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# Post-Acute Effectiveness of Lithium in Pediatric Bipolar I Disorder

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## Abstract

***Objective:*** This study examined the long-term effectiveness of lithium for the treatment of pediatric bipolar disorder within the context of combination mood stabilizer therapy for refractory mania and pharmacological treatment of comorbid psychiatric conditions.

***Methods:*** Outpatients, ages 7–17 years, meeting American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders,* 4th ed. (DSM-IV) diagnostic criteria for bipolar disorder I (BP-I) (manic or mixed) who demonstrated at least a partial response to 8 weeks of open-label treatment with lithium (Phase I) were eligible to receive open-label lithium for an additional 16 weeks (Phase II). Up to two adjunctive medications could be prescribed to patients experiencing residual symptoms of mania or comorbid psychiatric conditions, following a standardized algorithm.

***Results:*** Forty-one patients received continued open-label long-term treatment with lithium for a mean of 14.9 (3.0) weeks during Phase II. The mean weight-adjusted total daily dose at end of Phase II was 27.8 (6.7) mg/kg/day, with an average lithium concentration of 1.0 (0.3) mEq/L. Twenty-five of the 41 patients (60.9%) were prescribed adjunctive psychotropic medications for residual symptoms. The most frequent indications for adjunctive medications were refractory mania ($n = 13$; 31.7%) and attention-deficit/hyperactivity disorder (ADHD) ($n = 15$; 36.6%). At the end of this phase 28 (68.3%) patients met *a priori* criteria for response (≥ 50% reduction from Phase I baseline in Young Mania Rating Scale [YMRS] summary score and a Clinical Global Impressions-Improvement [CGI-I] score of 1 or 2), with 22 (53.7%) considered to be in remission (YMRS summary score ≤12 and CGI-Severity score of 1 or 2). These data suggest that patients who initially responded to lithium maintained mood stabilization during continuation treatment, but partial responders did not experience further improvement during Phase II, despite the opportunity to receive adjunctive medications. The most commonly reported (≥20%) adverse events associated with lithium treatment were vomiting, headache, abdominal pain, and tremor.

***Conclusions:*** Lithium may be a safe and effective longer-term treatment for patients with pediatric bipolar disorder who respond to acute treatment with lithium. Partial responders to acute lithium did not appear to experience substantial symptom improvement during the continuation phase, despite the possibility that adjunctive medications could be prescribed.

## Introduction

Lithium is an extensively researched, benchmark maintenance treatment for adults with bipolar disorder (Bowden et al. 2000, 2003; Calabrese et al. 2003; Muzina and Calabrese 2005). Despite its effectiveness in adults, long-term lithium treatment is associated with safety concerns, particularly regarding decreased renal function (Lepkifker et al. 2004; McCann et al. 2008; Tredget et al. 2010) and hypothyroidism (Zhang et al. 2006; Barbesino 2010). However, because bipolar disorder is a chronic

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condition (Manzano and Salvador 1993; Judd et al. 2002; Perlis et al. 2004, 2006; Yatham et al. 2009), long-term treatments are needed.

There are limited prospective long-term treatment data for bipolar disorder in children and adolescents. Prospective data for lithium as a long-term treatment for pediatric bipolar disorder are generally restricted to combination pharmacotherapy studies (Findling et al. 2003; Pavuluri et al. 2004, 2006). Despite the paucity of longer-term data, several randomized, double-blind, placebo-controlled trials to evaluate the efficacy of monotherapy with second generation antipsychotic medications for pediatric bipolar disorder have found that, although study patients typically experience symptom amelioration, the majority of study participants do not meet criteria for full remission (Tohen et al. 2007; Findling et al. 2009; Haas et al. 2009).

Considering that children and adolescents with bipolar disorder frequently do not respond to monotherapy, and considering that bipolar disorder is a highly comorbid condition (Geller et al. 2000; Findling et al. 2001; Tillman et al. 2003), long-term treatments for pediatric bipolar disorder are likely to include strategies extending beyond monotherapy. In fact, treatment with multiple mood stabilizers (Findling et al. 2003), as well as combination mood stabilizer-atypical antipsychotic agent therapy (Kafantaris et al. 2001; DelBello et al. 2002) have been found to be effective therapeutic strategies for pediatric bipolar disorder. Further, the addition of a stimulant to a mood stabilizer for the treatment of comorbid attention-deficit/hyperactivity disorder has demonstrated effectiveness in children and adolescents with bipolar disorder (Scheffer et al. 2005; Findling et al. 2007).

The purpose of this study is to describe the long-term effectiveness and safety of lithium in pediatric bipolar disorder within the context of combination mood stabilizer therapy and adjunctive treatment of comorbid psychiatric conditions. The work described herein was conducted under the auspices of the Collaborative Lithium Trials, a National Institute of Child Health and Human Development-funded contract to support research that will comprehensively test lithium as a potential treatment for pediatric patients with bipolar disorder I (BP-I) (Findling et al., 2008).

## Methods

The data presented herein were collected as part of a 16-week, open-label long-term effectiveness trial (Phase II) that followed a preliminary 8 week, open-label, randomized, escalating dose study (Phase I) that has been described elsewhere (Findling et al. 2011). Patients were seen at baseline (Week 8 of Phase I) and at study weeks 1, 2, 4, 6, 8, 10, 12, and 16/end of study (EOS). The Institutional Review Boards for Human Investigation at each of the multiple study sites approved the procedures of this outpatient study. Written informed consent was obtained from the subjects' guardians and written assent was obtained from the subjects before any study-related procedures were performed.

### *Subjects*

Subjects from Phase I continued to be study eligible if after 8 weeks of open lithium monotherapy treatment they demonstrated at least a 25% reduction in Young Mania Rating Scale (YMRS) (Young et al. 1978) score and a Clinical Global Impressions-Improvement (CGI-I) (National Institute of Mental Health 1985a) score $\leq 3$ (at least ''minimally improved''), and were able to tolerate at least 600 mg/day of lithium carbonate. To be enrolled in Phase I, subjects had to be between the ages of 7 and 17 (inclusive) and meet diagnostic criteria for BP-I, manic or mixed, without active psychotic symptoms. Subjects were required to be in good physical health, and be capable of swallowing study medication (lithium carbonate capsules) whole. For a complete listing of the inclusion/exclusion criteria for Phase I, please see Findling et al. (2011).

### *Diagnostic procedures*

Eligible study subjects underwent a psychiatric interview with a board-certified or board-eligible child and adolescent psychiatrist. Additionally, subjects were assessed by an interviewer trained on study-specific procedures using the Schedule for Affective Disorders and Schizophrenia for School Aged Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997) to confirm the clinician's diagnosis. The end of the previous lithium trial (Phase I) served as baseline for this continuation study (Phase II).

### *Pharmacotherapy*

During Phase I, subjects weighing $<30$ kg received a starting dose of 300 mg (Arm I). Subjects weighing $\geq 30$ kg were randomly assigned to receive either a starting dose of 600 mg (Arm I) or 900 mg (Arm II) of lithium. Lithium dose could be increased weekly by 300 mg, based on the subject's response and tolerability. The randomization methods for assignment into Arms I and II are described elsewhere (Findling et al. 2011). Arms I and II were run in parallel; Arm III was opened after 8 of the first 10 patients in Arm II completed 8 weeks of treatment and were determined to have tolerated the study drug. Once Arm III was opened, subjects weighing $\geq 30$ kg were randomly assigned to Arms I, II, or III until each arm was filled. The starting dose for Arm III was 900 mg, increasable by 300 mg every 3 days, based on response and tolerability.

The same dosage of lithium used at the conclusion of Phase I was maintained at the onset of Phase II. Subsequent dosage modifications were made using the procedures described previously. The dose was maintained in order to sustain a recommended trough level between 0.8 and 1.2 mEq/L, unless side effects precluded this level. The maximum level after which dose increases were not permitted was 1.4 mEq/L. Dosing was flexible, and it was based upon the achievement of the target serum level, apparent benefit, and apparent tolerability. Dose reductions or increases could be made at any time as clinically indicated. In order to accurately assess trough levels, lithium serum concentration was obtained after a minimum of 7 days after a dose change.

### *Adjunctive medication*

At any time during this phase, up to two adjunctive medications were allowed to be prescribed to patients, following a standardized algorithm (see Table 1). The algorithm was developed via consensus process during an investigator meeting in 2006, using the best available evidence at the time (Findling et al. 2008). The algorithm included a sequence of medications to treat residual symptoms of psychosis, mania and hypomania, depression, anxiety, and attention-deficit/hyperactivity disorder (ADHD), prioritized in that order and based upon patient need. It is of note that only one mood stabilizer could be used adjunctively at a time. During this study, the treating physician could prescribe either lorazepam or hydroxyzine as a rescue medication for sleeplessness and agitation. Neither medication counted toward the maximum of two allowable adjunctive medications.

Table 1. Concomitant Psychotropic Medication Treatment During Phase II

| *Rationale* | *Entry criteria* | *First line* | *Second line* | *Third line* | *Other* |
|---|---|---|---|---|---|
| Psychosis $n=1$ | Score ≥ 3 on one of the key positive psychotic items of Brief Psychiatric Rating Scale for Children | Risperidone $n=1$ | Quetiapine $n=0$ | Aripiprazole $n=0$ | N/A |
| Refractory mania $n=13$ | Young Mania Rating Scale score ≥12 | Valproate $n=11$ | Quetiapine $n=1$ | Aripiprazole $n=0$ | Risperidone $n=1$ |
| Depressive episode $n=0$ | Children's Depression Rating Scale-Revised score >28 for 2 weeks | Lamotrigine $n=0$ | Quetiapine $n=0$ | Citalopram $n=0$ | N/A |
| Comorbid anxiety $n=2$ | Pediatric Anxiety Rating Scale impairment score ≥3 | Valproate $n=1$ | Quetiapine $n=2$ | Lamotrigine $n=0$ | N/A |
| Comorbid ADHD $n=15$ | ADHD Rating Scale score ≥12 on hyperactivity-impulsivity or inattention subscale | Methylphenidate $n=11$ | Mixed amphetamine salts $n=4$ | Atomoxetine $n=0$ | Risperidone $n=1$ |
| Other[a] $n=1$ | | | | | Aripiprazole $n=1$ |

[a]Protocol deviation: patient was prescribed concomitant aripiprazole the reason for which was not discernable.
ADHD, attention-deficit/hyperactivity disorder.

### *Safety assessments*

Side effects were assessed at every study visit by direct, open-ended query of the subjects and guardians with ascertainment facilitated using the Side Effects Form for Children and Adolescents (SEFCA) (Klein et al. 1994), supplemented by specific items from the UKU Side Effect Rating Scale (Lingjærde et al. 1987) and the Safety Monitoring and Uniform Report Form (SMURF) (Greenhill et al. 2004). Neurological side effects were assessed using the Neurological Examination for Lithium (NELi) (Findling et al. 2008) and the Neurological Rating Scale (NRS) (Simpson and Angus 1970). The adverse events reported in the results are a summation of all ascertained events, regardless of methodology, that were determined by the study team to be adverse events.

Blood pressure, pulse, and weight were measured at each study visit. Comprehensive physical examinations, including measurement of height were performed at baseline and EOS participation.

A fasting comprehensive chemistry profile, lipid profile, thyroid profile, urinalysis, and urine toxicology screen were performed at baseline and EOS. These assessments were also performed, non-fasting, at week 8. Additionally, a non-fasting complete blood count with differential and a comprehensive chemistry profile were performed at week 4. In order to monitor renal function, creatinine clearance was measured at baseline, week 8, and week 16/EOS. Females of childbearing potential received a urine and serum pregnancy test at baseline, week 8, and week 16/EOS.

### *Outcome measures*

At each visit, psychometric outcome measures including the YMRS, Children's Depression Rating Scale-Revised (CDRS-R) (Poznanski et al 1984), Clinical Global Impressions-Severity (CGI-S) (National Institute of Mental Health 1985a), and CGI-I were obtained. In addition, completed at baseline and weeks 4, 8, and 16/EOS, were the Children's Global Assessment Scale (CGAS) (Shaffer et al. 1983), Irritation, Depression, and Anxiety Scale (IDA) (Snaith et al. 1978), Brief Psychiatric Rating Scale (BPRS) (Hughes et al. 2001), Pediatric Anxiety Rating Scale (PARS) (Research Units on Pediatric Psychopharmacology Anxiety Study Group 2002), Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M) (Youngstrom et al. 2008), Nisonger Child Behavior Rating Form-TIQ (NCBRF-TIQ) (Aman et al. 2008), and the ADHD Rating Scale (ARS-IV) (DuPaul et al. 1998). The Caregiver Strain Questionnaire (CSQ) (Brannan et al. 1997) was completed at baseline and weeks 8 and 16/EOS. Inter-rater reliability was established and maintained with quarterly assessments for the YMRS and CDRS-R.

### *Response criteria*

At the end of 16 weeks of treatment, all subjects were assessed and categorized as partial responders, responders, or non-responders based on *a priori* criteria. If a subject's YMRS score was reduced 25–49% from Phase I baseline and the subject's CGI-I score was ≤3, then the subject was considered a ''partial responder.'' If a subject's YMRS score decreased by ≥50% from Phase I baseline and the subject's CGI-I score was a 1 (very much improved) or 2 (much improved), then the subject was considered a ''responder.'' Remission was defined as a YMRS summary score ≤12 and CGI-I score equal to 1 (very much improved) or 2 (much improved).''Non-response'' criteria included a YMRS score reduction <25% or a CGI-I score ≥4.

## Results

### *Study participants*

One hundred and five patients were screened for possible open-label acute treatment with lithium (Phase I). Of the 61 patients who received study medications during Phase I, 60 youth completed at least 1 week of treatment and returned for a post-baseline assessment. Forty-one patients completed Phase I and entered the open-label long-term effectiveness phase (Phase II). The average treatment duration in Phase II was 14.9 (3.0) weeks. Patient participation through Phase I and Phase II is outlined in Figure 1. Demographic information for the 41 patients who participated in Phase II, the primary focus of this report, is shown in Table 2.

### *Lithium dosing and concomitant psychotropic medications*

At the beginning of Phase II, the mean total daily dose of lithium was 1441.5 (SD = 362.6) mg, whereas the mean weight-adjusted total daily dose was 28.2 (6.7) mg/kg/day with an average lithium concentration of 1.1 (0.3) mEq/L. The mean total daily dose at EOS participation was 1470.7 (384.2) mg, whereas the mean weight-adjusted total

daily dose at EOS participation was 27.8 (6.7) mg/kg/day, and there was an average lithium concentration of 1.0 (0.3) mEq/L.

Of the 41 patients receiving long-term treatment with lithium, 25 (60.9%) were prescribed concomitant psychotropic medications for residual symptoms as allowed by the protocol. More specifically, 1 patient was treated for residual psychosis, 13 for refractory mania, 2 for comorbid anxiety symptoms, and 15 for comorbid ADHD. No patients were treated for a depressive episode. Table 1 outlines the number of patients receiving each concomitant psychotropic medication.

### *Symptomatic response*

A summary of the outcome measure scores for all patients is provided in Table 3. Table 4 lists the overall and EOS measures for patients who received adjunctive psychotropic medication to those that did not, and Table 5 compares overall and EOS measures for patients who were treated for refractory mania with those who were not. Although there was no association with the YMRS change score by lithium dose or lithium concentration at the beginning of Phase II participation or patient age ($p > 0.05$), an association between YMRS score and gender was found. The mean change in YMRS score for females was 2.26 (7.51) compared with −2.57 (6.22) for males ($p = 0.03$).

The YMRS summary percentage improvement showed that the vast majority of patients (30 patients; 73.2%) had a ≥50% decrease in their YMRS summary score when compared with Phase I baseline. Further, the analysis of the CGI-I (overall illness) at the end of Phase II showed that 33 (80.5%) patients were considered to

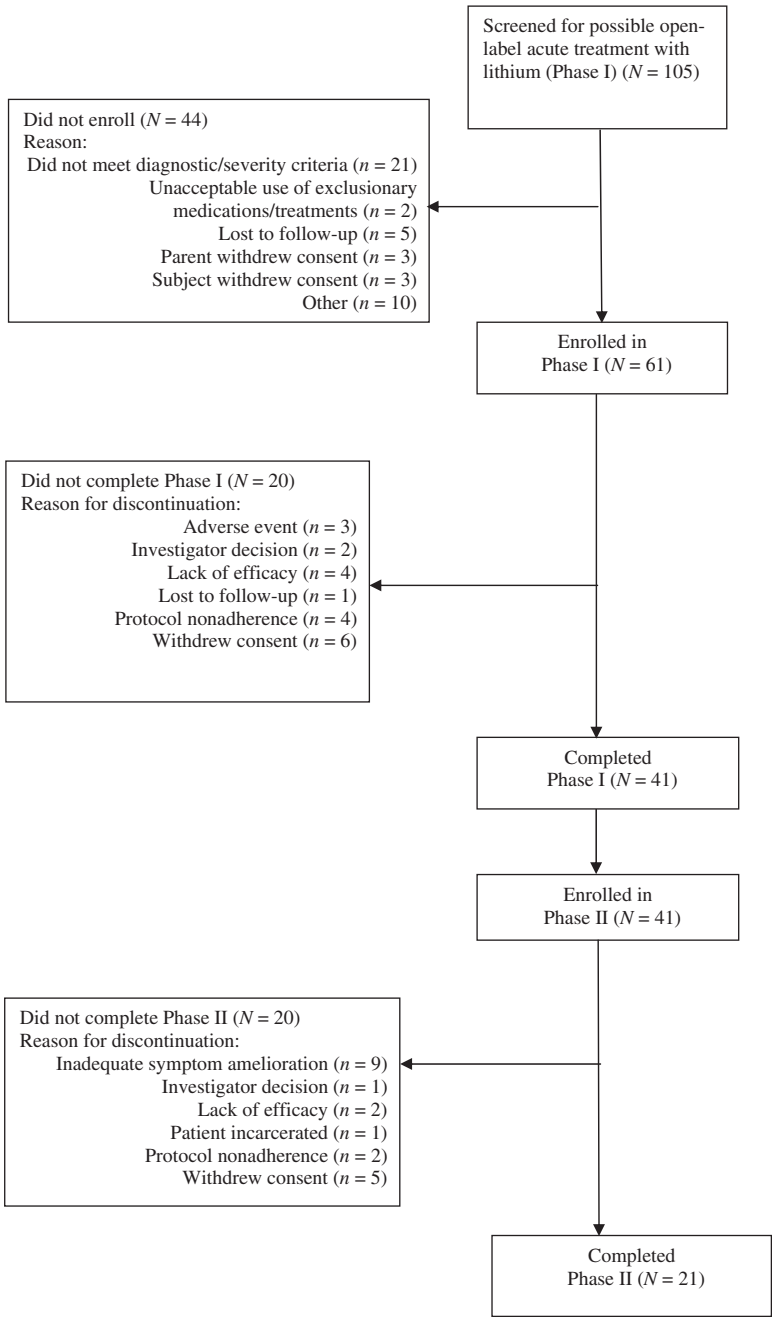


**FIG. 1.** Subject accountability.

Table 2. Patient Demographics and Clinical Characteristics

| | *Total participants* n = *41* |
|---|---|
| Mean (SD) age at Phase I baseline | 11.8 (2.8) |
| Sex (male) | 22 (54%) |
| Race | |
| Caucasian | 34 (83%) |
| African American | 5 (12%) |
| Caucasian/African American | 2 (5%) |
| Age of onset of bipolar disorder, years | 9.1 (3.3) |
| Mood state at Phase I study entry | |
| Manic | 18 (44%) |
| Mixed | 23 (56%) |
| Length of bipolar disorder illness, years at Phase I baseline | 2.3 (2.6) |
| Current psychiatric comorbid diagnoses | |
| Any ADHD[a] | 29 (71%) |
| Any DBD[b] | 11 (27%) |
| Any anxiety disorder[c] | 9 (22%) |
| Mean (SD) weight-adjusted total daily lithium dose at Phase II entry | 28.2 (6.7) mg/kg/day |
| Mean (SD) lithium concentration at Phase II entry | 1.1 (0.3) mEq/L |
| Mean length (weeks) of study participation in Phase II | 14.9 (3.0) |

[a]ADHD, attention-deficit/hyperactivity disorder; ADHD-combined; ADHD-hyperactive/impulsive; ADHD-inattentive; ADHD-not otherwise specified.
[b]DBD, disruptive behavior disorder; conduct disorder; oppositional defiant disorder.
[c]Generalized anxiety disorder; panic disorder; posttraumatic stress disorder; social anxiety disorder; social phobia; specific phobia. Three patients met diagnostic criteria for more than one anxiety disorder.

Table 3. Change in Mean Outcome Measure Scores during Phase II

| *Measure* | *Total participants* (n = *41*) | p |
|---|---|---|
| YMRS | | |
| Phase I baseline score Mean (SD) | 30.2 (5.9) | |
| Phase II baseline score Mean (SD) | 9.8 (6.3) | 0.77 |
| EOS score Mean (SD) | 9.4 (7.4) | |
| Change score Mean (SD) | −0.3 (7.2) | |
| CDRS-R | | |
| Phase I baseline score Mean (SD) | 39.5 (12.4) | |
| Phase II baseline score Mean (SD) | 24.0 (5.3) | 0.24 |
| EOS score Mean (SD) | 22.9 (6.2) | |
| Change score Mean (SD) | −1.1 (6.2) | |
| CGAS | | |
| Phase I baseline score Mean (SD) | 49.6 (6.8) | |
| Phase II baseline score Mean (SD) | 67.6 (14.1) | 0.36 |
| EOS score Mean (SD) | 69.0 (13.1) | |
| Change score Mean (SD) | 1.4 (9.8) | |
| CGI-S (Mania) | | |
| Phase I baseline score Mean (SD) | 4.6 (0.6) | |
| Phase II baseline score Mean (SD) | 2.3 (1.0) | |
| EOS score Mean (SD) | 2.2 (1.1) | 0.51 |
| Change score Mean (SD) | −0.1 (0.9) | |
| CGI-S (Depression) | | |
| Phase I baseline score Mean (SD) | 3.2 (1.2) | |
| Phase II baseline score Mean (SD) | 1.7 (0.9) | 0.64 |
| EOS score Mean (SD) | 1.8 (0.9) | |
| Change score Mean (SD) | 0.1 (1.0) | |
| CGI-S (Overall Illness) | | |
| Phase I baseline score Mean (SD) | 4.6 (0.6) | |
| Phase II baseline score Mean (SD) | 2.4 (0.9) | 0.23 |
| EOS score Mean (SD) | 2.2 (1.1) | |
| Change score Mean (SD) | −0.2 (1.0) | |

YMRS, Young Mania Rating Scale; CDRS-R, Child Depression Rating Scale Revised; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impressions-Severity; EOS, end of study.

be either ''much improved'' (score of 2) or ''very much improved'' (score of 1) compared with Phase I baseline. Three (42.9%) of the seven patients whose YMRS summary score decreased 25–50% were considered to be ''much improved'' (based upon CGI-I score of 2) compared with Phase I baseline.

At the end of Phase II, 28 (68.3%) patients met *a priori* criteria for response (≥50% reduction from Phase I baseline in YMRS summary score and a CGI-I score equal to 1 [very much improved] or 2 [much improved]), whereas 9 (22.0%) patients were considered to be partial responders (25–50% reduction from baseline in YMRS summary score and a CGI-I score ≤3, or ≥50% reduction from Phase I baseline in YMRS summary score and a CGI-I score of 3). The remaining four, or 9.7%, were non-responders. At the end of Phase II, 22 (53.7%) were considered to be in remission (YMRS summary score ≤12 and CGI-I score equal to 1 ([very much improved] or 2 [much improved]).

### *Lithium tolerability*

No suicides or deaths occurred during this study, and no patients discontinued study medication as the result of an adverse event. Forty (98%) out of 41 patients experienced at least one new treatment-emergent adverse event (TEAE) during Phase II, as reported by the SEFCA. Twenty-one (51%) patients experienced a new TEAE that was considered to be probably related to lithium, and 15 (37%) patients experienced a new TEAE that was considered to be possibly related. No patients experienced serious TEAEs. The most commonly experienced new AEs reported during Phase II are listed in Table 6.

Selected laboratory measurements obtained during Phase II are listed in Table 7. The mean thyrotropin concentration decreased from 5.9 (3.6) mIU/L at the beginning of Phase II to 5.0 (2.9) mIU/L at the end of Phase II ($p = 0.12$). Four patients had a thyrotropin concentration >10 mIU/L at Phase II baseline. During the course of Phase II, four other patients were found to have a thyrotropin concentration >10 mIU/L at one or more time points.

The mean white blood cell count was 8.0 (1.9) ×10E9/L at the beginning of Phase II and 8.0 (2.3) ×10E9/L at the end of Phase II ($p = 0.98$). The mean neutrophil percentage decreased from 60.1% (7.6) at the beginning of Phase II to 54.5% (16.0) at the end of Phase II ($p = 0.03$). The mean estimated creatinine clearance at the beginning of Phase II for these study participants was 115.7 (28.6) mL/min, and at end of Phase II was 121.6 (36.7) mL/min ($p = 0.11$).

While enrolled in Phase II, study participants experienced a statistically significant mean weight gain of 1.58 (3.85) kg (Phase II baseline weight: 53.88 (17.47) kg; end of Phase II weight: 55.46 (17.69) kg; $p = 0.013$). Body mass index did not significantly increase during study participation.

In addition, there was a subset of patients who had fasting lipid measurements obtained. Only a subset of patients had these

Table 4. Change in Mean Outcome Measure Scores during Phase II: Comparison of Participants Receiving Adjunctive Psychotropic Medications with Participants not Receiving Adjunctive Psychotropic Medications

| | *No adjunctive psychotropic medications* n = *16* | | *Adjunctive psychotropic medications* n = *25* | | *Mean difference in change scores* | |
|---|---|---|---|---|---|---|
| *Measure* | *Total participants* | p | *Total participants* | p | *Mean (SD)* | p |
| YMRS | | | | | | |
| Phase II baseline score Mean (SD) | 8.2 (5.4) | | 10.8 (6.8) | | | |
| EOS score Mean (SD) | 8.7 (8.2) | 0.76 | 9.9 (7.0) | 0.56 | 1.4 (7.2) | 0.55 |
| Change score Mean (SD) | 0.5 (6.8) | | −0.9 (7.5) | | | |
| CDRS-R | | | | | | |
| Phase II baseline score Mean (SD) | 24.8 (5.1) | | 23.5 (5.4) | | | |
| EOS score Mean (SD) | 23.6 (7.1) | 0.49 | 22.4 (5.7) | 0.35 | −0.2 (6.3) | 0.93 |
| Change score Mean (SD) | −1.2 (7.1) | | −1.1 (5.7) | | | |
| CGAS | | | | | | |
| Phase II baseline score Mean (SD) | 67.5 (14.4) | | 69.7 (14.2) | | | |
| EOS score Mean (SD) | 69.2 (13.2) | 0.48 | 68.9 (13.5) | 0.55 | 0.5 (9.9) | 0.86 |
| Change score Mean (SD) | 1.7 (9.8) | | 1.2 (10.0) | | | |
| CGI-S (Mania) | | | | | | |
| Phase II baseline score Mean (SD) | 2.2 (0.9) | | 2.4 (1.0) | | | |
| EOS score Mean (SD) | 2.2 (1.1) | 1.00 | 2.2 (1.1) | 0.46 | 0.2 (0.9) | 0.60 |
| Change score Mean (SD) | 0 (0.7) | | −0.2 (1.1) | | | |
| CGI-S (Depression) | | | | | | |
| Phase II baseline score Mean (SD) | 1.9 (1.0) | | 1.7 (0.8) | | | |
| EOS score Mean (SD) | 2.1 (0.9) | 0.48 | 1.7 (0.9) | 1.00 | 0.2 (1.0) | 0.56 |
| Change score Mean (SD) | 0.2 (1.0) | | 0.0 (1.0) | | | |
| CGI-S (Overall Illness) | | | | | | |
| Phase II baseline score Mean (SD) | 2.4 (0.9) | | 2.4 (1.0) | | | |
| EOS score Mean (SD) | 2.2 (1.1) | 0.42 | 2.2 (1.1) | 0.38 | 0.0 (1.0) | 0.97 |
| Change score Mean (SD) | −0.2 (0.9) | | −0.2 (1.1) | | | |

YMRS, Young Mania Rating Scale; CDRS-R, Child Depression Rating Scale Revised; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impressions-Severity; EOS, end of study.

assessments made owing to the substantial number of patients who were not fasting at the end of Phase II participation. With the exception of increased cholesterol/ high-density lipoprotein (HDL) ratio (Phase II baseline: 3.4 [1.1]; end of Phase II: 3.7 [1.2]; $p = 0.03$), there were no statistically significant changes in lipid measurements during Phase II participation (Table 7).

### *Other psychometric measures*

Mean (SD) scores at Phase I baseline, Phase II baseline, and end of week 16/end of Phase II for ARS-IV, BPRS-C, CSQ, PGBI-10M, IDA, NCBRF-TIQ, and PARS are summarized in Table 8. Table 9 compares the psychometric measure scores for patients who received adjunctive psychotropic medication with those who did not receive adjunctive psychotropic medication, and Table 10 compares psychometric measure scores for patients treated for refractory mania with those of patients who were not treated for refractory mania (i.e., treated for another comorbid condition or did not receive any adjunctive medications).

The comparisons summarized in Table 10 suggest that patients not treated for refractory mania were generally less symptomatic at Phase II baseline than those patients who were treated. Further, patients who were treated for refractory mania often worsened with time, whereas those who were not treated for refractory mania generally improved with time. Significant improvements in caregiver strain ($p = 0.02$) and parent-rated manic symptoms ($p = 0.03$) were noted in patients who did not receive adjunctive medications for refractory mania. Conversely, caregiver strain significantly increased ($p = 0.03$) and irritability worsened to a nearly significant degree ($p = 0.05$) in patients treated for refractory mania.

## Discussion

The goals of this study were to evaluate both the durability of the effectiveness and long-term safety of lithium in children and adolescents who were at least partial responders to 8 weeks of open-label lithium treatment. This study contributes to the existing literature (Findling and Pavuluri 2008) pertaining to the long-term effectiveness data for lithium in pediatric bipolar disorder, the body of which is relatively small. Only a few pediatric studies have prospectively evaluated lithium as a long-term treatment for bipolar disorder, and these data are generally limited to combination pharmacotherapy studies (Findling et al. 2003; Pavuluri et al. 2004, 2006).

An additional goal of this study was to explore the pattern of use and need for adjunctive treatment for refractory symptoms of mania and/or coexisting conditions, most frequently ADHD. Overall, patients remained stable, rather than improving during this phase, despite the addition of adjunctive medications in the majority of patients. However, comparison of psychometric measure scores for patients receiving adjunctive psychotropic medication for refractory mania with those of patients who did not receive adjunctive psychotropic medication for refractory mania reveal possible

Table 5. Change in Mean Outcome Measure Scores during Phase II: Comparison of Participants Receiving Adjunctive Psychotropic Medications for Refractory Mania with Participants Not Receiving Adjunctive Psychotropic Medications for Refractory Mania

| | *No adjunctive psychotropic medications for refractory mania* n = *28* | | *Adjunctive psychotropic medications for refractory mania* n = *13* | | *Mean difference in change scores* | |
|---|---|---|---|---|---|---|
| *Measure* | *Total participants* | p | *Total participants* | p | *Mean (SD)* | p |
| YMRS | | | | | | |
| Phase II baseline score Mean (SD) | 9.1 (6.1) | | 11.1 (6.8) | | | |
| EOS score Mean (SD) | 8.2 (7.4) | 0.51 | 12.1 (7.0) | 0.64 | −1.8 (7.2) | 0.45 |
| Change score Mean (SD) | −0.9 (7.3) | | 0.9 (7.0) | | | |
| CDRS-R | | | | | | |
| Phase II baseline score Mean (SD) | 23.5 (5.0) | | 25.1 (5.9) | | | |
| EOS score Mean (SD) | 22.7 (6.4) | 0.50 | 23.1 (6.2) | 0.32 | 1.1 (6.2) | 0.59 |
| Change score Mean (SD) | −0.8 (6.1) | | −1.9 (6.7) | | | |
| CGAS | | | | | | |
| Phase II baseline score Mean (SD) | 68.2 (14.9) | | 66.3 (12.7) | | | |
| EOS score Mean (SD) | 70.0 (12.9) | 0.32 | 67.1 (13.9) | 0.81 | 0.9 (9.9) | 0.78 |
| Change score Mean (SD) | 1.7 (9.0) | | 0.8 (11.5) | | | |
| CGI-S (Mania) | | | | | | |
| Phase II baseline score Mean (SD) | 2.2 (1.0) | | 2.5 (1.0) | | | |
| EOS score Mean (SD) | 2.1 (1.1) | 0.57 | 2.5 (1.2) | 0.75 | 0.0 (1.0) | 0.92 |
| Change score Mean (SD) | −0.1 (1.0) | | −0.1 (0.9) | | | |
| CGI-S (Depression) | | | | | | |
| Phase II baseline score Mean (SD) | 1.7 (0.9) | | 1.8 (0.8) | | | |
| EOS score Mean (SD) | 1.9 (0.8) | 0.44 | 1.8 (1.1) | 0.79 | 0.2 (1.0) | 0.51 |
| Change score Mean (SD) | 0.1 (1.0) | | −0.1 (1.0) | | | |
| CGI-S (Overall Illness) | | | | | | |
| Phase II baseline score Mean (SD) | 2.3 (0.9) | | 2.5 (1.0) | | | |
| EOS score Mean (SD) | 2.1 (1.1) | 0.24 | 2.5 (1.2) | 0.75 | −0.2 (1.1) | 0.62 |
| Change score Mean (SD) | −0.1 (0.9) | | −0.2 (1.1) | | | |

YMRS, Young Mania Rating Scale; CDRS-R, Child Depression Rating Scale Revised; CGAS, Children's Global Assessment Scale; CGI-S, Clinical Global Impressions-Severity; EOS, end of study.

trends, some of which are noteworthy. For example, patients who were only partial responders to lithium had some aspects of their clinical status that worsened with time, whereas those who were responders to lithium had some parameters that improved with time, suggesting that the need for adjunctive medication may be an overall sub-optimal prognostic indicator.

Further, over time, for some patients, either adjunctive psychosocial interventions or more than one psychotropic agent may be required to achieve and maintain manic symptom amelioration in pediatric bipolar disorder. This result is not surprising, as several double-blind, placebo-controlled trials of antipsychotic medications for the acute treatment of children and adolescents with bipolar disorder have also found that the majority of study participants do not experience full remission with drug monotherapy (Tohen et al. 2007; Findling et al. 2009; Haas et al. 2009). It is surprising that treatment with adjunctive mood stabilizer medication did not seem to make a notable impact upon symptom amelioration in this cohort. However, our choice of divalproex sodium as the first-line treatment for refractory mania, which was based on the best available data at the time this study was designed, may have played a role in the lack of improvement. Based on data from monotherapy studies, other agents, such as the second generation antipsychotic medications, might have proven to have been more efficacious as adjunctive treatments for those youth who did not respond to initial treatment with lithium monotherapy (Tohen et al. 2007; Findling et al. 2009; Haas et al. 2009; Wagner et al.

Table 6. Most Frequently Occurring (≥ 10% of Total Patients) Treatment-Emergent Adverse Events of New Onset during Phase II

| *Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class/Preferred Term* | *Total (%)* |
|---|---|
| Gastrointestinal disorders | |
| Vomiting | 17 (42) |
| Abdominal pain upper | 10 (24) |
| Nausea | 6 (15) |
| General disorders and administration site conditions | |
| Thirst | 7 (17) |
| Metabolism and nutrition disorders | |
| Decreased appetite | 6 (15) |
| Nervous system disorders | |
| Headache | 14 (34) |
| Tremor | 8 (20) |
| Dizziness | 4 (10) |
| Somnolence | 4 (10) |
| Psychiatric disorders | |
| Initial insomnia | 5 (12) |
| Renal and urinary disorders | |
| Enuresis | 7 (17) |
| Skin and subcutaneous tissue disorders | |
| Acne | 4 (10) |
| Rash | 4 (10) |

Table 7. Selected Physiologic Measurements at Phase II Baseline and End of Phase II[a]

| *Measure* | *Phase II baseline* | *End of Phase II* | p |
|---|---|---|---|
| Thyrotropin concentration (mIU/L) | 5.9 (3.6) | 5.0 (2.9) | 0.12 |
| White blood cell count (×10E9/L) | 8.0 (1.9) | 8.0 (2.3) | 0.98 |
| Neutrophil percentage (%) | 60.1 (7.6) | 54.5 (16.0) | 0.03 |
| Estimated creatinine clearance (mL/min) | 115.7 (28.6) | 121.6 (36.7) | 0.11 |
| Weight (kg) | 53.88 (17.5) | 55.46 (17.7) | 0.013 |
| Body mass index (kg/m$^2$) | 22.52 (4.7) | 22.80 (4.8) | 0.24 |
| Fasting LDL (mg/dL) $n=18$ | 93.8 (33.2) | 89.5 (21.2) | 0.48 |
| Fasting HDL(mg/dL) $n=18$ | 51.4 (14.9) | 57.4 (13.9) | 0.11 |
| Fasting cholesterol (mg/dL) n = 27 | 163.6 (38.9) | 156.8 (28.9) | 0.21 |
| Fasting cholesterol/HDL ratio $n=18$ | 3.4 (1.1) | 3.7 (1.2) | 0.03 |
| Fasting triglyceride (mg/dL) = 28 | 96.7 (61.8) | 106.5 (64.6) | 0.27 |

[a]Data presented as mean (standard deviation).
LDL, low-density lipoprotein; HDL, high-density lipoprotein.

2009; Geller et al. 2012). Future research on the effectiveness and tolerability of individual adjunctive medications within this study population may provide salient information regarding the treatment of pediatric bipolarity.

A small between-gender difference was found on change in YMRS scores during this trial. Importantly, there was no significant between-gender difference in YMRS scores at Phase II baseline (YMRS score for females = 8.84 [6.73] compared with 10.55 [6.01] for males [$p=0.40$]). Therefore this between-gender difference in YMRS score change could be a chance finding that is likely not to be clinically significant.

Long-term treatment with open-label lithium was generally safe and well tolerated. Thyrotropin levels were closely monitored throughout the study, as lithium has been found to be associated with significant rates of thyrotropin elevation in pediatric bipolar disorder (Gracious et al. 2004). Although a few patients experienced clinically significant changes in and/or elevated thyroid-related laboratory values during Phase II, none of these patients suffered from a thyroid-related adverse event. Renal function was also closely monitored throughout the study. No significant changes in creatinine clearance were found during this study, and no patients discontinued treatment as a result of decreased renal function.

A primary limitation of this study is its open, uncontrolled design. This study is further limited by its relatively small sample size. Additionally, study participants received lithium for 16 weeks, whereas treatment for pediatric bipolar disorder will generally extend beyond 16 weeks.

### *Conclusions*

Data from this open-label long-term effectiveness study suggest that lithium may be a safe, tolerable, and effective treatment option for pediatric bipolar disorder following mood stabilization with lithium. It is important to note, however, that overall, these patients maintained mood stabilization, rather than experiencing further improvement during this study, despite the opportunity to receive adjunctive medications. The subset of patients requiring adjunctive treatment for refractory mania had some aspects of their clinical status that worsened during study participation. This observation suggests that more effective treatment strategies are needed for this vulnerable patient population. Furthermore, longer studies that can more definitively evaluate the efficacy of lithium for the long-term treatment of pediatric bipolar disorder are needed.

Table 8. Change in Other Psychometric Measure Mean Scores during Phase II

| | *Phase I baseline* | *Phase II baseline* | | *End of Phase II* | |
|---|---|---|---|---|---|
| *Instrument* | *Mean (SD)* | *Mean (SD)* | p | *Mean (SD)* | p |
| ADHD Rating Scale-IV (ARS-IV) | | | | | |
| Total score | 34.4 (12.0) | 28.8 (11.6) | 0.002 | 27.9 (13.3) | 0.59 |
| Inattention | 19.0 (6.2) | 17.0 (5.7) | 0.04 | 16.1 (6.7) | 0.41 |
| Hyperactivity-Impulsivity | 15.4 (6.7) | 11.9 (6.8) | <0.0001 | 11.8 (7.5) | 0.84 |
| Brief Psychiatric Rating Scale for Children (BPRS-C) | | | | | |
| Total score | 33.2 (9.9) | 12.8 (7.7) | <0.0001 | 12.7 (9.2) | 0.92 |
| Caregiver Strain Questionnaire (CSQ) | | | | | |
| Total score | 65.7 (16.7) | 53.5 (19.3) | 0.0003 | 51.5 (17.8) | 0.52 |
| Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M) | | | | | |
| Total score | 17.5 (6.5) | 9.1 (6.5) | <0.0001 | 8.0 (7.7) | 0.37 |
| Irritability, Depression, and Anxiety (IDA) | | | | | |
| Total score | 9.8 (1.8) | 4.1 (3.1) | <0.0001 | 5.0 (4.2) | 0.14 |
| Nisonger Child Behavior Rating Form-TIQ (NCBRF-TIQ) | | | | | |
| Conduct Problem | 22.2 (5.7) | 17.0 (5.1) | <0.0001 | 16.5 (4.8) | 0.38 |
| ADHD-Total | 13.5 (4.2) | 9.5 (4.0) | <0.0001 | 9.2 (4.2) | 0.51 |
| Pediatric Anxiety Rating Scale (PARS) | | | | | |
| Total score with five items | 4.7 (6.2) | 3.4 (5.8) | 0.14 | 2.0 (4.5) | 0.15 |

ADHD, attention-deficit/hyperactivity disorder.

Table 9. Change in Other Psychometric Measures Mean Scores During Phase II: Comparison of Participants Receiving Adjunctive Psychotropic Medications with Participants Not Receiving Adjunctive Psychotropic Medications

| | *No adjunctive psychotropic medications* n = *16* | | | *Adjunctive psychotropic medications* n = *25* | | | *Mean difference in change scores* | |
|---|---|---|---|---|---|---|---|---|
| *Instrument* | *Phase II baseline Mean (SD)* | *End of Phase II Mean (SD)* | p | *Phase II baseline Mean (SD)* | *End of Phase II Mean (SD)* | p | *Mean (SD)* | p |
| ADHD Rating Scale-IV (ARS-IV) | | | | | | | | |
| Total score | 23.9 (9.4) | 21.3 (11.3) | 0.14 | 32.0 (11.9) | 32.3 (12.9) | 0.99 | 2.6 (12.0) | 0.45 |
| Inattention | 14.8 (4.9) | 13.1 (5.7) | 0.11 | 18.3 (5.9) | 18.2 (6.6) | 0.89 | 1.5 (6.3) | 0.40 |
| Hyperactivity-Impulsivity | 9.1 (5.7) | 8.2 (6.6) | 0.36 | 13.7 (6.9) | 14.1 (7.3) | 0.89 | 1.0 (6.2) | 0.56 |
| Brief Psychiatric Rating Scale for Children (BPRS-C) | | | | | | | | |
| Total score | 11.7 (7.7) | 10.7 (6.9) | 0.61 | 13.6 (7.8) | 14.0 (10.3) | 0.87 | −1.5 (10.7) | 0.67 |
| Caregiver Strain Questionnaire (CSQ) | | | | | | | | |
| Total score | 49.1 (19.9) | 44.1 (11.0) | 0.21 | 56.3 (18.8) | 56.1 (19.9) | 0.99 | −4.9 (18.0) | 0.41 |
| Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M) | | | | | | | | |
| Total score | 6.9 (6.5) | 4.5 (4.4) | 0.08 | 10.6 (6.2) | 10.4 (8.6) | 0.88 | −2.1 (7.9) | 0.37 |
| Irritability, Depression, and Anxiety (IDA) | | | | | | | | |
| Total score | 4.2 (2.9) | 5.4 (4.1) | 0.10 | 4.1 (3.3) | 4.8 (4.3) | 0.44 | 0.6 (3.8) | 0.65 |
| Nisonger Child Behavior Rating Form-TIQ (NCBRF-TIQ) | | | | | | | | |
| Conduct Problem | 16.0 (6.0) | 15.2 (4.5) | 0.60 | 17.7 (4.4) | 17.3 (5.0) | 0.49 | 0.0 (5.3) | 0.98 |
| ADHD-Total | 8.6 (4.7) | 7.3 (3.2) | 0.27 | 10.0 (3.4) | 10.4 (4.4) | 0.97 | −1.3 (4.5) | 0.38 |
| Pediatric Anxiety Rating Scale (PARS) | | | | | | | | |
| Total score with five items | 2.7 (4.5) | 2.5 (4.2) | 0.75 | 3.8 (6.5) | 1.8 (4.7) | 0.17 | 1.8 (5.9) | 0.28 |

ADHD, attention-deficit/hyperactivity disorder.

Table 10. Change in Other Psychometric Measures Mean Scores During Phase II: Comparison of Participants Receiving Adjunctive Psychotropic Medications for Refractory Mania with Participants not Receiving Adjunctive Psychotropic Medications for Refractory Mania

| | *No adjunctive psychotropic medications for refractory mania* n = *28* | | | *Adjunctive psychotropic medications for refractory mania* n = *13* | | | *Mean difference in change scores* | |
|---|---|---|---|---|---|---|---|---|
| *Instrument* | *Phase II baseline Mean (SD)* | *End of Phase II Mean (SD)* | p | *Phase II baseline Mean (SD)* | *End of Phase II Mean (SD)* | p | *Mean (SD)* | p |
| ADHD Rating Scale-IV (ARS-IV) | | | | | | | | |
| Total score | 27.4 (11.6) | 24.2 (12.4) | 0.09 | 31.9 (11.4) | 35.6 (12.1) | 0.38 | −7.0 (11.6) | 0.08 |
| Inattention | 16.5 (5.4) | 14.6(6.3) | 0.08 | 18.0 (6.5) | 19.5 (6.4) | 0.89 | −3.4 (6.1) | 0.11 |
| Hyperactivity-Impulsivity | 10.9 (7.1) | 9.7 (7.0) | 0.16 | 13.9 (5.7) | 16.1 (6.6) | 0.32 | −3.6 (6.0) | 0.08 |
| Brief Psychiatric Rating Scale for Children (BPRS-C) | | | | | | | | |
| Total score | 12.3 (7.6) | 10.6 (6.8) | 0.30 | 14.1 (8.0) | 17.1 (12.0) | 0.44 | −4.8 (10.5) | 0.27 |
| Caregiver Strain Questionnaire (CSQ) | | | | | | | | |
| Total score | 52.9 (20.5) | 44.8 (11.7) | 0.02 | 54.6 (17.0) | 65.0 (20.7) | 0.03 | −18.3 (15.9) | 0.002 |
| Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M) | | | | | | | | |
| Total score | 7.9 (6.9) | 4.7 (4.2) | 0.03 | 11.7 (4.9) | 14.9 (8.8) | 0.14 | −6.4 (7.4) | 0.01 |
| Irritability, Depression, and Anxiety (IDA) | | | | | | | | |
| Total score | 4.3 (3.2) | 4.3 (3.7) | 0.95 | 3.8 (2.8) | 6.5 (4.8) | 0.05 | −2.7 (3.6) | 0.03 |
| Nisonger Child Behavior Rating Form-TIQ (NCBRF-TIQ) | | | | | | | | |
| Conduct Problem | 17.1 (5.8) | 15.8 (4.0) | 0.13 | 16.8 (3.4) | 17.8 (6.2) | 0.49 | −2.6 (5.1) | 0.14 |
| ADHD-Total | 8.9 (4.3) | 7.7 (3.0) | 0.06 | 10.7 (2.8) | 12.2 (4.8) | 0.32 | −3.0 (4.4) | 0.05 |
| Pediatric Anxiety Rating Scale (PARS) | | | | | | | | |
| Total score with five items | 3.1 (5.3) | 1.7 (3.4) | 0.11 | 3.9 (6.9) | 2.8 (6.3) | 0.63 | −0.3 (6.0) | 0.91 |

ADHD, attention-deficit/hyperactivity disorder.

## Clinical Significance

These data add to the modest amount of literature that suggests that lithium may be a safe, tolerable and effective longer-term treatment option for children and adolescents with BP-I who respond to initial lithium treatment. Overall, lithium was generally well tolerated and associated with maintenance of symptom amelioration. However, although adjunctive medications could be prescribed during this study phase, symptomatic patients did not appear to experience substantial symptom improvement. Therefore, more effective interventions and longer-term studies of lithium treatment are needed for this patient population.

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