CME ACTIVITY

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CME Objectives
After completing this CME activity, the psychiatrist should be able to:
- Describe the extent of past and current neuroleptic exposure in a group of treatment-refractory bipolar patients
- Select a course of treatment for refractory bipolar patients

Statement of Need and Purpose
The use of adjunctive antipsychotics, including traditional neuroleptics, is common in bipolar disorder, and physicians responding to surveys in the *Journal* and related activities have requested information about combining treatments for bipolar disorder. This CME enduring material discusses the use of neuroleptics in patients with bipolar disorder. There are no prerequisites for this activity.

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In the spirit of full disclosure and in compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows:

Dr. Post has been or is currently a consultant for most major pharmaceutical companies.
Mss. Brotman, Fergus, and Leverich have no significant commercial relationships to disclose relative to the presentation.

High Exposure to Neuroleptics in Bipolar Patients: A Retrospective Review

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Background: Acute and long-term use of neuroleptics to treat bipolar disorder remains prevalent despite safety concerns. Neuroleptic-treated patients with bipolar disorder have been reported to have rates of tardive dyskinesia, akathisia, and acute dystonia as high as or higher than patients with schizophrenia. Moreover, the pattern of repeated, intermittent use of neuroleptics in bipolar disorder may increase rather than decrease the risk of tardive dyskinesia.

Method: Retrospective life charts of 133 treatment-refractory patients with bipolar disorder (diagnosed according to Research Diagnostic Criteria or a clinical interview with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version or the Structured Clinical Interview for DSM-IV Axis I Disorders) admitted to the National Institute of Mental Health (NIMH) were reviewed for prior neuroleptic use, medication exposure, and course of illness variables. Patients' medication response and degree of improvement while at NIMH were also assessed.

Results: A total of 72.2% (N = 96) of the bipolar patients examined had exposure to neuroleptics prior to referral to NIMH. Neuroleptic-treated patients had a mean of 5.6 neuroleptic trials with a mean duration of 166.4 days for each trial and a dose range of 25 to 960 mg in chlorpromazine equivalents. Life chart data showed that the neuroleptic-exposed and non-exposed bipolar patients were distinguished by 1 course-of-illness variable: increased suicidality in the neuroleptic-treated group. Patients with and without prior neuroleptic exposure experienced the same high degree of improvement at discharge from NIMH. Only 12.5% (N = 12) of the group previously treated with typical neuroleptics (N = 96) required neuroleptics at discharge.

Conclusion: Our data suggest that the majority of even treatment-refractory bipolar patients can be stabilized without neuroleptics. Given the high risk of tardive dyskinesia and the availability of other novel agents, the routine intermittent use of typical neuroleptics to treat patients with bipolar disorder should be minimized.

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The use of neuroleptics to treat patients with bipolar disorder continues to be a topic of substantial debate. Despite ongoing concerns about safety, efficacy, and the long-term side effects of exposure to the typical neuroleptics in this population, this treatment option is utilized chronically and frequently.[1–5] Sernyak and Woods[3] reported that a significant number of bipolar patients' current treatment regimens involved neuroleptics (40%–72%), and a vast majority of these patients had previous neuroleptic exposure (90%–100%). Similarly, in a review of nonhospitalized bipolar outpatients, Sernyak et al.[5] determined that 33 (67%) of 49 patients had been chronically exposed to neuroleptics. Additionally, many investigators have found that neuroleptics, once instituted, continue to be used even 6 months after the resolution of an acute manic episode.[3–6]

Recent research has focused on the behavioral and neurologic side effects of repeated, long-term neuroleptic exposure. The frequent, routine use of neuroleptics places bipolar patients at risk for akathisia, acute parkinsonian symptoms, and long-term tardive dyskinesia.[7,8] Neuroleptic-exposed bipolar patients have a 22% to 40% risk of developing tardive dyskinesia[9] and typically experience extrapyramidal side effects more often than patients with schizophrenia.[1,4,10–15] Furthermore, repeated, intermittent neuroleptic exposure has been found to increase the risk of tardive dyskinesia in clinical populations[9,16–18] and in animal models.[19,20]

The purpose of the current investigation was to evaluate the extent of past and current neuroleptic exposure in a group of treatment-refractory bipolar inpatients at the National Institute of Mental Health (NIMH).

METHOD

Bipolar patients with a history of poor response to conventional agents were referred by their treating psychiatrists for inpatient studies at the Biological Psychiatry Branch, NIMH. Each patient met diagnostic criteria for bipolar disorder; diagnoses were determined initially by clinician assessment and retrospective life chart and later according to the Research Diagnostic Criteria (RDC)[21] or a clinical interview with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L)[22] or the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IP).[23]

While participating in studies on the inpatient unit, patients met with research staff to develop a retrospective life chart (LCM-R).[24] A thorough review of patients' childhood, first symptoms, progression of illness, and medication exposure was completed using the LCM-R to create a graphic representation of the longitudinal course of their illness from earliest symptoms to entry in the study. The patients and their family members furnished details about affective episodes and major life events, and previous medical records were reviewed to assess and corroborate prior course of illness, medication exposure, and treatment response.

Data for this analysis were obtained from the retrospective life charts of bipolar inpatients consecutively admitted to the 3 West Clinical Research Unit of the Biological Psychiatry Branch, NIMH, who were discharged between 1974 to 1997. Patients treated in the unit for unipolar depression, schizophrenia, panic disorder, or posttraumatic stress disorder were excluded from the record review. The total number of neuroleptic trials per patient and the duration of each trial were recorded, as well as the class and number of concomitant medications during each neuroleptic trial. A trial lasted a minimum of 1 week. A trial interrupted by a lapse in neuroleptic therapy for 1 week or more was counted as 2 separate trials. Doses of all neuroleptics used were converted into chlorpromazine equivalents (CPZe),[25] and all dosages utilized in this retrospective time frame were of typical rather than atypical neuroleptics. The neuroleptic dose, based on prior records, was typically stated on the life chart; in instances when no dose was indicated, we used an estimated minimal dose of 100 mg of CPZe.

Course-of-illness variables were also examined. Age at onset of the first mild and moderate symptoms of mania or depression was noted, as well as age at first medication treatment. The number of suicide attempts and the number of hospitalizations were also obtained from each life chart. Patients were considered to be rapid cycling if they had experienced 4 or more mood episodes in the year prior to admission to NIMH.[26]

Finally, we determined the number of patients who were discharged from NIMH on neuroleptic therapy, as well as the total number of medications required for each patient at discharge. A global measure of each patient's degree of improvement was completed at the time of discharge from NIMH using a modified version of the Clinical Global Impressions scale (CGI),[27] the CGI-Bipolar Version (CGI-BP).[28] We used the change rating of the patient's overall degree of improvement from the worst phase of illness, which could be a placebo period of evaluation at the NIMH or a time on ineffective medications. Ratings on the CGI-BP are as follows: 1 = very much improved (essential clinical remission), 2 = much improved (distinct and robust improvement, but the patient remains symptomatic), 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, and 7 = very much worse. An improvement rating of either 1 or 2 at discharge was considered a positive treatment response to the NIMH hospitalization, which typically included a clinical treatment stabilization phase after the completion of formal research protocols.[29]

RESULTS

Prior to admission to the NIMH, 96 (72.2%) of 133 bipolar patients had been exposed to neuroleptics (Table 1). A chi-square test revealed that bipolar I disorder patients were more likely to be exposed to neuroleptics than patients diagnosed with bipolar II disorder ($p = .001$). The groups did not significantly differ in age at admission to NIMH, gender, or rapid cycling status (see Table 1).

The patients previously exposed to neuroleptics had a mean of 5.6 neuroleptic trials with a dose range of 25 to 960 mg/day in CPZe (Table 2). The mean duration of each neuroleptic trial was 166.4 days, or 5.6 months (see Table 2). While taking neuroleptics, these patients had a mean number of 3.2 concomitant medications, which were most frequently mood stabilizers (81%) and/or antidepressants (68%).

Two-way analyses of variance (ANOVAs; neuroleptic exposure × diagnosis) revealed no significant differences between those exposed and not exposed to neuroleptics

Table 1. Demographic and Clinical Characteristics of Patient Sample

Variable[a]	Neuroleptic Exposure	No Neuroleptic Exposure
Total sample (N = 133)	96 (72.2)	37 (27.8)
Mean age, y	40.2	38.5
Diagnosis		
Bipolar I (N = 78)	67 (85.9)*	11 (14.1)
Bipolar II (N = 55)	29 (52.7)	26 (47.3)
Gender		
Male (N = 53)	34 (64.2)	19 (35.8)
Female (N = 80)	62 (77.5)	18 (22.5)
Cycling		
Rapid cycling (N = 44)	32 (72.7)	12 (27.3)
Non–rapid cycling (N = 89)	64 (71.9)	25 (28.1)

[a]Values shown as N (%) unless otherwise specified.
*p = .001 vs. patients with bipolar II disorder.

Table 2. Descriptive Variables Within the Previously Neuroleptic Exposed Group[a]

Neuroleptic trials per patient	
Mean ± SD	5.6 ± 5.1
Range	1–28
Duration of neuroleptic trials, d	
Mean ± SD	166.4 ± 207.8
Range	30–2440
Cumulative duration of neuroleptic exposure, d	
Mean ± SD	972.2 ± 1953.2
Range	30–14,640
Neuroleptic dose in mg/d CPZe, range	25–960

[a]Abbreviation: CPZe = chlorpromazine equivalents.

Table 3. Course of Illness Variables and Previous Neuroleptic Exposure

	Neuroleptic Exposure		No Neuroleptic Exposure	
Variable	Mean	SD	Mean	SD
Age at onset of first symptoms, y	22.52	10.20	18.13	6.88
Age at first medication treatment, y	28.82	10.54	27.81	8.65
No. of hospitalizations	6.81	6.60	3.52	3.20
No. of suicide attempts	1.34	2.20*	0.50	0.97

*p < .05 vs. patients not exposed to neuroleptics.

regarding age at onset of first symptoms, first medication treatment, and number of hospitalizations (Table 3). However, patients with previous neuroleptic exposure had made more suicide attempts (1.34) than patients without prior neuroleptic exposure (0.50; F = 21.44, df = 1,119; p = .021).

Of the 96 patients previously exposed to neuroleptics, only 12.5% (N = 12) required neuroleptics at discharge from NIMH (Figure 1). Moreover, the majority (81%; N = 78) of these patients previously exposed to neuroleptics achieved much or very much improved ratings at discharge. Two-way ANOVAs (neuroleptic exposure × diagnosis) revealed that patients previously exposed and not exposed to neuroleptics did not differ in their degree of improvement and number of medications required at discharge (Table 4).

Figure 1. High Use of Neuroleptics Prior to Hospitalization at the National Institute of Mental Health (NIMH), but Little Required at Discharge

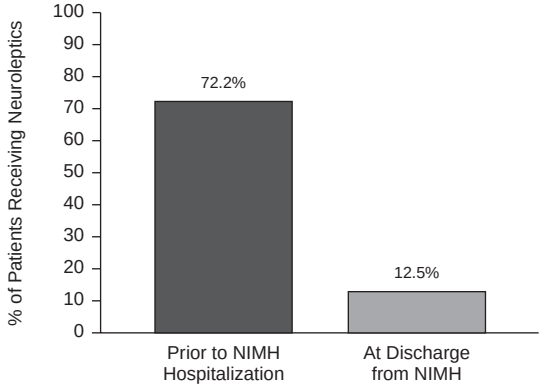

Table 4. Previous Neuroleptic Exposure and Improvement at NIMH Discharge[a]

	Neuroleptic Exposure		No Neuroleptic Exposure	
Variable	Mean	SD	Mean	SD
CGI-BP score[b]	1.92	0.92	2.13	0.96
No. of medications	1.98	1.32	1.58	1.26

[a]Abbreviations: CGI-BP = Clinical Global Impressions scale-Bipolar Version, NIMH = National Institute of Mental Health.
[b]Score: 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

DISCUSSION

This retrospective study of treatment-refractory bipolar patients revealed that the majority of patients (72%) had had multiple intermittent neuroleptic trials prior to their NIMH hospitalization, although very few (12.5%) required neuroleptics at discharge from NIMH. Neuroleptic-exposed patients averaged over 5 trials of neuroleptics with a mean duration for each of approximately 5.6 months. Our data, convergent with that in many other clinical populations, suggest that repeated, intermittent exposure to neuroleptics is frequent in this bipolar population.[9,13] Traditional thinking held that brief periods of neuroleptic treatment might decrease the risk

of extrapyramidal symptoms; however, repetitive, intermittent exposure appears to increase the risk of tardive dyskinesia.[9,16–18]

Neuroleptic-exposed and nonexposed patients were distinguished by only 1 course of illness variable: increased suicidality in the neuroleptic-exposed group. This finding could suggest that the neuroleptic-exposed patients were more severely ill than the nonexposed group and, therefore, required more aggressive treatment. Conversely, the finding might indicate that typical neuroleptics may have increased the number or duration of depressive episodes.[30,31] Thus, whether neuroleptic exposure per se might have contributed directly or indirectly to the heightened suicidality observed cannot be ascertained from this analysis.

In addition to examining the number of patients discharged from NIMH who were taking neuroleptics, we also assessed the overall degree of improvement and number of medications required at discharge in both previously neuroleptic-exposed and nonexposed patients. Our results indicate that the vast majority of both groups were able to be stabilized without neuroleptics at discharge. Only 12.5% (N = 12) of the previously neuroleptic-exposed and 8.1% (N = 3) of the nonexposed bipolar patients were discharged from NIMH on neuroleptic therapy. Additionally, the majority of both the previously neuroleptic-exposed (81%) and nonexposed patients (68%) were much or very much improved upon discharge from NIMH. Patients with and without neuroleptic use prior to NIMH did not differ in their degree of improvement and the number of medications required at discharge, indicating that the exposed and nonexposed groups had comparable responses to treatment at NIMH. Thus, even a highly treatment-refractory, preselected group of bipolar inpatients can be substantially improved and stabilized without neuroleptics. After the completion of formal research protocols, treatment regimens typically utilized 1 or more mood stabilizers, often with thyroid augmentation,[29] and a low dose of unimodal antidepressants.

Because of recent advances in psychopharmacology, clinicians now have many options beyond the typical neuroleptics and lithium for the treatment of acute mania, depression, and cycling, such as the anticonvulsants carbamazepine and divalproex sodium,[2,32–35] as well as the putative but not established mood stabilizers lamotrigine, gabapentin, and topiramate.[8,36–48] Preliminary results examining the atypical neuroleptics clozapine, risperidone, and olanzapine have proved to be promising,[8,36,38–43] particularly for patients with psychotic features.[8,36–39,42,43]

The interpretation of these study results is affected by several methodological limitations. The population studied is a treatment-refractory, tertiary-referral group sent for clinical research evaluation. Thus, they have more serious illnesses and may have required more frequent neuroleptic exposure than a nonrefractory bipolar population. However, data from nonrefractory populations of patients with bipolar illness are consistent with our findings of high neuroleptic exposure.[3,6,49,50] Yassa and colleagues[12] reported that 61% of their bipolar inpatients and outpatients were prescribed neuroleptics. Similarly, Verdoux et al.[50] reported that more than two thirds of the bipolar outpatients in their survey of prescribing practices were prescribed at least 1 neuroleptic in long-term maintenance or prophylaxis treatment.

Only 12.5% of the neuroleptic-exposed patients required neuroleptics at discharge from NIMH, a low figure in an otherwise severely ill and previously highly treatment-refractory patient population. The decreased use of neuroleptics may have been strongly influenced by the clinicians' unique opportunity to explore multiple mood-stabilizing options over an extended period of time in an inpatient clinical research facility providing free care. In traditional inpatient settings, characterized by pressing time constraints and financial pressures, the use of neuroleptics as an acute or long-term augmentation strategy is understandably more highly prevalent.[51] We were often able to keep patients under close supervision for periods long enough to suggest that their improvement was substantially longer than previous cycle frequencies and thus was not likely to represent a spontaneous remission. Whether this improvement would be sustained in long-term follow-up without further need for neuroleptics, however, remains to be examined.

Despite these limitations, our data suggest that when given the opportunity to explore other treatment options, such as in the context of the treatment phase in our research unit, most bipolar patients can be effectively treated without neuroleptics.[31] Bipolar patients with and without prior neuroleptic exposure showed similar high rates of improvement at discharge from NIMH.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), olanzapine (Zyprexa), risperidone (Risperdal), topiramate (Topamax).

Disclosure of off-label usage: The following drugs mentioned in this article are not approved by the U.S. Food and Drug Administration for the treatment of bipolar illness: carbamazepine, chlorpromazine, clozapine, gabapentin, lamotrigine, olanzapine, risperidone, topiramate.

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Instructions

Physicians may receive up to 1 hour of Category 1 credit toward the American Medical Association Physician's Recognition Award by reading the article starting on page 68 and correctly answering at least 70% of the questions in the posttest that follows.

1. Read each question carefully and circle the correct corresponding answer on the Registration form.
2. Type or print your full name and address and Social Security, phone, and fax numbers in the spaces provided.
3. Send the Registration form along with a check, money order, or credit card payment in the amount of $10 to: Physicians Postgraduate Press, Office of CME, P.O. Box 752870, Memphis, TN 38175-2870.
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All replies and results are confidential. Answer sheets, once graded, will not be returned. Unanswered questions will be considered incorrect and so scored. Your exact score can be ascertained by comparing your answers with the correct answers to the posttest, which will be printed in the *Journal* issue after the submission deadline. The Physicians Postgraduate Press Office of CME will keep only a record of participation, which indicates the completion of the activity and the designated number of Category 1 credit hours that have been awarded.

1. Previous research has found that neuroleptics continue to be used for how long following initial use?
a. 3 months
b. 6 months
c. 9 months
d. 4 weeks

2. Neuroleptic-exposed bipolar patients have what percentage risk of developing tardive dyskinesia?
a. 10%–12%
b. 57%–60%
c. 22%–40%
d. 75%–80%

3. There was no difference in past neuroleptic use based on diagnostic classification as either bipolar I or bipolar II.
a. True
b. False

4. The mean duration of the bipolar patients' previous neuroleptic trials was:
a. 30 days
b. 2 weeks
c. 5–6 months
d. 1 year

5. In comparing course-of-illness variables, patients with and without prior neuroleptic exposure differed on which variable?
a. Number of hospitalizations
b. Number of siblings with bipolar disorder
c. Number of suicide attempts
d. Age at onset of moderate bipolar symptoms

6. Upon leaving the National Institute of Mental Health (NIMH), what percentage of patients required neuroleptics as part of their pharmacotherapy?
a. 72.2%
b. 49.9%
c. 12.5%
d. 22%

7. How many neuroleptic trials did the bipolar patients average prior to hospitalization at the NIMH?
a. 1
b. More than 5
c. More than 10
d. 3

8. Patients who were previously exposed to neuroleptics before treatment at the NIMH did not show improvement as great as that of patients who previously were not exposed to neuroleptics.
a. True
b. False

9. Which of the following would be the best alternative to typical neuroleptics for treating psychotic symptoms?
a. Clozapine
b. Risperidone
c. Olanzapine
d. All of the above

Answers to the July 1999 CME posttest

1. a 2. d 3. a 4. c 5. b 6. a 7. b 8. a

Circle the one correct answer for each question.

1.	a	b	c	d	6.	a	b	c	d
2.	a	b	c	d	7.	a	b	c	d
3.	a	b			8.	a	b		
4.	a	b	c	d	9.	a	b	c	d
5.	a	b	c	d					

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Keeping a copy for your files

Retain a copy of your answers and compare them with the correct answers, which will be published after the submission deadline.

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Please evaluate the effectiveness of this CME activity by answering the following questions.

1. Was the educational content relevant to the stated educational objectives? ❑ Yes ❑ No
2. Did this activity provide information that is useful in your clinical practice? ❑ Yes ❑ No
3. Was the format of this activity appropriate for the content being presented? ❑ Yes ❑ No
4. Did the method of presentation hold your interest and make the material easy to understand? ❑ Yes ❑ No
5. Achievement of educational objectives:
   A. Enabled me to describe the extent of past and current neuroleptic exposure in a group of treatment-refractory bipolar patients ❑ Yes ❑ No
   B. Enabled me to select a course of treatment for refractory bipolar patients. ❑ Yes ❑ No
6. Did this CME activity provide a balanced, scientifically rigorous presentation of therapeutic options related to the topic, without commercial bias? ❑ Yes ❑ No
7. Does the information you received from this CME activity confirm the way you presently manage your patients? ❑ Yes ❑ No
8. Does the information you received from this CME activity change the way you will manage your patients in the future? ❑ Yes ❑ No
9. Please offer comments and/or suggested topics for future CME activities.

   _____
   _____
   _____
   _____
   _____

10. How much time did you spend completing this CME activity?

    _____

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