ORIGINAL ARTICLE

A Double-Blind Placebo-Controlled Study of Lithium in Hospitalized Aggressive Children and Adolescents With Conduct Disorder

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Background: A subgroup of children and adolescents with conduct disorder are characterized by severe and persistent aggression. Although there is no agreed on treatment for such aggression, lithium carbonate has shown promise in some studies involving children. Our study was designed to critically assess the efficacy of lithium in the treatment of aggression in children and adolescents using a measure specific for aggression.

Methods: Subjects were inpatients with conduct disorder hospitalized because of severe and chronic aggression. A parallel-groups design was used in this double-blind, placebo-controlled trial with randomization to lithium or placebo. Only those who met the aggression criterion during the 2-week placebo-baseline period were randomized to 4 weeks of treatment. Outcome measures included Clinical Global Impressions, the Global Clinical Judgements (Consensus) Scale, and the Overt Aggression Scale.

Results: Eighty-six inpatients enrolled in the study; 40 (33 male and 7 female; median age, 12.5 years) entered and completed the treatment phase. Lithium was statistically and clinically superior to placebo. Sixteen of 20 subjects in the lithium group were responders on the Consensus ratings vs 6 of 20 in the placebo group ($P=.004$). Ratings on the Overt Aggression Scale decreased significantly for the lithium group vs the placebo group ($P=.04$). More than half of the subjects in the lithium group experienced nausea, vomiting, and urinary frequency.

Conclusions: Lithium is a safe and effective short-term treatment for aggression in inpatients with conduct disorder, although its use is associated with adverse effects.

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AGGRESSION in children and adolescents is common and a major public health concern.[1-5] It is generally accepted that aggression in childhood predicts poor prognosis[6-11] and serious antisocial behavior in adulthood.[7,12] A subgroup of children and adolescents with conduct disorder exhibit aggression that is severe and persistent.[13-18] Various treatments, psychopharmacological and behavioral, have been studied in this population,[19-21] but there is no generally accepted effective treatment. Of the psychoactive agents, antipsychotics may reduce aggression, but use is limited by sedation and extrapyramidal side effects, including tardive dyskinesia,[19,22-24] and controlled studies of stimulants are not in agreement regarding efficacy.[25-31]

Lithium carbonate has shown promise for reducing aggressive behavior in animals and humans.[32] Findings are mixed regarding its efficacy in children and adolescents. In 2 major double-blind, placebo-controlled studies,[22,33] lithium yielded a clinically and statistically significant reduction of aggression. Other studies yielded negative results: one in adolescent inpatients[34] and the other in outpatients, aged 6 through 15 years.[30]

Our study critically assessed the safety and efficacy of lithium for reducing aggression in inpatients with conduct disorder, aged 10 through 17 years. In a different setting, it studied an older sample than the recent studies of Campbell and associates[22,33] and added a specific measure of aggression, the Overt Aggression Scale (OAS).[35]

RESULTS

CHARACTERISTICS OF THE TREATMENT GROUPS

Eighty-six inpatients enrolled in the study. Of these, 46 (53%) dropped from the study after the baseline period. Forty patients (87%) dropped for not meeting the ag-

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SUBJECTS AND METHODS

SUBJECTS

The study was conducted in the acute-care child and adolescent psychiatric inpatient service that had a behaviorally oriented milieu, in a teaching hospital. We included male and female patients aged 10 through 17 years with a *DSM-III-R* diagnosis of conduct disorder.[36] All were admitted to the hospital with histories of severe aggression, often resistant to previous treatment. The diagnosis of conduct disorder was made by consensus of 2 board-certified child psychiatrists (R.P.M. and J.F.L.), after they had independently examined the subject. The Diagnostic Interview for Children and Adolescents–Revised[37] was administered by trained interviewers to verify diagnoses. Excluded were patients with the following disorders: mental retardation, pervasive developmental disorder, major depressive disorder or dysthymic disorder, bipolar disorder, any psychotic disorder, and substance dependence in the previous month. Also excluded were patients who were pregnant, received psychoactive medication within 2 weeks of the study, had a previous lithium trial, or had major medical problems including cardiac, renal, thyroid, or seizure disorders. Written informed consent was obtained from guardians and assent from all subjects.

DESIGN

This was a 6-week, double-blind, placebo-controlled trial with a parallel-groups design. After a 2-week, single-blind placebo baseline period, subjects meeting the study criterion for aggression were randomized to 4 weeks of double-blind treatment with lithium or matching placebo. The purpose of the baseline period was to (1) allow for stabilization of behavior, (2) eliminate possible placebo-baseline responders, and (3) provide for frequency and severity ratings of aggression.[38] Randomization was performed by the research pharmacist with the use of a computer-generated schedule. The blind was broken for each subject after final ratings were completed.

The aggression criterion for randomization to treatments was based on the OAS ratings from the 2-week baseline period. To meet the criterion, a subject had to demonstrate a weekly minimum of 3 aggressive acts, 2 of which were physical aggression, and have a mean weekly OAS severity score of at least 18 points.[39] This criterion was based on our previous experience with the OAS in this population.[40] Those who did not meet the aggression criterion at the end of baseline were not assigned to the treatment phase of the study.

MEDICATION

Initial lithium dosages were determined by means of the prediction method of Cooper and colleagues[41,42] and Malone et al.[43] At baseline, each subject was given a single dose of lithium carbonate, 600 mg, and a 24-hour serum lithium level was obtained. The serum lithium level, in combination with the nomogram of Cooper and colleagues,[41] was used to determine the initial target dosage. Similar dosage strategies were used for lithium and placebo groups. Initial medication dosage was 600 mg/d and was increased by 300 mg/d to the initial target dosage. Medication was administered in 3 equally divided doses. Final medication dosages were individually titrated between 300 and 2100 mg/d, with the aim of obtaining a steady state therapeutic level of 0.8 to 1.2 mmol/L and no or minimal side effects. Serum lithium levels were monitored weekly from baseline and whenever clinically indicated. All serum lithium measurements were performed at the Analytic Psychopharmacology Laboratory of the Nathan Kline Institute, Orangeburg, NY (director, Thomas B. Cooper, MA), and reported to an off-ward psychiatrist (M.A.D.) not involved in subject ratings. To protect the blind, fake serum lithium levels were given to the research team for placebo-treated subjects by means of a yoking procedure.

Subjects did not receive concurrent psychoactive medications during the study.

EFFICACY MEASURES

The primary outcome measures were the Global Clinical Judgements (Consensus) Scale (GCJCS),[22,33] the Clinical Global Impressions (CGI),[44] and the OAS.[35]

The GCJCS[22,33] is a real-life measure of change in global clinical condition by staff involved in the daily care and treatment of the subjects. At the end of the treatment period, before the blind was broken, all ward staff met to discuss each subject, comparing the subject's condition during the final week of the treatment period with that observed during the placebo baseline period. Staff consensus was reached regarding whether the subject was better, worse, or showed no change. A rating of better was further classified as slight, moderate, or marked improvement. The GCJCS has been

gression criterion; 2 patients (4%), because of discharge from the hospital; 1 patient (2%), after withdrawing consent; 1 patient (2%), because of substance dependence; 1 patient (2%), because of mental retardation; and 1 patient (2%), for not meeting conduct disorder criteria. Subjects who were dropped from the study did not differ by age, sex, race, or socioeconomic status from those who continued in the study and were randomized to treatment. Forty subjects were randomized to the treatment phase, and all completed the study. Twenty received lithium and 20 received placebo. There were no statistically significant differences between treatment groups on background variables including age, race, sex, IQ, and CGI severity of illness (**Table 1**).

The final medication dosage for subjects receiving lithium carbonate ranged from 900 to 2100 mg/d (mean ± SD, 1425 ± 321 mg/d) with corresponding serum lithium levels ranging from 0.78 to 1.55 mmol/L (mean ± SD, 1.07 ± 0.19 mmol/L). Every effort was made to ensure that subjects received medication as confirmed by serum lithium levels and pill counts.

EFFICACY RESULTS

By use of the GCJCS, subjects completing treatment were classified as responders or nonresponders. In the lithium treatment group, 16 (80%) of 20 were responders, whereas, in the placebo treatment group, 6 (30%) of 20

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useful for measuring drug effect in this population.[22,33,45] None of the staff members involved in the GCJCS completed the CGI; both measures were rated independently.

The CGI,[44] a 7-point scale, is a measure of global clinical change with the following 3 items: (1) severity of illness, (2) global improvement, and (3) drug side effects. This measure was completed by the primary investigator (R.P.M.) and a trained research assistant weekly during the baseline period and at the end of the 4-week treatment period. The intraclass correlation coefficient was 0.81 for the raters.

Subjects were categorized as responders or nonresponders on the basis of ratings from the GCJCS and, separately, from the CGI. Subjects rated as moderately or markedly improved were classified as responders. Subjects rated as worse, the same, or mildly improved were classified as nonresponders. The data were collapsed because a psychopharmacological agent should produce at least moderate improvement to be recommended for use in children and adolescents.

The OAS[35] was specifically designed to rate aggression in adults, and adolescents and children. It measures the frequency and severity of the following 4 categories of aggression: (1) verbal aggression, (2) aggression against objects, (3) self-directed aggression, and (4) aggression against others. The OAS has been shown to measure drug effect in studies of aggression in children and adolescents.[40,46] The reliability of the OAS has been established with intraclass correlation coefficients ranging from 0.50 to 0.97 for verbal aggression and 0.72 to 1.00 for physical aggression.[35] Aggressive acts were recorded on the OAS by trained nursing staff (each shift, 24 h/d) during the 2-week baseline period and throughout the study.[40] The OAS ratings were monitored by comparing ratings with the staff notes in the subject's clinical chart. Any discrepancies with the chart were rectified by interviewing staff who observed the aggressive event.

SAFETY MEASURES

Height was measured on day 1 of the baseline period. Blood pressure and pulse rate were measured daily, and weight was measured weekly at a fixed time. Side effects were monitored daily using the Dosage Record and Treatment Emergent Symptom Scale,[47] Treatment Emergent Symptoms Scale,[47] and Lithium Untoward Effect Checklist.[48] When potential side effects occurred, the dosage of study medication was reduced.

The following laboratory studies were obtained at baseline and repeated at the end of treatment and whenever indicated: complete blood cell count with differential, liver enzyme studies, thyroid studies, levels of electrolytes, serum urea nitrogen, and creatinine, urine osmolality, urinalysis, serum pregnancy in menstruating female subjects, and electrocardiography.

STATISTICAL ANALYSIS

Two-tailed significance levels of .05 were used for all statistical tests. All statistical analyses were conducted with the use of SAS software (SAS Institute Inc, Cary, NC). When multiple raters were used for a given measure, the subjects' scores were computed as the average of the ratings.

Preliminary descriptive and univariate analyses of baseline data from both groups were conducted, including means, medians, and SDs for continuous variables and frequency counts with percentages for discrete variables. Treatment group differences at baseline were assessed by *t* tests and Wilcoxon rank sum tests for continuous variables and Fisher exact tests for discrete variables. For the main GCJCS and CGI efficacy variables, Fisher exact test was used to determine differences between treatment groups.

Background variables (including age, race, sex, IQ, and baseline scores for the CGI severity of illness) were considered as possible covariates in subsequent multivariate analyses for the main efficacy outcomes on the GCJCS and CGI measures. A stratified Cochran-Mantel-Haenszel test was used for discrete covariates (such as race) and a stratified logistic regression for the continuous covariates. The advantage of using the former test is that it can be used even when there are zero cells to compute a stratified odds ratio (OR).[49]

For the OAS efficacy measure, a mixed-model analysis of variance (ANOVA) was used to determine whether changes from baseline to weeks 1, 2, 3, and 4 in the OAS scores were significantly different between groups. In essence, the design was a 2×5 (treatment group $\times$ time) factorial, with repeated measures on the last factor. The treatment group factor was modeled as a fixed effect; the time variables were considered as a random factor. The covariance structure that resulted in the smallest Akaike information criterion statistic was chosen for the final model.[50] The Fisher exact test was used to compare differences in each untoward effect between the lithium and placebo groups, considering the relatively small sample size of our study for any safety analysis.

were responders. The difference between groups was statistically significant (Fisher exact test, $P = .004$). The OR for the GCJCS of 9.3 (95% confidence interval [CI], 2.2-40.0) indicated that a subject was more than 9 times as likely to be a responder in the lithium group compared with the placebo group. The **Figure** shows the distribution of subjects' outcome scores for the GCJCS.

Using the CGI, subjects were classified as responders or nonresponders. In the lithium treatment group, 14 (70%) of 20 were responders. In the placebo treatment group, 4 (20%) of 20 were responders. The difference between groups was statistically significant (Fisher exact test, $P = .004$). The OR for the CGI of 9.3 (95% CI, 2.2-40.0) indicated that a subject was more than 9 times as likely to be a responder in the lithium group compared with the placebo group.

To identify whether any of the background variables (including age, race, sex, IQ, and baseline scores for CGI severity) were potential confounders of the treatment difference between placebo and lithium for the GCJCS or the CGI outcome measures, each covariate was entered one at a time into a 2-variable model along with treatment group. Unadjusted ORs for the GCJCS and CGI were compared with ORs adjusted for each of the potential covariates (when entered into a bivariable model). Results indicated that none of the factors appreciably attenuated the effect of treatment on outcome, as the OR for the placebo vs lithium groups did not change appre-

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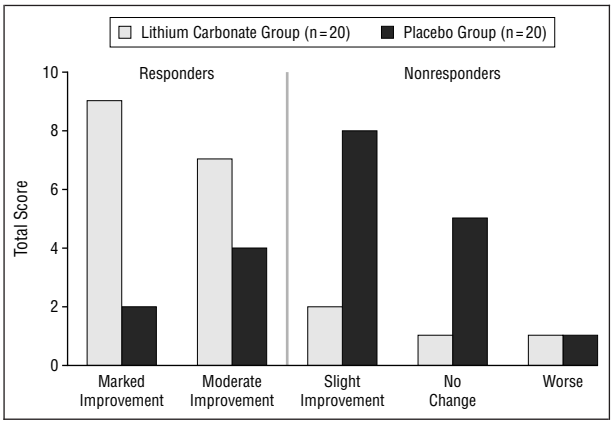
Table 1. Comparison of Each Covariate by Treatment Group*

Covariate	Treatment Group: Placebo (n = 20)	Treatment Group: Lithium Carbonate (n = 20)	P†
Age, mean (SD), y	12.3 (1.1)	12.6 (2.0)	.54
Race			
African American	12	16	.55
White	3	1	
Hispanic	5	3	
Sex			
Male	16	17	>.99
Female	4	3	
Socioeconomic status‡			
Class I-IV	4	7	.27
Class V	16	13	
IQ, mean (SD)	81.4 (9.7)	87.9 (12.2)	.14
CGI severity of illness, mean (SD)	5.4 (0.8)	5.5 (0.7)	.60

*Unless otherwise indicated, data are given as number of subjects. CGI indicates Clinical Global Impressions scale.
†Determined using Fisher exact test, 2 tailed.
‡From Hollingshead.[51]



Global Clinical Judgements (Consensus) Scale ratings.

ciably when adjusted for each covariate. When adjusting for one other covariate in a bivariable model, the OR estimate for lithium vs placebo group ranged from 7.5 for race to 11.2 for CGI severity score.

The mixed-model ANOVA showed similar results for the OAS. Table 2 contains the descriptive statistics for the mean changes in OAS total severity scores from baseline to each of weeks 1, 2, 3, and 4 by treatment group. By week 4, the mean (SD) decrease from baseline in the placebo group was –1.17 (4.15) compared with –2.40 (2.44) for the lithium group.

The difference in the mean decrease from baseline between groups was statistically significant, as indicated by the significant interaction between treatment group and time in **Table 2** ($F_{1,119}$=4.14; P=.04). The initial decrease seen in the placebo group at week 1 remained fairly constant during the 4-week period, whereas the lithium group continued to exhibit decreasing OAS aggression levels during the 4-week period (data not shown).

Table 2. Mean Changes in OAS Total Severity Score by Treatment Group*

Treatment Group, wk	OAS Total Severity Score, Mean (SD)	Change From Baseline, Mean (SD)†
Placebo (n = 20)		
Baseline‡	5.84 (2.58)	. . .
1	4.38 (3.10)	–1.26 (2.80)
2§	4.02 (2.48)	–1.46 (2.80)
3	4.39 (3.53)	–1.09 (3.25)
4	4.31 (4.26)	–1.17 (4.15)
Lithium carbonate (n = 20)		
Baseline‡	4.69 (2.43)	. . .
1	4.03 (2.53)	–0.67 (2.25)
2	3.12 (2.08)	–1.57 (1.78)
3	2.72 (2.30)	–1.98 (1.97)
4	2.29 (2.65)	–2.40 (2.44)

*Total severity scores are mean score per day per week. OAS indicates Overt Aggression Scale.
†Significant effects from analysis of variance include main effect for time ($F_{1,38}$ = 31.76; P<.001) and treatment by time interaction ($F_{1,119}$ = 4.14; P = .04).
‡Baseline data are the average for the 2 weeks in the baseline period.
§For week 2 of treatment, n = 19 because of missing data for 1 patient.

Table 3. Untoward Effect Associated With Lithium and Placebo

Adverse Effect	Treatment Group, No. of Subjects: Lithium Carbonate (n = 20)	Treatment Group, No. of Subjects: Placebo (n = 20)	P
Increased thirst	12	8	.34
Nausea	12	5	.05
Vomiting*	11	4	.048
Urinary frequency*	11	4	.048
Tremor (moderate)	5	1	.18
Stomachache	7	2	.13
Headache	6	5	>.99
Diarrhea	4	0	.11
Vertigo	3	1	.61
Rash	3	0	.23
Nocturnal enuresis	1	1	>.99
Weight gain	17	16	>.99
Weight loss	3	4	>.99
Other†	7	3	.27
Any adverse effect	20	17	.23

*P<.05, Fisher exact test, 2 tailed.
†Includes constipation, decreased appetite, sore throat, muscle pain, painful urination, twitching, depression, or weakness.

SAFETY MEASURES

No subject dropped from the study because of lithium-associated side effects. Of the side effects, only nausea, vomiting, and urinary frequency were more frequently associated with lithium than with placebo (**Table 3**). Weight gain was similar for both groups. The placebo group gained a mean of 1.9±2.7 kg (4.2±6.0 lb); and the lithium group, 1.6±1.7 kg (3.5±3.7 lb). There were no abnormalities of vital signs. One subject treated with lithium had increased liver enzyme levels at the end of the treatment period.[52]

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COMMENT

In our study, lithium was effective for reducing aggression in child and adolescent inpatients. This was found on a specific measure of aggression (OAS) and on more global measures (GCJCS and CGI). The OAS documented that aggression improved significantly in the lithium group but remained unchanged in the placebo group. The global measures also demonstrated overall clinical improvement, including reduced aggression. The GCJCS and CGI showed similar efficacy. The hospital treatment team and the researchers independently agreed that lithium was effective.

Our study, in a different clinical setting (city vs university hospitals) and using subjects with a wider age range, replicated the findings of Campbell and associates[22,33] regarding efficacy, safety, dosage, and serum lithium levels. Replication decreases the likelihood that findings are the result of biased sampling or study design and increases the possibility that findings will be generalizable outside the study sample. Subjects in the above studies[22,33] were younger (5.1-12.9 years) than those in our study (9.5-17.1 years); daily lithium carbonate doses (500-2000 mg/d) were similar to our range of 900 to 2100 mg/d.

Although our findings in inpatients agree with those of Campbell and associates[22,33] (also inpatients), they disagree with a report involving adolescent inpatients[34] and a report involving children and adolescents who were outpatients.[30] It is conceivable that the differing results are a function of study design and/or patient samples. The study by Rifkin et al[34] had a short treatment period (2 weeks), probably insufficient for a full therapeutic effect for lithium.[53] The subjects in the Klein study[30] were all outpatients and likely had less severe, less explosive aggression than our subjects, and there was no clear description of an aggression criterion for entering treatment. We eliminated many placebo responders after a 2-week baseline period, whereas it does not appear that this was true for the Klein study.[30]

To date, the only controlled outpatient trials of lithium for aggression in children have yielded negative results[30] or have involved small numbers of subjects.[54,55] The single long-term controlled study (N=11) reported equal improvement in the lithium and placebo groups.[54] DeLong and Aldershof[56] reported that long-term lithium therapy could be used safely in clinical settings. Subjects were 196 children and adolescents with a variety of diagnoses. They were treated with lithium for periods ranging from 1 to 10 years.

We used the OAS, an instrument specifically developed and validated for measuring aggression. Based on OAS ratings, as noted above, lithium was significantly superior to placebo in decreasing aggression. To our knowledge, ours is the first double-blind and placebo-controlled study of lithium to yield positive results on a specific measure of aggression such as the OAS.

Future research with lithium should involve aggressive child and adolescent outpatients and critically assess the efficacy and safety of long-term lithium treatment. Our study was conducted in an inpatient setting and likely had the advantage of selecting for patients with the most severe aggression. Lithium may not be as effective in treating milder aggression. In such a population, placebo response may be greater, and the difference between the lithium and placebo responses may not be clinically or statistically significant. We have demonstrated that hospitalization itself is associated with decreased aggression and that a significant number of children respond while receiving placebo.[38,57] It is possible that particular types of aggression are decreased by hospitalization[58] and that those types of aggression were not included in the final treatment sample. In our study, half of the subjects were not randomized because they did not display aggression in the hospital during baseline. Had they not been hospitalized, they may have continued to display aggression and met the aggression criterion for randomization to treatments as outpatients, possibly changing important characteristics of the sample and the findings.

It is clear from experience with lithium in bipolar adults that compliance demands a good physician-patient relationship. Side effects such as weight gain occur over time and are important concerns for the patient. In our study, weight gain occurred with lithium and placebo, perhaps owing to the hospital environment and the length of the study. With long-term use, weight gain from lithium could be a significant problem. A report involving a relatively large number of subjects shows that lithium-associated side effects are more common in younger than older children.[59]

The limitations of our study include the lack of long-term follow-up. It is possible that the response to lithium did not continue after discharge from the hospital to less structured settings. In addition, long-term side effects, such as weight gain and thyroid dysfunction, may not be evident with short-term use. The findings from this study may not apply to children and adolescents with milder aggression or to those with disorders excluded in our study (eg, psychotic disorders, substance abuse, or mental retardation).

Based on our data and a few reports by others,[22,23] it is suggested that, when administered judiciously under careful clinical and laboratory monitoring, lithium is a safe and effective treatment for reducing aggression in psychiatrically hospitalized children and adolescents with conduct disorder and severe aggression. Clearly, more research is required to establish the efficacy and safety of lithium as a long-term treatment for aggression in children and adolescents.

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