Lithium Augmentation Fails to Reduce Symptoms in Poorly Responsive Schizophrenic Outpatients

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Background: Nearly one third of patients suffering from schizophrenia do not fully respond to antipsychotic medication. Safe, effective, and cost-efficient methods to reduce symptoms are clearly needed; therefore, lithium as an adjunct to fluphenazine decanoate was tested in a placebo-controlled trial in outpatients who were part of the Treatment Strategies of Schizophrenia (TSS) study.

Method: Forty-one patients with DSM-III schizophrenia or schizoaffective disorder were assigned to either adjunctive lithium or placebo after at least 6 months of fluphenazine decanoate treatment to stabilize symptoms had failed. The trial was designed for 8 weeks of treatment, and patients assigned to placebo could afterward be administered lithium in an 8-week, open-label study.

Results: Assessment of the intent-to-treat analysis revealed no significant differences in demographic variables between the lithium and placebo groups. Although both groups showed significant ($p = .00135$) improvement as measured by total scores on the Brief Psychiatric Rating Scale (BPRS), there were no significant differences in response between the lithium and placebo groups. Patients originally treated with placebo added to neuroleptic did not have significantly greater improvement when receiving open-label adjunctive lithium.

Conclusion: Although success with lithium augmentation therapy for persistent psychosis has been reported in the past, this study of well-characterized patients showed no benefit for this common strategy, thus indicating that care be used in utilizing lithium augmentation.

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Lithium and matching placebo capsules for the trial were provided by Ciba-Geigy Corporation. Fluphenazine decanoate was provided by Bristol Myers Squibb Company.

The results of the study have been presented in poster format at the American College of Neuropharmacology (ACNP) 31st Annual Meeting, December 14–18, 1992, San Juan, Puerto Rico, and the New Clinical Drug Evaluation Unit (NCDEU) meeting, June 3, 1993.

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Since the introduction of antipsychotic medications, there has been a recognition that not all patients are responsive. A review of the clinical trials reveals that 32% of patients were classified as poor responders in the 1950s.[1] The early National Institute of Mental Health (NIMH) studies of the efficacy of antipsychotic medications revealed that, although antipsychotic medications were more effective than placebo, approximately 30% of patients assigned to antipsychotic medication had "worsening," "no change," or "minimal improvement."[2] More recent reports examining pharmacologic treatment response have concurred with these rates.[3,4] In addition to persistent illness, poor response to antipsychotic medication poses other significant problems. Limited response to antipsychotic medication may be an important factor in long-term outcome.[5,6] In addition, clinicians indicate that poor pharmacologic response may be a factor in use of health resources and homelessness.

Poor response has been approached by a number of pharmacologic strategies. The earliest approaches focused on dosing and compliance.[7] Although clinical intuition may have indicated that more medicine or increased speed of delivery of medicine would improve outcome, studies of high doses,[8] or rapid "neuroleptization,"[9,10] did not prove to be more effective for schizophrenic patients in general or for nonresponders. Dose-lowering approaches based on notions of a therapeutic window have been reported to be useful for some[11] and have been credited for lowering the amount of antipsychotic medications used in routine treatment. Although dose-lowering strategies have been credited with improving quality of life and diminishing side ef-

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fects, there have not been trials demonstrating the effectiveness of this strategy in poorly responsive patients.

Augmentation strategies to improve responsiveness or to treat comorbid conditions such as depression or anxiety have been described for over 30 years.[1,12] However, because of concerns about the practice of polypharmacy, augmentation strategies were not vigorously pursued until the late 1970s and early 1980s. When the addition of nonneuroleptic medications was tested, the results were initially encouraging for a number of agents. Lithium was demonstrated to be a useful augmenting agent in studies that addressed the issue of poor response.[13–16] Other medications were also noted to diminish symptoms of psychosis or other psychiatric symptoms. Reserpine,[17,18] propranolol,[19–21] benzodiazepines,[12,22,23] and carbamazepine[24–26] have all been demonstrated to have an impact on refractory symptoms.

Most recently, the atypical antipsychotic medication clozapine has been demonstrated to reduce symptoms of schizophrenia in markedly ill and persistently psychotic patients.[27] However, clozapine has a number of significant side effects and requires white cell monitoring, limiting its usage in all poorly responsive patients. Expense of clozapine is also a factor, especially if other treatments are as effective. To date, there has not been a comparison of clozapine with an augmentation approach.

An opportunity to examine persistently psychotic patients arose during the conducting of the multicenter NIMH Treatment Strategies in Schizophrenia Study (TSS). During this multicenter trial of 3 different dosing strategies of fluphenazine decanoate and 2 family therapy approaches, it was noted that nearly 40% of the patients were not able to reach study-defined criteria of stabilization.[28] A treatment trial was designed to examine the usefulness of lithium added to the patients' neuroleptic regimen after specific prospective criteria for persistent illness were met.

Lithium was chosen as the augmenting agent based on an assessment of the literature at the beginning of the proposed study. Lithium had been demonstrated to decrease symptoms of psychosis and "psychotic excitement" in schizophrenic and schizoaffective patients. In addition, lithium does not have an impact on blood neuroleptic levels,[29] can be easily measured to assess the adequacy of the trial and compliance, is generally a safe medication used with neuroleptics when both are given in moderate doses,[30–32] and can be discontinued quickly at the end of a trial, unlike added benzodiazepines.[33] Also, lithium has been widely used as an augmenting agent so that the results of the current trial would be meaningful to many clinicians.

A factor to consider in augmenting strategies is the activity of each agent by itself. Lithium has been shown to decrease symptoms in patients with schizophrenia in some studies.[34,35] However, other studies[36,37] have not shown this effect. In the one study of added lithium that prospectively addressed lithium and antipsychotic synergy, Carman et al.[14] noted that patients who had responded to the combination of antipsychotic and lithium had return of symptoms when the neuroleptic was withdrawn and the patient was treated with lithium alone. Thus, results of any lithium trial would need to be interpreted in light of the mixed results of lithium monotherapy.

The significance of this lithium study compared with the previous trials includes the following:

1. The trial was conducted with patients who were persistently ill in an outpatient setting—a setting where many symptomatic patients are seen.
2. The patients in the study had received clinically significant prospective assessments and attempts at stabilization on treatment with neuroleptics (6 months or longer).
3. The schizophrenic outpatients were all treated with depot neuroleptics, thus ensuring compliance with the antipsychotic part of the trial.
4. The multicenter design provided for a larger sample than had been studied to date.

In summary, because of the large scope and substantial burden of persistent psychosis in patients with schizophrenia, a study of lithium compared with placebo in persistently psychotic schizophrenic outpatients was performed. To further address the effect of lithium, all patients who were assigned to placebo were offered the opportunity to try lithium in an open trial.

METHOD

Subjects

The patients were seen at the 5 sites participating in the NIMH TSS study. The sites were (1) Cornell University Medical College/Payne Whitney Clinic, (2) Emory University/Grady Memorial Hospital, (3) Long Island Jewish Medical Center/Hillside Hospital, (4) Medical College of Pennsylvania at Eastern Pennsylvania Psychiatric Institute, and (5) University of California San Francisco/San Francisco General Hospital. Patients in the lithium study were in outpatient sections, and their treatment was overseen by TSS investigators. They were assessed by the Structured Clinical Interview for DSM-III–Psychotic Disorders Version (SCID-PD)[38] at their entry into TSS and again upon referral to the lithium study. Any subject who did not meet criteria for schizophrenia or for schizophreniform or schizoaffective disorder immediately prior to the lithium study was not included. Patients entered the lithium study in the following 4 ways:

1. The design of the TSS study called for patients to be "stabilized" before entry into the trial of medi-

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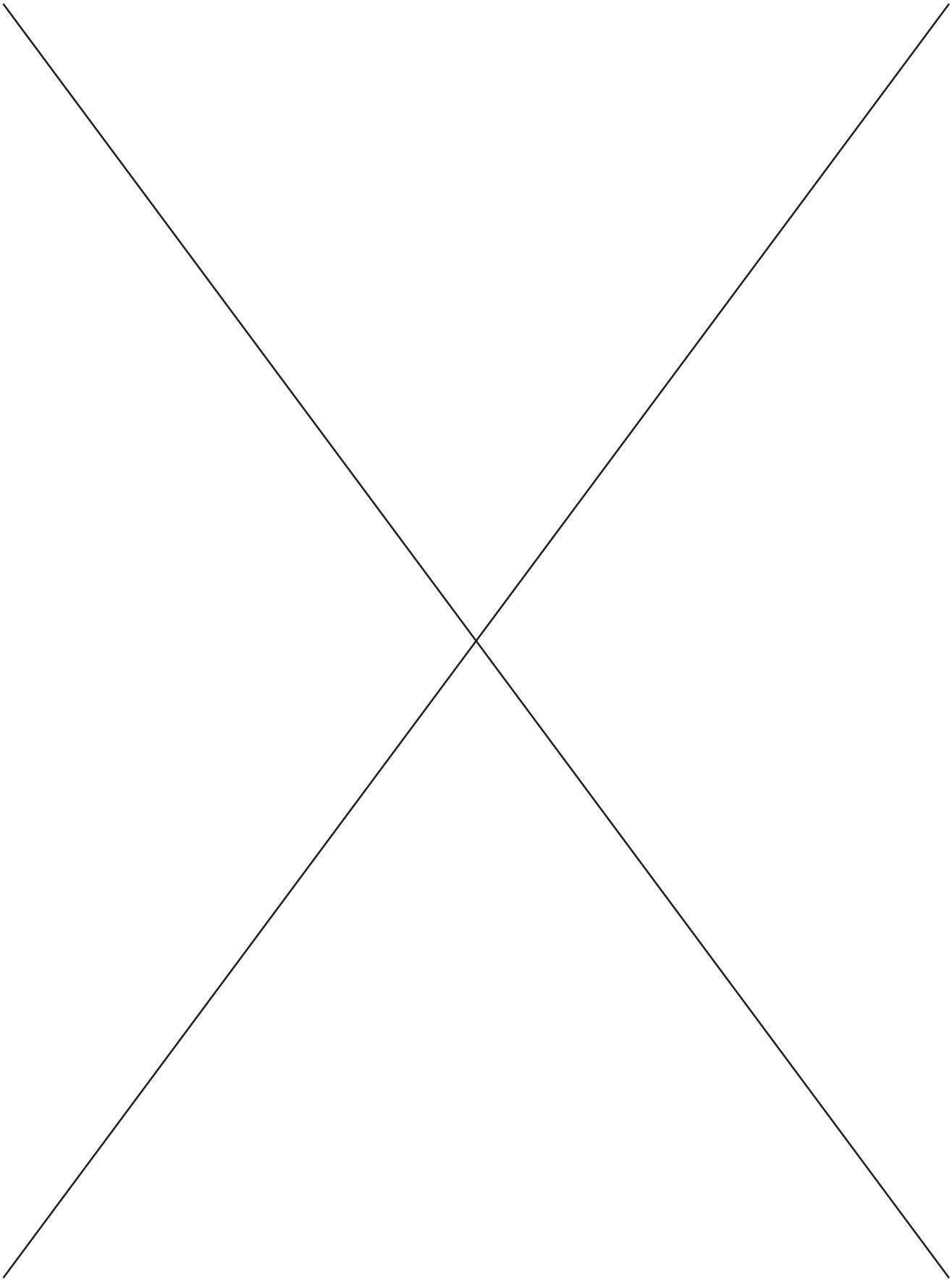

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cation dosing strategies and family treatments. The TSS protocol called for initial assessment followed by up to 6 months of treatment with fluphenazine decanoate with the goal of patient stabilization. Patients were eligible for the lithium study if they failed to fulfill TSS stabilization criteria. This a priori stabilization criteria included the following: stable dosage of fluphenazine decanoate 12.5 to 50 mg every 2 weeks for 4 weeks, without the use of other antipsychotic medication or psychotropic medications; stable psychotic symptoms on the Brief Psychiatric Rating Scale (BPRS) for 4 weeks; no psychotic symptom (conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content) greater than "moderate."

2. During the TSS study, subjects who became symptomatic received open-label antipsychotic medication. If they were not stabilized after 140 days, they were considered as nonstabilized and eligible for the lithium study. Nonstabilization was considered to be:
   a. "Moderate" or worse on hallucinatory behavior, unusual thought content, grandiosity, or
   b. "Moderate" or worse on conceptual disorganization or suspiciousness.
3. Subjects in the TSS study who were not stable by the "140 day" criterion at the end of the 2-year study were also eligible for the lithium trial.
4. After the blind, controlled trial, patients who had been assigned to placebo were offered the opportunity to participate in an open, 8-week trial of lithium.

After complete description of the study to the subjects, written informed consent was obtained.

Design

The study examined the effect of lithium added to fluphenazine decanoate in a double-blind, placebo-controlled trial lasting 8 weeks. Following the 8 weeks, patients assigned to placebo had the opportunity to try lithium added to neuroleptic in an open trial for 8 weeks. Fluphenazine decanoate doses were stabilized for 1 month prior to the addition of lithium and were held constant during the augmentation phase. Patients who required greater than 75 mg every other week were not eligible for the study to avoid the possibility of lithium/antipsychotic side effects. Subjects were administered 900 mg/day of lithium or placebo in a 1-week supply blister pack. A nonblinded physician assessed side effects and monitored lithium levels. Changes in dosage of lithium were based on patient examination results and lithium levels. The nonblinded physician aimed for lithium levels to be maintained between 0.8 and 1.0 mEq/L. Compliance was assessed by the weekly determinations of lithium levels.

Table 1. Demographic Information

Variable	Treatment Group	
	Placebo	Lithium
Sex, M/F	17/3	17/4
Diagnosis, schizophrenia/ schizoaffective disorder	16/4	15/6
Age, y, mean ± SD	30.6 ± 9.2	28.3 ± 6.5

Assignment to lithium or placebo was randomized, but stratified to account for gender differences and differences between schizophrenia and schizoaffective illness groups.

Clinical Assessments

Baseline assessments and weekly assessments of symptoms were performed by a blinded psychiatrist and study nurse. The assessment tools utilized included the following: (1) the BPRS,[39] (2) the Hamilton Rating Scale for Depression (HAM-D),[40] (3) the Clinical Global Impressions scale (CGI),[41] and (4) the Simpson-Angus Neurologic Rating Scale.[42] Side effects were also measured using the Scale for Assessment of Treatment Emergent Events (SAFTEE).[43]

Statistical Analysis

The study analysis is a split-plot analysis of variance (ANOVA) (SAS Institute Inc., SAS/STAT User's Guide, Version 6.03, Cary, N.C., 1988), with a within-subject factor of time (BPRS scores at baseline and endpoint) and a between-subjects factor of drug (BPRS scores for placebo and lithium).[44] The data for the double-blind, placebo-controlled trial were examined using both an intent-to-treat approach[45] and a completer analysis. The data for the open lithium trial were examined in a repeated-measures ANOVA. Means were calculated using all valid values. When missing items for the BPRS were found, a subscale score was calculated only when more than half of the appropriate items were present.

RESULTS

Table 1 presents descriptive demographic information for the 2 treatment groups. It is clear from Table 1 that the groups do not differ on these variables, thus confirming the usefulness of the strategy of stratification by gender and diagnosis.

The means and standard deviations of the BPRS scores for the intent-to-treat placebo- and lithium-treated groups are shown in Table 2. As seen in Table 2, patients in both the placebo and lithium groups were severely ill at the start of the trial.

Main Analysis

The main question addressed in the experiment is, Do scores on the BPRS and other measures of psychopathol-

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Table 2. Brief Psychiatric Rating Scale (BPRS) Total and Subscale Scores for Intent-to-Treat Sample[a]

	Treatment Group			
	Placebo (N = 20)		Lithium (N = 21)	
Score	Baseline	Endpoint	Baseline	Endpoint
BPRS Total	47.26 ± 9.89	44.69 ± 12.39	46.58 ± 10.07	42.74 ± 15.19
BPRS subscales				
Negative	9.16 ± 3.34	8.05 ± 3.66	9.52 ± 3.44	9.33 ± 3.28
Positive	14.11 ± 4.36	12.70 ± 5.24	14.62 ± 4.52	12.84 ± 6.28
Conceptual disorganization	3.84 ± 1.54	3.80 ± 1.28	4.29 ± 2.12	4.15 + 2.03

[a]All scores reported as mean ± SD. Individual items included in BPRS subscales are as follows: negative (items 3, 13, 16, and 18), positive (4, 11, 12, and 15), conceptual disorganization (4 and 18).

Table 3. BPRS Total and Subscale Scores for Completer Sample[a]

	Treatment Group			
	Placebo (N = 9)		Lithium (N = 7)	
Score	Baseline	Endpoint	Baseline	Endpoint
BPRS Total	50.47 ± 8.98	42.97 ± 12.77	45.82 ± 9.40	47.02 ± 16.42
BPRS subscales				
Negative	9.75 ± 4.23	8.22 ± 4.06	10.57 ± 3.78	10.14 ± 4.10
Positive	15.00 ± 4.11	13.00 ± 6.14	13.57 ± 4.08	14.00 ± 6.51
Conceptual disorganization	3.88 ± 1.81	3.89 ± 1.45	4.29 ± 2.69	3.83 ± 2.14

[a]All scores reported as mean ± SD.

Table 4. BPRS Scores and Factors: Comparing Patients Scores During Their Controlled-Trial Placebo Condition With Those During Open Lithium Treatment

	Treatment Group			
	Placebo (N = 14)		Lithium (N = 13)	
Score	Baseline	Endpoint	Baseline	Endpoint
BPRS Total, mean ± SD	47.66 ± 9.66	45.13 ± 11.29	46.70 ± 10.93	42.19 ± 10.88

ogy change differentially for lithium and placebo over time? To examine this question, the interaction was examined in the split-plot analysis for BPRS total score. No significant interaction was present ($F = 0.23$, $df = 1,39$; $p = .6360$). Similarly, there was no difference between groups ($F = 0.01$, $df = 1,39$; $p = .9177$). No differences between the lithium and placebo groups were found for BPRS subscales (positive, negative, conceptual disorganization, paranoid disturbance, thought disorder, withdrawal-retardation, anxiety-depression) or any of the 18 individual items of the BPRS. Therefore, lithium did not produce a change which is different from that produced by placebo. BPRS total scores did significantly improve for both the placebo group and the lithium group over time ($F = 6.70$, $df = 1,39$; $p = .0135$), as seen in Table 2. Significant improvements were found for the positive and anxiety-depression subscales as well. Thus, subjects improved over time in both groups. Figure 1 portrays individual changes for both conditions.

Since all patients did not complete the trial (9 of 20 completed placebo treatment; 7 of 21 completed lithium treatment), it is important to consider whether completion affected the outcome. When completion was considered as a between-subjects factor, no effects involving this factor were significant for BPRS total score (completion × drug × time: $F = 2.21$, $df = 1,37$; $p = .1457$; completion: $F = 0.94$, $df = 1,37$; $p = .3389$). Thus, no differences associated with completion were important or statistically significant. When the mean values for only the patients who finished the entire trial were considered (Table 3), the patients in the lithium group had higher BPRS total scores at endpoint. The interaction between drug and time was not significant for this subgroup ($F = 1.91$, $df = 1,14$; $p = .1886$), nor were there significant time ($F = 1.00$, $df = 1,14$; $p = .3336$) or drug ($F = 0.01$, $df = 1,14$; $p = .9260$) effects. Thus, completing the trial did not have a significant effect on the manifest psychopathology as measured by BPRS total score.

Compliance to the medical regimen was assessed for patients in the lithium group by weekly blood lithium level assessments. Recall that the nonblinded psychiatrist adjusted dose to blood levels during the trial. Patients who had a weekly lithium value of 0.8 mEq/L were considered fully compliant. The patients judged compliant to regimen (N = 12) were compared with patients who were judged noncompliant (N = 9) for the lithium group. The time-by-compliance interaction (examining BPRS total score) was not significant ($F = 1.42$, $df = 1,19$; $p = .2483$). In comparing the compliant and noncompliant cases, the overall difference between groups was not found to be significant ($F = 0.34$, $df = 1,19$; $p = .5652$). The difference over time was not significant in this comparison as well, which involved only the lithium-treated cases ($F = 1.84$, $df = 1,19$; $p = .1912$).

After the completion of the blinded trial, patients randomly assigned to the placebo condition were given the opportunity to enter an open lithium trial. Of the 20 patients who started in the placebo condition, 14 chose to enter the open lithium trial (9 had completed the blinded trial), and a final rating was obtained for 13 of these. Mean values for the comparison are given in Table 4, which demonstrates that the lithium condition does show some improvement.

Data for patients who completed the open trial of lithium were compared, in a repeated-measures design, with data from the placebo condition of the blinded trial for these same patients. There was no drug-by-time interaction ($F = 0.11$, $df = 1,12$; $p = .7439$); that is, there is no

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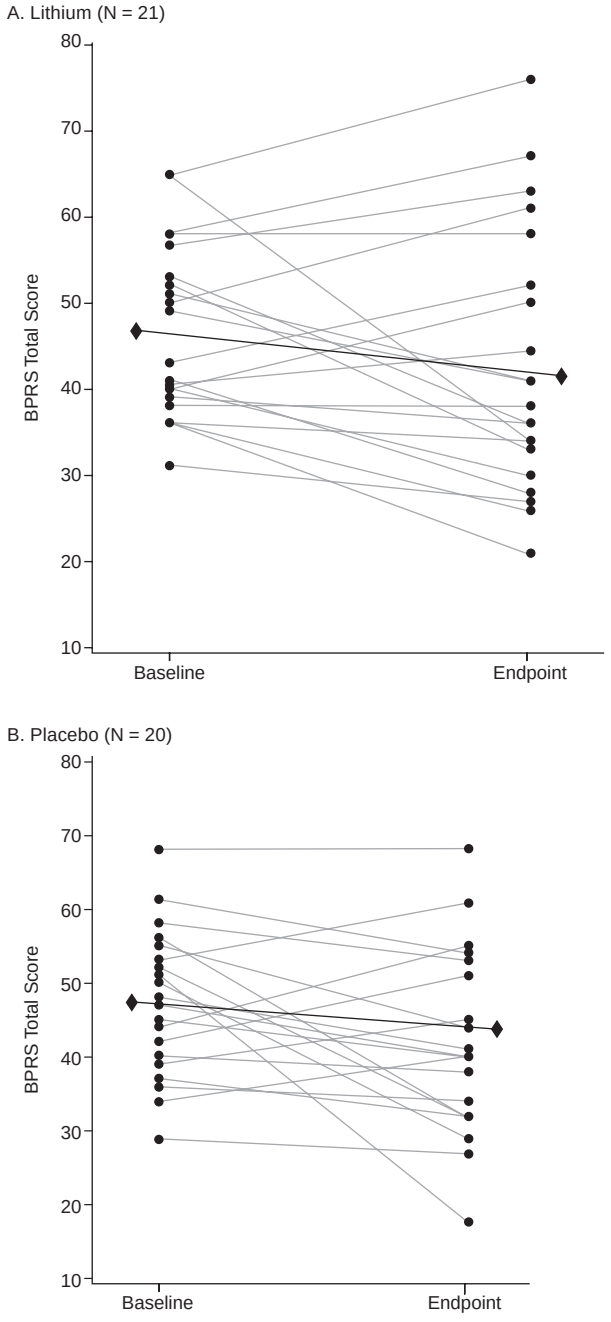
Figure 1. Change in BPRS Total Score for Intent-to-Treat Patients Taking Either Lithium or Placebo[a]



[a]Diamonds represent group means. The lines connecting the points do not indicate rate of change, but merely link baseline and endpoint for each individual. There was no significant difference between the 2 treatment conditions, although scores for some individual patients in both groups changed substantially.

difference in the change in BPRS total score over time between lithium and placebo conditions. There is a time difference ($F = 5.02$, $df = 1,13$; $p = .0432$) and a drug difference ($F = 2.21$, $df = 1,13$; $p = .1609$). However, there is no evidence that the lithium condition provides a significantly greater improvement over time than the placebo condition.

The antidepressant effects of lithium in schizophrenia have been reported.[34] The values for HAM-D were examined for the subjects, for cases with both baseline and endpoint values. Mean ± SD values at baseline (placebo: 42.01 ± 9.04, N = 20; lithium: 42.2 ± 8.7, N = 21) were quite similar, while mean values at endpoint (placebo: 37.1 ± 7.9, N = 9; lithium: 40.5 ± 13.2, N = 7) were only slightly lower for lithium. Examining the differences using a split-plot ANOVA for complete case, there is neither a significant difference between lithium and placebo groups in change in HAM-D score over time ($F = .67$, $df = 1,36$; $p = .42$), a time effect ($F = 3.28$, $df = 1,36$; $p = .0786$), nor an interaction ($F = .90$, $df = 1,36$; $p = .3503$). In examining the groups separately, neither shows a significant difference in HAM-D score over time (using a simple main effects approach; placebo: $F = 3.66$, $df = 1,36$; $p = .0636$; lithium: $F = .51$, $df = 1,36$; $p = .4806$).

DISCUSSION

This study was the first to assess the possible efficacy of lithium in poorly responsive schizophrenic patients in an outpatient setting. It is also the largest number of patients to be studied in a double-blind, placebo-controlled trial of lithium. As lithium is in wide use in clinical practice, the investigators were surprised that there was no statistically significant advantage compared with placebo. There are several possible reasons for these results.

The first conclusion is that the medication is not effective in this patient group. Recently, 2 other studies have examined lithium augmentation and have found similar results. Wilson[46] reported that for patients studied in a state hospital inpatient setting, lithium was not superior to placebo. Wilson surmised that patients may receive lithium during the course of treatment before they find their way into a state hospital setting. Thus, he reasoned, all potential lithium augmentation responders would be eliminated. He indicated that one strategy to assess this issue would be to attempt a lithium withdrawal study in patients who were currently taking the combination of neuroleptic and lithium. Collins et al.[47] examined the effects of lithium in a single-blind study of inpatients in a maximum security setting. No differences were seen between the lithium group and the control group, thus adding to the data that lithium augmentation may not, in contrast to previous thought, be efficacious.

Secondly, patients were not fully compliant with their medication as evidenced by the lithium level data. Interestingly, there was not a greater improvement in the lithium compliant patients than in the placebo group. The outpatient nature of this trial carries importance in that it parallels clinical practice in most clinics. That many pa-

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tients are not fully compliant with a medication taken twice daily for 8 weeks is not surprising.

Thirdly, it may be hypothesized that previous positive studies were performed in an era when diagnostic precision was not as accurate as when this study was performed. However, examination of the earlier articles reveals that Feighner criteria[16] and Research Diagnostic Criteria[14,15] were used to make the assessments of patients in the studies. These criteria are generally acknowledged to be reliable between diagnosticians and not overly inclusive of bipolar patients in the schizophrenic category. Therefore, we do not think that changes in the diagnostic habits of clinical investigators explain the differences between earlier papers and this report.

In addition, although the current study is the largest placebo-controlled trial of lithium augmentation, there could be a question about whether enough subjects were studied to prove the null hypothesis (that lithium is no better than placebo). Determining effect sizes from previous studies is difficult because of their preliminary report nature (e.g., amount of change and variance not included).[14,16] However, if one were to assume that a 20% (9 points) decrease in BPRS total score would indicate medication activity and that a small placebo change (2 points) could be present, a large study (N = 50) would be required to achieve 0.79 power (under 1-tailed condition with standard deviation of 10). Therefore, this study by itself does not completely refute the lithium augmentation hypothesis.

Lastly, the patients who participated in the study were told whether they received placebo or lithium at the conclusion of the study, and the patients who were taking placebo were then given the opportunity to try lithium in an open-label fashion (again, without substantial benefit). Although FDA policy would indicate that the blind not be broken, our research group wanted to assure participants that if they participated in this placebo-controlled lithium augmentation study, they would at some point receive a lithium trial. Breaking the blind and administering lithium to patients who received placebo is a straightforward manner to accomplish these goals. The downside of this method is that investigators will determine which patient is in which condition and the results will be biased. In addition, some have suggested that if the blind is broken and patients on active treatment are not doing well, enrollment may cease. Our group did not see evidence of either of these issues.

At the time this study was designed, clozapine was not yet available, but its promise was known. It was reasoned that augmentation may perhaps play a role in the overall strategy of treating the persistently psychotic patient. Wilson,[46] in his discussion, notes that clozapine was effective in a number of patients at the state hospital where a lithium trial was conducted. He concluded that there may not be a role for lithium augmentation in the evaluation of patients for clozapine treatment. Some patients who were nonresponsive in this study went on to receive clozapine with significant benefit.

Considering the above, why is lithium in such common use as an augmenting agent? Perhaps mild reductions in some symptoms reinforce lithium use. In this study, there was a decrease in some individual symptoms that if seen in an uncontrolled trial might indicate usefulness (e.g., paranoia, depression). Other, nonspecific factors, such as sedation or the possible need of patients and psychiatrists to keep trying to decrease symptoms, could play a role in continued use of lithium augmentation. It should be noted that there was a decrease of symptoms for the placebo group, indicating that in the short term (8 weeks) there can be a response to any intervention, thus underscoring the importance of placebo control in this study.

In conclusion, there have recently been 2 negative reports about the effect of lithium augmentation in schizophrenic patients,[46,47] to which is added this study of outpatients. The results of these recent studies are in contrast to the earlier reports from 1975 through 1981. The reasons for the apparent change in results is not apparent and suggests that further assessment of the role of lithium in schizophrenia needs to be addressed. However, current data suggest that clinicians should use caution in the use of this strategy. This is all the more important as newer agents with potential for treating the persistently ill patient are developed.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril), propranolol (Inderal and others), reserpine (Serpasil and others).

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