Placebo Effect in Randomized, Controlled Maintenance Studies of Patients with Bipolar Disorder

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The prevention of mood episodes is an important goal of the maintenance treatment of patients with bipolar disorder. The rate of relapse on placebo compared with that on active treatment is an important issue in the design of future clinical trials of maintenance treatment. We examine the range and time course of placebo relapse rates in studies of patients with bipolar I disorder. In addition, we address the potential variables associated with placebo response, strategies to minimize placebo response, the optimum duration of placebo-controlled maintenance trials, possible alternatives to placebo control groups, and the impact of these considerations in maintenance studies of children, adolescents, and older adults with bipolar disorder. Biol Psychiatry 2000;47:756–761 © *2000 Society of Biological Psychiatry*

Key Words: Placebo, bipolar disorder, maintenance, prophylaxis, clinical trials

Introduction

Bipolar disorder is a recurrent illness in 80–90% patients (Goodwin and Jamison 1990; Kessing et al 1998). Recurrent manic, mixed manic, and depressive episodes are associated with substantial morbidity and may lead to disability (Keck et al 1998; Strakowski et al 1998). Prevention of recurrent mood episodes is the goal of pharmacologic maintenance treatment of bipolar disorder (Dunner 1998). A number of placebo-controlled studies conducted 25 to 30 years ago established lithium's superiority over placebo in preventing recurrent mood episodes (Baastrup et al 1970; Coppen et al 1971; Cundall et al 1972; Fieve et al 1976; Hullin et al 1972; Melia 1970; Prien et al 1973a, 1973b; Stallone et al 1973). Since that time, clinical trial methods have evolved (Calabrese and Rapport 1999), nosologic conceptualizations of bipolar disorder have expanded (Calabrese and Rapport 1999; Pope and Lipinski 1978), and only one subsequent placebo-controlled maintenance study has been conducted in patients with bipolar I disorder (Bowden et al, in press). Recently, a number of atypical antipsychotic and antiepileptic medications have shown promise as potential mood-stabilizing alternatives to lithium. The efficacy of these agents in the maintenance treatment of patients with bipolar disorder needs to be established. The role and justification for a placebo control group in such trials is an important issue in the design of future maintenance studies.

In this article we examine the range and time course of placebo relapse rates in maintenance treatment trials of patients with bipolar I disorder. In addition, we review potential variables associated with placebo response, strategies in trial designs to minimize placebo response, possible alternatives to placebo control groups, the optimum duration of placebo-controlled maintenance trials, and the implication of these issues in studies of children, adolescents, and older adults with bipolar disorder.

Methods and Materials

We searched the scientific literature for all placebo-controlled maintenance treatment trials in patients with bipolar I disorder using Paperchase. This search was augmented by reviewing all bibliographies of identified papers. Fourteen studies were identified. Of these, three were excluded because all patients had bipolar II or major depressive disorder (Dunner et al 1976; Kane et al 1982; Quitkin et al 1978), three because data presented were inadequate to estimate relapse rates within 12 months of randomization (Coppen et al 1971; Fieve et al 1976; Hullin et al 1972), and one because of utilization of a crossover design (Cundall et al 1972). After exclusion of these studies, seven parallel group, placebo-controlled maintenance treatment trials in patients with bipolar I disorder remained for analysis (Tables 1 and 2). The placebo effect in these studies was examined by comparing drug and placebo relapse rates for studies that presented such data at 20–24 weeks (Baastrup et al 1970; Melia 1970; Prien et al 1973a, 1973b) and/or at 48–60 weeks (Bowden et al, in press; Okuma et al 1981; Stallone et al 1973). In general, relapse was defined

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Table 1. Parallel Group, Placebo-Controlled Maintenance Treatment Trials: Demographic and Clinical Characteristics

Study	*N*	Criteria	M/F	Age (years) and mean (SD)	Age onset (years) and mean (SD)	Entry status
Baastrup et al 1970	50	ND	ND	49 (−)	31 (−)	Stable outpatients on lithium
Melia 1970	29	ICD	4/25	45 (−)	32 (−)	Stable outpatients on lithium
Stallone et al 1973	52	ND	25/25	52 (12)	ND	Stable outpatients, "some" on lithium
Prien et al 1973a	205	ND	133/72	44 (−)	ND	Prospective at hospital discharge for mania
Prien et al 1973b	44	ND	34/10	43 (12)	29 (11)	Prospective at hospital discharge for depression
Okuma et al 1981	22	ICD-9	10/12	43 (−)	ND	Stable inpatient and outpatient
Bowden et al, in press	372	DSM-III-R	182/190	39 (11)	22 (10)	Stabilized manic episode within 3 months

ND, no data provided.

as a manic, mixed, or depressive episode requiring hospitalization or an alteration in medication regimen. Since data suggest that abrupt withdrawal of lithium may precipitate mania (Faedda et al 1993; Suppes et al 1991), relapse rates were calculated for all seven studies together and also by dividing them into discontinuation studies (studies in which patients had been maintained on lithium for at least 9 months before abrupt randomization; Baastrup et al 1970; Melia 1970; Okuma et al 1981; Stallone et al 1973) and nondiscontinuation studies (randomization after periods of acute stabilization of 3 months or less; Bowden et al, in press; Prien et al 1973a, 1973b). Only the study by Bowden et al (in press) attempted to control for abrupt discontinuation effects by incorporating a 2-week taper of open-label stabilization treatment with divalproex or lithium at the beginning of randomization; however, patients who had been treated with both agents were required to have one discontinued before randomization.

Among the early pioneering studies of lithium maintenance treatment, only the Veterans Administration (VA)/National Institute of Mental Health (NIMH) Collaborative Studies (Prien et al 1973a, 1973b) standardized enrollment by index episode (according to whether patients were manic or depressed). Moreover, enrollment in the early lithium maintenance studies consisted primarily of patients who had responded to acute and, often, long-term maintenance treatment with lithium. Thus, patient groups constituted enriched samples of lithium responders (Calabrese and Rapport 1999). Finally, it is likely that the first generation of lithium maintenance studies recruited patients with characteristics different than patients with bipolar disorder defined by the DSM-III-R or DSM-IV criteria (American Psychiatric Association 1987, 1994). For example, the Research Diagnostic Criteria (Feighner et al 1972) were utilized at the time of many of the early lithium maintenance trials (Calabrese and Rapport 1999). By these criteria, manic patients with mood-incongruent psychotic symptoms were classified as having the "mainly affective variant of schizoaffective disorder." Such patients would not have been included in these early studies but would be in current trials. Since manic patients with mood-incongruent delusions may have a worse prognosis than patients with mood-congruent features (Tohen et al 1992), the exclusion of these patients from early studies may have influenced response and relapse rates (Calabrese and Rapport 1999).

Results

The demographic and clinical characteristics of the seven maintenance studies are presented in Table 1. Only the recent Bowden et al (in press) study used modern criteria to define bipolar disorder (American Psychiatric Associa-

Table 2. Parallel Group, Placebo-Controlled Maintenance Treatment Trials: Study Methods

Study	Blindness	Medications	Concomitant rescue medications	Duration (weeks)	Primary outcome measure
Baastrup et al 1970	Relapse rated unblind	Li	None	20	Hospitalization or change in medications
Melia 1970	Double blind	Li	None; ↑ if symptoms	104	Episodes
Stallone et al 1973	Double blind	Li	None	60	Change in medications
Prien et al 1973a	Single blind	Li	None; ↑ if symptoms	96	Hospitalization or change in medications
Prien et al 1973b	Single blind	Li	None; ↑ if symptoms	96	Hospitalization or change in medications
Okuma et al 1981	Double blind	CBZ	Any other than CBZ or Li for ↑ symptoms	48	Rating Scale for Mania and Depression
Bowden et al, in press	Double blind	Divalproex, Li	Lorazepam × 14, 7 days Haloperidol × 7 days in 1st month Parox or Sert for depression	52	Time to manic or depressive episode

Li, lithium; CBZ, carbamazepine; Parox, paroxetine; Sert, sertraline.

tion 1987), and in four studies diagnostic criteria were not formally specified (Baastrup et al 1970; Prien et al 1973a, 1973b; Stallone et al 1973). Overall the sex distribution was nearly 1:1, although the two VA/NIMH Collaborative Studies (Prien et al 1973a, 1973b) had more men than women. Patients were on average in their mid-40s with an average duration of illness of 14 years.

The study methods are summarized in Table 2. Four studies were double blind (Bowden et al, in press; Melia 1970; Okuma et al 1981; Stallone et al 1973). In the two VA/NIMH Collaborative Trials (Prien et al 1973a, 1973b) the physicians actually treating the patients were not blind, and in the study by Baastrup et al (1970) relapse was rated unblinded. Three studies allowed flexible dosing of lithium (i.e., the ability to adjust dosages upward in response to the emergence of subsyndromal symptoms; Melia 1970; Prien et al 1973a, 1973b). In the only placebo-controlled maintenance study of carbamazepine (Okuma et al 1981), the use of any adjunctive psychotropic rescue medications other than carbamazepine or lithium was permitted for breakthrough symptoms. The liberal use of these adjunctive treatments limits the degree to which relapse rates can be attributed to carbamazepine or placebo in this study. Finally, in the study by Bowden et al (in press), lorazepam up to 6 mg/day was permitted for a maximum 14-day period during the first month and for no more than 7 days for the duration of the study. In addition, haloperidol up to 10 mg/day was permitted during the 2nd week of lorazepam use in the 1st month only. These interventions were permitted to minimize discontinuation effects from withdrawal of open-label treatment.

Maintenance studies ranged in duration from 20 to 104 weeks. Only the Bowden et al (in press) study used survival analyses to determine time to relapse to a mood episode. Earlier studies assessed outcome by calculating the proportion of patients who relapsed at various time intervals (e.g., at 6 months, 1 year, or 2 years), leaving the time course of relapse unexamined. Patients who dropped out of all of these maintenance studies without experiencing a mood episode were not incorporated into primary analyses of outcome (Calabrese and Rapport 1999). Premature withdrawal early in the course of maintenance studies because of protocol violations, withdrawn consent, and administrative reasons occurred more frequently in patients receiving placebo (Bowden et al, in press; Calabrese and Rapport 1999). Thus, fewer patients on placebo at risk for relapse remained in these studies, reducing their power. With omission of these patients, the placebo relapse rate is vulnerable to being artificially reduced if premature withdrawal was related to the unobserved outcome.

Relapse rates are difficult to compare because they were calculated at disparate time points among the different studies. In an attempt to estimate relapse rates among the group of maintenance studies analyzed, we estimated the probability of relapse for placebo and drug at 20–24 weeks (Baastrup et al 1970; Melia 1970; Prien et al 1973a, 1973b) and/or at 48–60 weeks (Bowden et al, in press; Okuma et al 1981; Stallone et al 1973) from relapse rates reported in these respective studies. The odds of relapse for placebo (0.9) at 20–24 weeks were significantly higher than for drug treatment (0.2), with an odds ratio favoring a relapse in the placebo group of 4.1 (95% confidence interval: 2.1, 7.7). Similarly, the odds of relapse for placebo at 48–60 weeks (1.9) were significantly higher than those for drug treatment (0.5), with an odds ratio again of 4.1 (95% confidence interval: 2.0, 7.7) favoring a relapse in the placebo group. The odds of relapse on placebo at 20–24 or 48–60 weeks did not appear to be influenced by whether studies discontinued lithium in long-stable outpatients or in newly treated patients. The odds of relapse on placebo at 20–24 weeks and 48–60 weeks were identical regardless of the length of time patients had been receiving lithium for stabilization before abrupt discontinuation.

The relapse rates in the two largest maintenance studies, each of which standardized enrollment by an index manic episode and provided data at 1 year, are interesting to compare (Bowden et al, in press; Prien et al 1973a). In the Prien et al study (1973a), 68% of patients receiving placebo relapsed by 1 year, compared with 36% of patients on lithium. Severe relapse (i.e., requiring hospitalization) occurred in 55% of patients on placebo and in 26% of patients on lithium. In the 1-year Bowden et al (in press) study, 38% of patients receiving placebo relapsed, compared with 31% on lithium and 24% on divalproex. The disparity in placebo response rates between these two landmark studies is likely due to several factors. First, patients in the Prien et al (1973a) study had all been recently hospitalized for a manic episode, whereas only 18% in the Bowden et al (in press) study had been hospitalized for the index manic episode. Second, relapse was defined differently in the two studies. In the Prien et al study, relapses were events that required hospitalization or supplementary drug therapy; in the Bowden et al study, relapse was defined as the occurrence of any mood episode. Third, patients in the Prien et al study consisted of a more homogeneous group of lithium responders diagnosed by narrower criteria.

The importance of including patients who terminate prematurely from maintenance studies in analyses of outcome is illustrated by the data from the Bowden et al (in press) study. The proportion of patients who terminated from the study for all reasons (mood episode, intolerance or noncompliance, lost to follow-up, intercurrent illness, administrative reasons) was significantly higher in the

placebo group (75%) than in the divalproex group (62%; $p = .04$). These data were not provided in the Prien et al (1973a) study.

Discussion

There are a number of variables that could be associated with placebo response in these studies. These include severity of illness (including number and recent frequency of prior mood episodes), enriched versus heterogeneous patient populations, number of sites, prior treatment response, standardization according to index episode, abrupt discontinuation versus taper of open-label treatment at randomization, trial duration, the influence of frequent outpatient assessment visits, outcome measures, and spontaneous remission. Attempts to assess the impact of the variables on the placebo response rate are limited to the Bowden et al (in press) study. Severity of illness may have contributed to the low placebo relapse rate on the primary outcome measure of relapse to a manic or depressive episode in this study. Patients with less severe illness may have been selected for by the enrollment criterion of two consecutive Global Assessment Scale scores greater than 60 and remission of mania within 3 months of the manic episode. Some patients were randomized whose index manic episodes had remitted spontaneously without treatment. Furthermore, the index manic episode appeared to be less severe in those patients who were randomized. Some patients with histories of severe or frequent episodes may also have been reluctant to participate in a placebo-controlled study with restricted use of adjunctive medications.

As previously described, the choice of outcome measures and method of statistical analysis are also likely to have influenced the placebo response rate in this study. Bowden et al (in press) speculated that outcome measures similar to those of earlier maintenance studies (e.g., time to change in medication regimen, duration of symptom-free treatment) might have provided greater sensitivity to group treatment differences.

Data addressing the question of the optimum duration of a placebo-controlled maintenance study are difficult to glean from the available studies because only the Bowden et al (in press) study utilized survival analyses to assess time to relapse in placebo and drug-treatment groups. The lack of data regarding time to relapse before 20 weeks in all but the Bowden et al (in press) study—which, in turn, used a taper rather than abrupt discontinuation design—makes it unclear how much earlier than 20–24 weeks placebo relapse rates begin to significantly differ from drug treatment. Nevertheless, the available data suggest that placebo-controlled maintenance studies can probably be accomplished within 20–24 weeks.

As in acute treatment studies, potential alternatives to a placebo control group in maintenance studies include add-on studies (Müller-Oerlinghausen and Retzow 1998; Solomon et al 1997; Stoll et al 1999), variable dose designs (Gelenberg et al 1989), and use of active comparator control groups. Add-on designs have the advantage of mimicking clinical practice in the pharmacologic management of breakthrough symptoms during maintenance treatment. Add-on designs do not obviate the need for placebo but eliminate placebo monotherapy. In addition, very large sample sizes are likely to be needed for add-on active comparator studies to have sufficient power to detect between group differences. Variable dose designs in maintenance trials have an important role in establishing minimal effective dosage ranges (or plasma concentrations) and dosage ranges optimizing efficacy and tolerability; however, it must be clearly specified in the informed consent process that some doses may not exert a therapeutic affect. Active comparator designs run the risk of failing to find a significant difference in efficacy between groups (Leber 1996). The results of such a trial would be unlikely to establish the efficacy of the study medication but could be used to examine potential differences in tolerability. Finally, the inherently unpredictable nature of the course of bipolar disorder makes the use of historical controls untenable.

Recently, Calabrese and Rapport (1999) suggested a number of innovations in clinical trial methodology for studies of maintenance treatment of patients with bipolar disorder. Some of these suggestions (e.g., use of survival analyses that incorporate study dropouts into outcome measures) have already been discussed. Other innovations suggested by these authors that may reduce placebo response include using multiple outcome measures and using time to any premature termination or to any clinically necessary treatment change for an emerging episode as more sensitive measures of relapse. In addition, they suggest using rating instruments such as the Life Chart Method (LCM; Leverich and Post 1998) that allow episodes to be quantified and are sensitive to the emergence of subsyndromal symptoms and time spent well. For example, the LCM provides sensitivity by day in time to relapse, rather than by week or by month.

As far as we know, there are no placebo-controlled maintenance studies in children, adolescents, or older adults with bipolar disorder. As with acute treatment studies, substantial differences in the clearance and tolerability of psychotropic agents need to be addressed in clinical trial designs (Geller et al 1998; Malone and Simpson 1998). Because older adults with bipolar disorder appear to be at greater risk of relapse than young patients, the duration of maintenance studies may not need to be as long (Tohen et al 1994).

Conclusion

The risk of relapse on placebo in maintenance studies of bipolar disorder is much greater than with active treatment, with an odds ratio of 4.1 at 6 months. It is still possible that this high risk of relapse with placebo is due, in part, to abrupt discontinuation from active treatment at randomization. Gradual taper of open-label treatment over a 2–4-week period might reduce the impact and potential confounding effect of abrupt withdrawal. Add-on and variable dose studies appear to be viable alternatives in maintenance studies but would require substantially larger sample sizes and take longer. Ensuring adequate informed consent and establishing safeguards for outpatients participating in such trials are critical.

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References

American Psychiatric Association (1987): *Diagnostic and Statistical Manual of Mental Disorders,* 3rd ed rev. Washington, DC: American Psychiatric Press.

American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. Washington, DC: American Psychiatric Press.

Baastrup PC, Poulsen JC, Schou M, Thomsen K, Andisen A (1970): Prophylactic lithium: Double blind discontinuation in manic-depressive and recurrent-depressive disorders. *Lancet* 2:326–330.

Bowden CL, Calabrese JR, McElroy SL, Gyulai L, Wassef A, Petty F, et al (in press): A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. *Arch Gen Psychiatry.*

Calabrese JR, Rapport DJ (1999): Mood stabilizers and the evolution of maintenance study designs in bipolar I disorder. *J Clin Psychiatry* 60(suppl 5):5–13.

Coppen A, Noguera R, Bailey J (1971): Prophylactic lithium in affective disorders. *Lancet* 2:275–279.

Cundall RL, Brooks PW, Murray LG (1972): Controlled evaluation of lithium prophylaxis in affective disorders. *Psychol Med* 2:308–311.

Dunner DL (1998): Lithium carbonate: Maintenance studies and consequences of withdrawal. *J Clin Psychiatry* 59(suppl 6):48–55.

Dunner DL, Stallone F, Fieve RR (1976): A double-blind study of prophylaxis of depression in bipolar illness. *Arch Gen Psychiatry* 33:117–121.

Faedda GL, Tondo L, Baldessarini RJ, Suppes T, Tohen M (1993): Outcome after rapid vs gradual discontinuation of lithium treatment of bipolar disorders. *Arch Gen Psychiatry* 50:448–455.

Feighner JP, Robins E, Guze SB (1972): Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry* 26:57–63.

Fieve RR, Kumbaraci T, Dunner DL (1976): Lithium prophylaxis of depression in bipolar I, bipolar II and unipolar patients. *Am J Psychiatry* 133:925–929.

Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, et al (1989): Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. *N Engl J Med* 321:1489–1493.

Geller B, Cooper TB, Sun K, Zimmerman B, Frazier J, Williams M, et al (1998): Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. *J Am Acad Child Adolesc Psychiatry* 37:171–178.

Goodwin FK, Jamison KR (1990): *Manic-Depressive Illness.* New York: Oxford University Press.

Hullin RP, McDonald R, Allsopp MNE (1972): Prophylactic lithium in recurrent affective disorders. *Lancet* 1:1044–1046.

Kane JM, Quitkin FM, Rifkin A, Rames-Lorenzi JR, Nayak DD, Howard A (1982): Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness. *Arch Gen Psychiatry* 39:1065–1069.

Keck PE Jr, McElroy SL, Strakowski SM, West SA, Sax KW, Hawkins JM, et al (1998): Twelve-month outcome of bipolar patients following hospitalization for a manic or mixed episode. *Am J Psychiatry* 155:646–652.

Kessing LV, Andersen PK, Mortensen PB, Bolwig TG (1998): Recurrence in affective disorder. 1 Case register study. *Br J Psychiatry* 172:23–28.

Leber P (1996): Challenges to the ethicality of clinical research. *Psychopharmacol Bull* 32:11–20.

Leverich GS, Post RM (1998): Life charting of affective disorders. *CNS Spectrums* 3:21–37.

Malone RP, Simpson GM (1998): Use of placebos in clinical trials involving children and adolescents. *Psychiatr Serv* 49:1413–1414.

Melia PI (1970): Prophylactic lithium: A double-blind trial in recurrent affective disorders. *Br J Psychiatry* 116:621–624.

Müller-Oerlinghausen B, Retzow A (1998): Valproate as an adjunct to neuroleptic medication in the treatment of episodes of mania. Presented at the annual meeting of the International Academy of Biomedical and Drug Research, Workshop on Novel Therapeutic Strategies in the Schizophrenic Spectrum and Mood Disorders, Venice, Italy.

Okuma T, Inanaga K, Otsuki S, Sarai K, Takahashi R, Hazama H, et al (1981): A preliminary double-blind study on the efficacy of carbamazepine in prophylaxis of manic-depressive illness. *Psychopharmacology* 73:95–96.

Pope HG Jr, Lipinski JF (1978): Diagnosis in schizophrenia and manic-depressive illness: A reassessment of specificity of

"schizophrenic" symptoms in the light of current research. *Arch Gen Psychiatry* 35:811–828.

Prien RF, Caffey EM Jr, Klett CJ (1973a): Prophylactic efficacy of lithium carbonate in manic-depressive illness. Report of the Veterans Administration and National Institute of Mental Health Collaborative Study Group. *Arch Gen Psychiatry* 28:337–341.

Prien RF, Klett CJ, Caffey EM Jr (1973b): Lithium carbonate and imipramine in prevention of affective episodes. *Arch Gen Psychiatry* 29:420–425.

Quitkin F, Rifkin A, Kane J (1978): Prophylactic effect of lithium and imipramine in unipolar and bipolar II patients: A preliminary report. *Am J Psychiatry* 135:570–572.

Solomon DA, Ryan CE, Keitner GI, Miller IW, Shea MT, Kazim A, et al (1997): A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. *J Clin Psychiatry* 58:95–99.

Stallone F, Shelley E, Mendlewicz J, Fieve RR (1973): The use of lithium in affective disorders, III: A double-blind study of prophylaxis in bipolar illness. *Am J Psychiatry* 130:1006–1010.

Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, et al (1999): Omega 3 fatty acids in bipolar disorder: A preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 56:407–412.

Strakowski SM, Keck PE Jr, McElroy SL, West SA, Sax KW, Hawkins JM, et al (1998): Twelve-month outcome following a first hospitalization for affective psychosis. *Arch Gen Psychiatry* 55:49–55.

Suppes T, Baldessarini RJ, Faedda GL, Tohen M (1991): Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. *Arch Gen Psychiatry* 48:1082–1088.

Tohen M, Shulman KI, Satlin A (1994): First-episode mania in late life. *Am J Psychiatry* 151:130–132.

Tohen M, Tsuang MT, Goodwin DC (1992): Prediction of outcome in mania by mood-congruent or mood-incongruent psychotic features. *Am J Psychiatry* 149:1580–1584.