a research protocol with clear guidelines on when to prescribe adjunctive antipsychotics. The protocol specified use of lorazepam for management of agitation or insomnia, and unless patients had actual psychotic symptoms, antipsychotics were not prescribed, except in cases of severe agitation that had not responded to lorazepam. We also had clear guidelines mandating that, when prescribed, adjunctive antipsychotics were to be tapered as soon as stabilization was achieved. These guidelines were carefully monitored by the study coordinator and the senior investigators in the study by means of weekly meetings with the clinical staff to discuss the care of all patients in the protocol.

The preference for perphenazine (45% of the times when an antipsychotic was prescribed) reflects local preference in terms of selection of antipsychotics at the time when these patients were studied (the patient sample reported here entered the study from August 1991 to October 1996). Perphenazine was the recommended adjunctive antipsychotic medication in this protocol, but other choices were also allowed if indicated. The second most used antipsychotic was thioridazine (38% of the times), which also reflects local preference.

The patients who received adjunctive antipsychotics had significantly higher mania scores and lower depression scores upon entering the study than those who did not. Also, the use of antipsychotics was significantly more frequent in the first 6 months after a manic than a depressive index episode. These findings confirm that in our sample the use of antipsychotics occurred mostly as an adjunctive treatment of a manic episode. Another very interesting finding is that the group of patients who had prolonged antipsychotic use (more than 15 weeks of the 6 month follow-up period) did not differ significantly from the other groups of antipsychotic users (transient or intermediate) in any demographic or baseline clinical variables. There were no statistically significant gender effects when comparing the prolonged use group with the other patients (50% males compared to 38% males, respectively; $P = 0.376$, Fisher's exact test), which is not consistent with previously reported findings that male gender is a risk factor for higher antipsychotic exposure in bipolar subjects (Keck et al., 1996). In our present study, the majority of the patients who received antipsychotics (62%) had only one treatment episode (period), whereas fewer (26%) had two episodes, and only a small proportion of the patients (12%) had three or more episodes in which antipsychotics were prescribed during the 6-month period. This suggests that in this patient sample, and in the context of this research protocol, the use of antipsychotics occurred in most cases for a limited period of time, and usually during a single period of use.

The presently reported findings are from a secondary analysis of the data on antipsychotic use collected in a prospective follow-up study of bipolar disorder patients (MTBD) designed for a different purpose. Therefore, it has potential limitations associated with the fact that the hypotheses here examined were not among the primary hypotheses that

led to the conceptual design of the primary study. However, the data here presented was prospectivelly collected under very careful clinical research conditions, with appropriate diagnostic and follow-up instruments, and contained all the necessary information for conduction of the analyses presented, and therefore we do not believe that this constitutes a significant limitation. Future studies specifically designed to prospectively address the use of adjunctive antipsychotics in comparison to other more acceptable treatment alternatives under controlled conditions in bipolar populations need to be conducted. Other limitation of our current findings is the relatively modest sample size in each of the individual sub-groups when patients were divided by patterns of antipsychotic use; the group of prolonged users in our study was particularly small, with only eight subjects. It is possible that a larger patient sample would permit the identification of small differences that the current analysis did not reveal, and that would characterize this sub-group of patients.

The diagnostic category of bipolar disorder appears to be more broadly defined nowadays, as compared to the earlier treatment studies (Soares et al., 1997; Gershon and Soares, 1997; Soares and Gershon, 1998). The more broadly defined and heterogeneous samples of bipolar disorder patients that we currently treat may be a reason why a substantial proportion of these patients need extensive antipsychotic use. As suggested by our current findings, the prolonged use of antipsychotics is relatively uncommon in a homogeneous sample of bipolar disorder type I subjects, suggesting that the higher rates of antipsychotic use reported in other studies may be related to diagnostic comorbidities and heterogeneous characteristics of the samples used. However, it is also likely that the lower rates of antipsychotic use observed in our study may be due to the fact that under strict protocol rules it is easier to limit the use of antipsychotics. This data would therefore suggest that in a substantial number of cases practitioners may overprescribe antipsychotics to bipolar patients, which corroborates the conclusions of previous studies reviewed here.

Future studies in this field should attempt to further characterize the sub-group of bipolar disorder subjects who end up receiving extensive adjunctive antipsychotic treatment. Our present sample is a homogeneous sample of bipolar type I subjects, without significant comorbidities, and in this sample the group of subjects with prolonged antipsychotic exposure did not differ significantly from those who did not receive antipsychotics, or from the groups of transient or intermediate antipsychotic users. Less homogeneous samples of bipolar disorder subjects with comorbidities should also be examined to further characterize the sub-groups who end up receiving adjunctive antipsychotic treatment.

The advent of newer atypical antipsychotics with a more favorable side-effect profile, e.g. olanzapine, risperidone, quetiapine, can dramatically change practice in this field. If these new antipsychotics are clearly shown to be related to lower rates of tardive dyskinesia, we will be able to use them much more liberally as adjuncts in the treatment of bipolar disorder subjects. In addition, if atypical antipsychotics are proven to be more effective than typical antipsychotics in refractory mood disorder patients, this will be additional reason for their use as adjuncts in the treatment of this patient population.

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