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Original Articles

Dosing Strategies for Lithium Monotherapy in Children and Adolescents with Bipolar I Disorder

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Abstract

Objective: The primary goal of this exploratory study was to obtain data that could lead to evidence-based dosing strategies for lithium in children and adolescents suffering from bipolar I disorder.

Methods: Outpatients aged 7–17 years meeting *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, diagnostic criteria for bipolar I disorder (manic or mixed) were eligible for 8 weeks of open label treatment with lithium in one of three dosing arms. In Arm I, participants began treatment at a dose of 300 mg of lithium twice daily. The starting dose of lithium in Arms II and III was 300 mg thrice daily. Patients in Arms I and II could have their dose increased by 300 mg/day, depending on clinical response, at weekly visits. Patients in Arm III also had mid-week telephone interviews after which they could also have their dose of lithium increased by 300 mg per day. Youths weighing <30 kg were automatically assigned to Arm I, whereas youths weighing ≥ 30 kg were randomly assigned to Arm I, II, or III. Randomization was balanced by age (7–11 years, 12–17 years) and sex in approximately equal numbers. *A priori* response criteria were defined as a Clinical Global Impressions-Improvement scale score of ≤ 2 and a 50% decrease from baseline on the Young Mania Rating Scale.

Results: Of the 61 youths [32 males (52.5%)] who received open-label lithium, 60 youths completed at least 1 week of treatment and returned for a postbaseline assessment. Most patients had a $\geq 50\%$ improvement in Young Mania Rating Scale score, and more than half of the patients (58%) achieved response. Overall, lithium was well tolerated. All three treatment arms had similar effectiveness, side effect profiles, and tolerability of lithium.

Conclusions: On the basis of these results, a dosing strategy in which pediatric patients begin lithium at a dose of 300 mg thrice daily (with an additional 300 mg increase during the first week), followed by 300 mg weekly increases until *a priori* stopping criteria are met, will be used in an upcoming randomized, placebo-controlled trial.

Introduction

Recently, bipolar disorder has become a clinical entity that is becoming better characterized in children and adolescents (Findling et al. 2001; Kowatch et al. 2005; McClellan et al. 2007). Because of the chronicity and severity of this illness (Geller et al. 2004; Biederman et al. 2005; Birmaher et al. 2006), it is important that safe and effective treatments for pediatric bipolar disorder be developed.

Lithium has been known to be an effective treatment option for adults with bipolar disorder for over 50 years (Cade 2000), and lithium's potential benefits in adults have been well documented (reviewed by Goodwin 2002; Muzina and Calabrese 2005; Thase and Denko 2008). Despite the fact that lithium is a benchmark treatment for bipolarity in adults, prior lithium research in pediatric bipolarity has generally lacked methodological rigor (Findling and Pavuluri 2008). Most prior studies that have examined the biodisposition of lithium in pediatric patients, or that have sought to develop evidence-based dosing strategies for lithium in children and adolescents have generally recruited small sample sizes (Vitiello et al. 1988; Hagino et al. 1998). However, previous pharmacokinetic work performed by our group suggests that the

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dosing interval for lithium that is used in adults may be suitable when treating children and adolescents with this agent (Findling et al. 2010). Additional research that has been performed in the young has suggested that lithium may produce salutary effects when prescribed to pediatric-aged patients. Most likely owing to the fact that definitive dosing studies have not been performed with lithium in children and adolescents, dosing paradigms for lithium frequently have varied across clinical trials in youths (Findling and Pavuluri 2008).

As the result of a Written Request being issued by the Food and Drug Administration (FDA), the work described herein was conducted under the auspices of a National Institute of Child Health and Human Development (NICHD)–supported contract. The purpose of that contract is to support research that will comprehensively test lithium as a potential treatment for pediatric patients suffering from bipolar I disorder (BP-I) (Findling et al. 2008). The primary goal of this exploratory study was to obtain data that could lead to evidence-based dosing strategies for lithium in children and adolescents suffering from BP-I. The decision to employ a sample size of $\sim$20 patients being enrolled into each arm was based upon specific directions from the FDA's Written Request.

As part of this endeavor, the following parameters were examined: (1) the range of therapeutic lithium blood concentrations, (2) the safety and effectiveness of different starting doses of lithium, and (3) the risks and benefits associated with different rates of lithium dose escalation.

Methods

The Institutional Review Boards for Human Investigation at each of the seven participating sites approved the procedures of this study. The parent/guardians of all study participants provided written informed consent, and all youths provided written assent before any study-related procedures were performed. In addition, an independent Data Safety and Monitoring Board reviewed the progress of this clinical trial.

Study overview

This was an 8-week study with three parallel arms (Arm I, Arm II, and Arm III). Medically healthy children and adolescents aged 7–17 years suffering from a manic or mixed episode were eligible to participate. Additional inclusion and exclusion criteria are described in Table 1. After a screening period, participants were seen at baseline and weekly thereafter. In this study, lithium was provided as 300 mg lithium carbonate capsules.

Screening procedures

Once informed consent and assent were obtained, youths participated in a screening phase to determine participant eligibility. Information about inclusion and exclusion criteria was collected, and pretreatment laboratories and safety measures were obtained. The screening period was 3–28 days. However, if the patient was currently receiving fluoxetine at the initial assessment, the screening period was extended to last up to 6 weeks (see below).

Enrollment to Arm I and Arm II

At the start of the trial, only enrollment into the first two dosing initiation arms (Arm I and Arm II) was allowed. The purpose of this first portion of the trial was to determine an evidence-based starting dose for lithium.

In Arm I, participants began treatment at a dose of 300 mg of lithium twice daily. The starting dose of lithium in Arm II was 300 mg thrice daily. To ensure participant safety, youths who weighed $<$30 kg were automatically assigned to Arm I, with a 600 mg starting dose, and could not be enrolled into any other treatment arm. At the time this study was designed, there were limited data about starting lithium treatment at a dose above 30 mg/kg/day (Weller et al. 1986). In addition, a recent prior study of lithium in pediatric bipolar disorder had mean final doses that were $<$30 mg/kg/day (Findling et al. 2003).

The first participants weighing 30 kg or more were randomly assigned to either Arm I or II, with randomization being balanced by age (7–11 years, 12–17 years) and sex in approximately equal numbers. After receiving this starting dose, participants who were randomized to Arms I and II were to have their doses of lithium increased by 300 mg each week unless one or more of four different ''stopping'' criteria were met (Table 2). It should be noted that a patient's dose of lithium could be reduced at any time to address concerns about lithium tolerability. However, youths who could not

Table 1. Inclusion/Exclusion Criteria

Inclusion	*Exclusion*
Good physical health	Allergy to or intolerance for lithium
Capable of swallowing study medication (lithium carbonate capsules) whole	Unstable medical illness that might be adversely affected by lithium
Wechsler Abbreviated Scales of Intelligence (WASI) Vocabulary and Matrix Reasoning Subscales (Wechsler 1999) intelligence quotient of 70 or greater	Comorbid diagnosis of: Schizophrenia, schizoaffective disorder, a pervasive developmental disorder, anorexia nervosa, bulimia nervosa, substance dependence, or obsessive-compulsive disorder
Comorbid psychiatric diagnosis of attention-deficit/hyperactivity disorder or a disruptive behavior disorder (allowed, not required)	Concomitant nonstimulant psychotropic agents within the preceding 2 weeks; stimulant use within the preceding week; fluoxetine or depot antipsychotics in the past month
Negative urine toxicology screen (if initial screen positive, may be retested 1 to 3 weeks later)	Psychiatric hospitalization for psychosis or serious homicidal/serious suicidal ideation within 1 month of screening
Sexually active women using adequate forms of birth control	Current active hallucinations or delusions
Negative urine and serum pregnancy tests for sexually active women	Symptoms of mania attributable to a general medical condition or secondary to use of medications
Washout of exclusion medications during screening period and before administration of lithium	Initiation of concomitant psychotherapeutic treatments within 4 weeks before screening
No clinically significant abnormalities in ECG and blood work	Pregnant or lactating women

Table 2. Stopping Criteria for Dose Escalation

(1) The participant achieved therapeutic response: CGI-I Scale score of ≤ 2 and a 50% decrease in YMRS score from baseline assessment
(2) The youth experienced/reported adverse events that had a significant impact on functioning and was putatively due to lithium treatment
(3) The lithium dose exceeded 40 mg/kg/day
(4) The patient's current serum lithium concentration was expected to be greater than 1.4 mEq/L

CGI-I = Clinical Global Impressions-Improvement; YMRS = Young Mania Rating Scale.

tolerate a minimum lithium dose of 600 mg per day were to be withdrawn.

The decision to test a 600 mg versus a 900 mg per day starting dose was based on a typical starting dose of 900 mg for adults with bipolar disorder (Bowden et al. 1994). As children and adolescents are generally smaller than adults, and potentially more vulnerable to lithium-related adverse events (AEs), it was believed that it would be important to examine whether youths could tolerate an adult-sized starting dose of lithium.

Opening enrollment into Arm III

Once it was determined that a starting dose of 900 mg of lithium per day with weekly increases was tolerable by at least 8 out of first 10 patients who completed 8 weeks of lithium treatment, randomization into Arm III became possible. Once Arm III became open for enrollment, participants weighing 30 kg or greater were randomly assigned (balanced for age and sex as noted above) to receive treatment in Arm I, II, or III until each arm was filled.

Similar to participants in Arm II, participants in Arm III began treatment with a starting dose of lithium of 300 mg of lithium administered thrice daily and were to have their dose of lithium increased by 300 mg per day at the weekly study visits until one or more stopping criteria were met. However, based upon the strategy employed by Bowden et al. (1994), all participants in Arm III could also have their dose of lithium increased by 300 mg per day after regularly scheduled mid-week telephone interviews were conducted with the participant and their parent/guardian. These telephone calls, during which dosing decisions were made based on salutary effects and tolerability, were conducted at the mid-point of each week until the participant met one or more stopping criteria for dose escalation. Thus, the purpose of Arm III was determine whether or not twice weekly increases in lithium dosing could safely increase the rapidity with which the patient achieved their therapeutic dose of lithium.

Dose escalation

As mentioned above, the dose of lithium the participants were receiving was to be increased by 300 mg at the weekly study visits (as well as after the mid-week telephone interviews in Arm III) unless one or more of the stopping criteria for dose escalation were reached. All scheduled study visits (including the mid-week telephone calls, as noted below) were to occur within a ± 2 day window.

For participants who were enrolled in Arm III, their dose of lithium was to be increased after the mid-week telephone call was conducted [on days 3, 10, 17, and 24 (± 2 days)] as well as after the weekly study visits. During these mid-week telephone calls, the prescribing clinician interviewed the patient's parent/guardian, and as developmentally appropriate, the patient. The clinicians discussed medication adherence, global impressions of clinical response, and AEs during these telephone calls. Unless there were dose limiting AEs, clinical response (defined as Clinical Global Impressions-Improvement (CGI-I) (NIMH 1985) score of ≤ 2 and a 50% decrease in Young Mania Rating Scale (YMRS) (Young et al. 1978) score from baseline assessment), and adequate medication adherence (see below), the participant was to have their daily lithium dose increased by 300 mg.

The maximum daily weight-adjusted dose for lithium was set at 40 mg/kg/day. As noted above, a recent study that flexibly dosed lithium had mean daily doses of lithium that were generally <30 mg/kg/day (Findling et al. 2003). Thus, it was believed that this maximum weight adjusted dose would be an important safeguard for study participants.

Typically, the target maximum lithium serum concentration in adults is 1.3 mEq/L, with 1.5 mEq/L representing the lower limit for toxicity (Amdisen 1980). For this study, 1.4 mEq/L was chosen as the maximum serum lithium concentration above which further dose increases could not occur. This concentration was selected based on several observations. First and foremost, with 1.5 mEq/L reportedly being the lower limit of lithium toxicity in adults, exceeding that concentration in children would have raised concerns about participant safety.

Prior lithium studies in children and adolescents with bipolar disorder had target lithium blood and serum concentrations substantially below 1.4 mEq/L. For example, a trial in which children and adolescents were treated with risperidone in combination with either lithium or divalproex sodium used a target serum level of 0.6–1.0 mEq/L (Pavuluri et al. 2004). Similarly, another combination therapy trial's (lithium plus divalproex sodium) target blood level was 0.6–1.2 mEq/L (Findling et al. 2003). Two studies of lithium monotherapy, one open-label and one double-blind, placebo-controlled, used target serum levels of 0.6–1.2 mEq/L (Kafantaris et al. 2003) and 0.8–1.2 mEq/L (Kowatch et al. 2007). However, prior work with lithium monotherapy also suggested the possibility that lithium may have been under-dosed in prior trials. In prior research that tested lithium carbonate, youths overall appear to receive benefit from lithium monotherapy treatment, but generally neither achieve nor maintain remission with lithium monotherapy.

Daily dosing of lithium

As lithium is typically dosed three times daily in adults (FDA 2003), the lithium dose for this study was divided thrice daily (morning, after school, and evening). No dose at the three different daily administration time points differed from each other by >300 mg. To allow for the monitoring of potential treatment-emergent adverse events (TEAEs) during periods of wakefulness, if doses were unequal, the highest dose was given in the morning. Trough lithium serum concentrations were obtained weekly.

Study participants

Outpatient youths aged between 7 and 17 years of age were eligible. To be enrolled, participants had to meet *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (American Psychiatric Association 1994), criteria for BP-I, currently in a manic or mixed episode and without active psychotic symptoms, based on a psychiatric interview by a child and adolescent psychiatrist. In addition, a trained interviewer administered the Schedule for Affective Disorders and Schizophrenia for School-Age

Children-Present and Lifetime Version (Kaufman et al. 1997) to confirm the diagnosis of BP-I. Participants also needed to receive a score of 20 or greater on the YMRS at screening and baseline.

Psychometric measures

Beginning at baseline, weekly psychometric assessments included the YMRS, Children's Depression Rating Scale Revised (Poznanski et al. 1984), the CGI-I, and the Clinical Global Impressions-Severity (CGI-S) Scale (NIMH 1985). The Suicide Severity Rating Scale (Posner et al. 2007) was also completed weekly. The *a priori* primary outcome measure was the change from baseline to the end of 8 weeks in the summary/rater assessment of the YMRS.

At weeks 4 and 8, the following additional measures were completed: Parent General Behavior Inventory-10 Item Mania Scale (Youngstrom et al. 2008), Children's Global Assessment Scale (Shaffer et al. 1983), Child Mania Rating Scale-Parent (Pavuluri et al. 2006), Nisonger Child Behavior Rating Form-Typical IQ Version (Aman et al. 2008), Irritability, Depression, and Anxiety Scale (Snaith et al. 1978), attention-deficit/hyperactivity disorder Rating Scale-IV (DuPaul 1998), Brief Psychiatric Rating Scale (BPRS) (Hughes et al. 2001), Pediatric Anxiety Rating Scale (The Research Units on Pediatric Psychopharmacology Anxiety Study Group 2002). The Social Adjustment Inventory for Children and Adolescents (John et al. 1987), Caregiver Strain Questionnaire (Brannan et al. 1997), Family Environment Scale (Moos and Moos 1984), and Drug Use Screening Inventory (Tarter and Hegedus 1991) were obtained at week 8.

Response criteria

At the end of study participation, patients' status was determined. Criteria for ''Response'' are listed above. ''Partial Response'' was defined a priori as having a YMRS reduction of 25%–49% from baseline assessment and a CGI-I $\leq$3. ''Nonresponse'' was defined a priori as having a YMRS reduction of $<$25% from baseline assessment or a CGI-I $\geq$4, or an inability to tolerate a dose of 600 mg/day of lithium.

AE monitoring

Patients were monitored for the presence of TEAEs using the Side Effects Form for Children and Adolescents (SEFCA) (Klein et al. 1994), the Neurological Examination for Lithium (NELi) (Findling et al. 2008), and the Neurological Rating Scale (NRS) (Simpson and Angus 1970) at baseline and each subsequent, weekly study visit. A 13-item expanded version of the 10-item NRS was used in this study to assess for potential additional extrapyramidal side effects. These additional items are (1) cogwheeling; (2) acute dystonic reaction; and (3) subjective sense of stiffness.

The SEFCA is a 54-item scale that rates both the frequency and severity of TEAEs that commonly occur in pediatric psychopharmacology trials. The NELi, administered by a study physician, measured the presence/absence of hand tremors as well as difficulties with the finger-nose test, tandem walk, gait, grip strength, and the Romberg Test. The NRS, also administered by a physician, assessed for additional neurological adverse effects. In addition, youths and their parents/guardians were also asked about any other potential AEs not asked about in the aforementioned instruments in an open-ended fashion.

Items from the SEFCA, NELi, NRS, or open-ended inquiry that were reported as being present at study visits were documented. The study physician who conducted the visit determined whether or not what was reported constituted an AE. The intensity or severity of AEs was graded as follows: Mild (awareness of sign of symptom, but easily tolerated; not expected to have a clinically significant effect on the subject's overall health and well being; not likely to require medical attention); moderate (discomfort enough to cause interference with usual activity or affects clinical status; may require medical intervention); and severe (incapacitating or significantly affecting clinical status; likely requires medical intervention and/or close follow-up). Further, the study physician assessed the relationship of AEs to the study medication using the following definitions: Probable (a clinical event, including a laboratory test abnormality, in which a relationship to the study drug seems probable because of such factors and consistency with known side effects of the drug, a clear temporal association with the use of the drug, improvement upon withdrawal of the drug, lack of alternative explanations for the experience, or other factors); possible (a clinical event, including a laboratory test abnormality, with a reasonable time sequence to administration of the study drug, but which could not be explained by concurrent disease or other drugs or chemicals); and unlikely (a clinical event, including a laboratory test abnormality, with a temporal relationship to study drug administration, which makes a causal relationship improbable and in which other factors suggesting an alternative etiology exist; such factors known include a known relationship of the adverse experience to concomitant medication, the subject's disease state, or environmental factors, including common infections and diseases).

Laboratory and other safety assessments

Before receiving study medications, participants received a fasting comprehensive chemistry profile (measuring blood concentrations of glucose, urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, creatinine, creatinine kinase, uric acid, total protein, direct and total bilirubin, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and gamma glutamyl transferase, complete blood count with differential, coagulation function (measuring prothrombin time, partial thromboplastin time, and fibrinogen), lipid profile (measuring total cholesterol, triglycerides, high density lipoproteins, low density lipoproteins, and cholesterol/high density lipoprotein ratio), thyroid profile (measuring thyroid stimulating hormone (TSH), triiodothyronine, thyroxine, and antithyroglobulin and antithyroidperoxidase antibodies), urinalysis, and urine toxicology screen. Additionally, women of child-bearing potential received a urine and serum pregnancy test.

A chemistry profile, complete blood count and differential, urine toxicology screen, and urinalysis were obtained at weeks 2, 4, and 8. Thyroid functioning (TSH, triiodothyronine, thyroxine, and antithyroglobulin and antithyroidperoxidase antibodies) were obtained at weeks 4 and 8. An ECG and a repeated height were also measured at week 8. Blood pressure, pulse, and weight were also obtained at each of the weekly study visits.

Medication adherence

Patients were asked to complete a lithium dosing diary; the dosing diaries and study medication were collected at each visit. Medication adherence was assessed by comparing the actual number of capsules returned and the expected number of capsules returned, and by the dosing diary. Additionally, medication compliance was assessed by the review of the lithium trough serum levels. Patients who missed $>$40% of the medication doses between two appointments were discontinued from the study.

Statistical methods

Descriptive statistics are provided for all consented patients who received at least one dose of study medication by treatment group (Arms I, II, and III). Continuous, quantitative variable summaries include the number of patients, mean, standard deviation, median, and ranges (minimum and maximum). Where applicable (primarily for mean change from baseline), 95% confidence intervals are provided. Categorical, qualitative variable summaries include the frequency and percentage of patients who were in the particular category. Within-group *t*-tests were used to determine the significance of the mean change from baseline values (are mean values significantly different from zero). Last observation carried forward (LOCF) methods were implemented for summarization and analysis of change from baseline values for efficacy parameters. The level of significance was set at 0.05 for all analyses. Due to the exploratory nature of this trial, the alpha level for statistical significance was not adjusted for the multiple comparisons performed.

All data summaries and statistical analyses were generated using SAS® software, Version 8.2 (or later).

Results

Study participants

One hundred five patients were screened for possible treatment with lithium under the auspices of this clinical trial. Participant accountability is summarized in Figure 1.

Of the 61 patients who received study medications, 60 youths completed at least 1 week of treatment and returned for a post-baseline assessment. Eight out of the first 10 patients in Arm II completed 8 weeks of treatment and were determined to have tolerated the study drug; as a result, randomization into Arm III became possible. Descriptive information for the 60 patients who both received study medication and completed 1 week of treatment is summarized in Table 3.

Lithium dosing

Of the 60 patients who both received study medication and completed 1 week of treatment, 57 provided reliable dosing data. For these 57 patients, the mean total daily dose was 1500.0 (400.9) mg, whereas the mean weight-adjusted total daily dose was 29.1 (8.0) mg/kg/day. The mean serum concentration at the end of open label treatment/end of study was 1.05 (0.39) mEq/L (range: 0.27–2.08 mEq/L). Additional lithium dosing data by treatment arm are presented in Table 4.

Of the 18 patients who participated in Arm III and provided reliable data, 11 (61.1%) had upward dosing adjustments made during the middle of the first week of treatment. However, only 5 (27.8%) had dosing increases made in the middle of the second week of treatment that were subsequently maintained.

Symptomatic response

A summary of the overall and end of study measures across all three treatment arms are provided in Table 5. The analysis of the CGI-I (overall illness) status at the end of the study showed that most patients (42 patients; 70%) were either very much improved or were much improved on treatment. End of week 8/ET/LOCF scores on the CGI-I across treatment arms are displayed in Figure 2. The YMRS summary percentage improvement showed that more than half of patients (37 patients; 61.7%) had a $\geq$50% improvement in their YMRS summary score. Response status at the end of the study showed that more than half of patients (35 patients; 58.3%) had response ($\geq$50% reduction in YMRS summary score and CGI-I score equal to 1 or 2). Remission status at the end of the study showed the majority of patients (43 patients; 71.7%) were not in remission (YMRS summary score $>$12 or CGI-S $>$2).

Medication tolerability

No deaths occurred in this study. Fifty-nine out of 60 patients experienced at least one TEAE during study participation. Nineteen patients (31.7%) experienced a TEAE that was considered to be possibly related to lithium, and 37 patients (61.7%) experienced a TEAE that was considered to be probably related. Serious TEAEs were experienced by a total of 6 patients (10.0%), only 1 of which (suicidal ideation) was considered to be possibly or probably related to lithium. A total of 3 patients (5.0%) discontinued study medication due to a TEAE. A description of AE

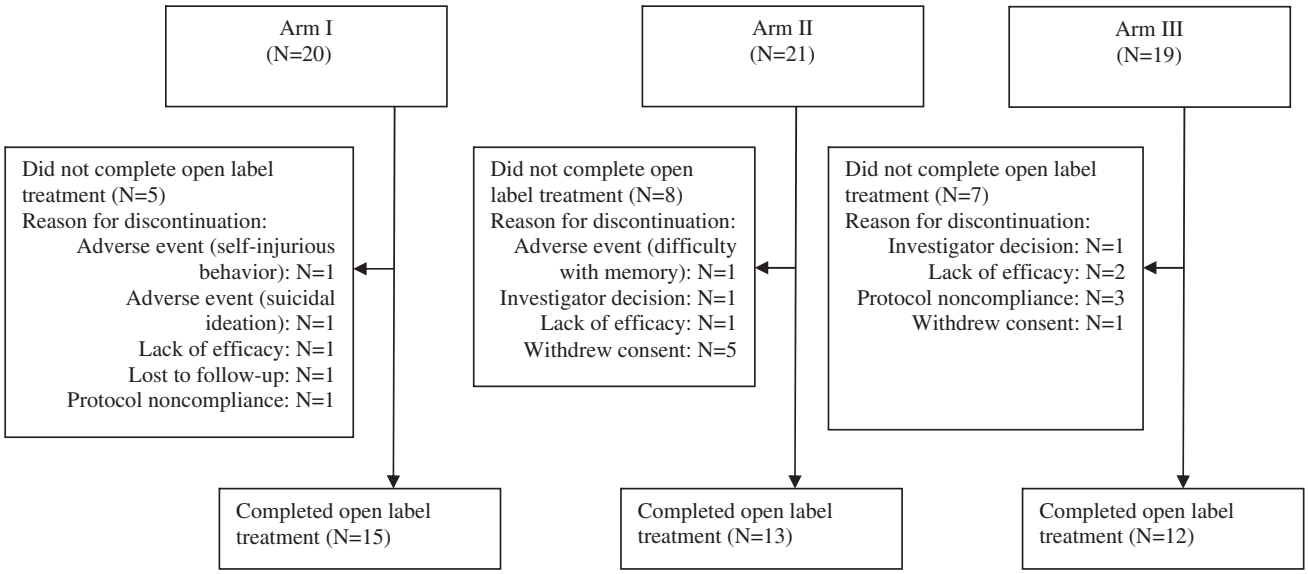

FIG. 1. Participant accountability.

Table 3. Baseline Demographics

	Treatment Arm			
	Arm I (n = *20*)	*Arm II* (n = *21*)	*Arm III* (n = *19*)	*Total participants* (n = *60*)
Age at randomization, years				
Mean (SD)	11.7 (2.7)	12.5 (2.4)	13.5 (3.1)	12.6 (2.8)
Median	12.4	12.2	14.8	12.8
Range	7.9–15.7	8.5–17.7	8.7–17.5	7.9–17.7
Sex (male)	11 (55.0%)	9 (42.9%)	11 (57.9%)	31 (51.7%)
Race				
Caucasian	14 (70.0%)	19 (90.5%)	14 (73.7%)	47 (78.3%)
African American	4 (20.0%)	2 (9.5%)	5 (26.3%)	11 (18.3%)
Caucasian/African American	2 (10.0%)	0	0	2 (3.3%)
Age of onset of bipolar disorder, years				
Mean (SD)	8.1 (2.8)	9.9 (3.1)	10.0 (3.7)	9.3 (3.3)
Median	7.8	10.3	9.3	9.2
Range	2.0–12.8	4.0–16.0	3.3–17.0	2.0–17.0
Mood state at study entry				
Manic	10 (50.0%)	9 (42.9%)	4 (21.1%)	23 (38.3%)
Mixed	10 (50.0%)	12 (57.1%)	15 (78.9%)	37 (60.7%)
Length of bipolar disorder illness, years				
Mean (SD)	3.7 (2.7)	2.7 (1.7)	3.5 (3.2)	3.3 (2.6)
Median	2.9	2.5	2.3	2.5
Range	0.4–9.1	0.3–6.2	0.4–12.1	0.3–12.1
Psychiatric co-morbidity				
Any ADHD[a]	16 (80.0%)	15 (71.4%)	12 (63.2%)	43 (71.7%)
Any disruptive behavior disorder[b]	3 (15.0%)	6 (27.3%)	6 (31.6%)	15 (25.0%)
Any anxiety disorder[c]	4 (20.0%)	6 (28.6%)	2 (10.5%)	12 (20.0%)
Participant length of study participation (days)				
Mean (SD)	53.2 (12.8)	48.8 (14.5)	51.0 (17.4)	50.9 (14.8)
Median	57	56	56	56
Range	15–59	20–61	13–78	13–78

[a]ADHD, attention-deficit/hyperactivity disorder; ADHD-combined; ADHD-inattentive; ADHD-hyperactive/impulsive; ADHD-not otherwise specified (NOS).
[b]oppositional defiant disorder; conduct disorder.
[c]generalized anxiety disorder; separation anxiety disorder; social phobia; specific phobia; panic disorder; post-traumatic stress disorder; anxiety disorder-not otherwise specified (NOS). Note: no patients met diagnostic criteria for co-morbid obsessive compulsive disorder.

Table 4. Lithium Dosing and Serum Levels

	Treatment Arm			
Mean (SD) *Median (Range)*	*Arm I* (n = *20*)	*Arm II* (n = *19*)	*Arm III* (n = *18*)	*Total participants* (n = *57*[a])
Baseline dose, mg/day	615.8 (68.8) 600 (600–900)	900.0 (0.0) 900 (900–900)	900.0 (0.0) 900 (900–900)	801.8 (142.1) 900 (600–900)
Baseline dose, mg/kg/day	14.8 (5.8) 13.8 (6.1–25.2)	16.9 (3.4) 16.0 (12.3–25.5)	17.2 (6.8) 16.2 (5.7–30.0)	16.3 (5.5) 15.5 (5.7–30.0)
Baseline weight, kg	48.1 (20.2) 43.5 (23.8–98.7)	55.9 (10.2) 57.0 (35.3–73.4)	62.3 (30.8) 55.8 (30.0–157.0)	55.2 (22.2) 53.3 (23.8–157.0)
End dose, mg/day	1455.0 (438.3) 1200 (900–2400)	1547.4 (377.7) 1500 (900–2400)	1500.0 (398.5) 1500 (900–2700)	1500.0 (400.9) 1500 (900–2700)
End dose, mg/kg/day	32.7 (8.1) 35.7 (17.9–44.0)	27.2 (5.3) 25.9 (14.2–37.6)	27.7 (9.6) 27.2 (11.3–49.2)	29.1 (8.0) 27.7 (11.3–49.2)
End lithium serum level, mEq/L	1.15 (0.34) 1.10 (0.70–2.08)	0.96 (0.40) 0.91 (0.27–1.80)	1.05 (0.42) 1.00 (0.41–1.92)	1.05 (0.39) 1.00 (0.27–2.08)
End weight, kg	48.9 (21.9) 40.4 (24.2–100.5)	57.4 (10.3) 58.2 (35.7–75.0)	57.0 (20.1) 55.2 (30.30–105.9)	54.6 (18.0) 54.5 (24.2–105.9)

[a]Three of the 60 patients who received study medication and completed 1 week of treatment were considered to be unreliable reporters; therefore, dosing data for these patients are not included in these analyses.

TABLE 5. MEAN OUTCOME MEASURE SCORES BY TREATMENT GROUP

	Treatment Arm			
Measure	*Arm I (n = 20)*	*Arm II (n = 21)*	*Arm III (n = 19)*	*Total participants (n = 60)*
YMRS				
Baseline score *Mean (SD)*	31.3 (5.4)	30.3 (5.0)	29.5 (6.0)	30.3 (5.4)
EOS score *Mean (SD)*	14.0 (8.3)	12.1 (6.2)	14.2 (11.27)	13.4 (8.6)
Change score *Mean (SD)*	−17.3 (7.2)	−18.1 (8.4)	−15.3 (10.9)	−17.0 (8.9)
				$p < 0.0001$
CDRS-R				
Baseline score *Mean (SD)*	40.0 (7.6)	39.4 (13.0)	36.3 (12.8)	38.6 (11.3)
EOS score *Mean (SD)*	28.5 (9.7)	28.0 (8.9)	25.5 (6.4)	27.4 (8.4)
Change score *Mean (SD)*	−11.5 (12.2)	−11.3 (12.2)	−10.8 (12.9)	−11.2 (12.2)
				$p < 0.0001$
CGAS				
Baseline score *Mean (SD)*	47.5 (5.6)	50.8 (5.9)	49.6 (6.6)	49.3 (6.1)
EOS score *Mean (SD)*	62.9 (13.6)	65.2 (13.0)	64.7 (16.3)	64.3 (14.1)
Change score *Mean (SD)*	15.4 (11.3)	14.5 (11.2)	15.3 (14.1)	15.1 (12.0)
				$p < 0.0001$
CGI-S (Mania)				
Baseline score *Mean (SD)*	4.6 (0.6)	4.7 (0.7)	4.7 (0.7)	4.7 (0.7)
EOS score *Mean (SD)*	2.8 (1.1)	2.8 (1.2)	2.9 (1.8)	2.8 (1.3)
Change score *Mean (SD)*	−1.8 (1.1)	−1.9 (1.3)	−1.8 (1.6)	−1.9 (1.3)
				$p < 0.0001$
CGI-S (Depression)				
Baseline score *Mean (SD)*	3.1 (1.3)	3.3 (1.4)	3.2 (1.0)	3.2 (1.2)
EOS score *Mean (SD)*	2.0 (1.0)	2.1 (1.3)	2.2 (1.0)	2.1 (1.1)
Change score *Mean (SD)*	−1.2 (1.4)	−1.2 (1.4)	−0.9 (1.0)	−1.1 (1.3)
				$p < 0.0001$
CGI-S (Overall Illness)				
Baseline score *Mean (SD)*	4.7 (0.6)	4.8 (0.7)	4.7 (0.7)	4.7 (0.7)
EOS score *Mean (SD)*	2.9 (1.1)	2.9 (1.2)	3.0 (1.7)	2.9 (1.3)
Change score *Mean (SD)*	−1.8 (1.0)	−2.0 (1.3)	−1.7 (1.5)	−1.8 (1.2)
				$p < 0.0001$

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

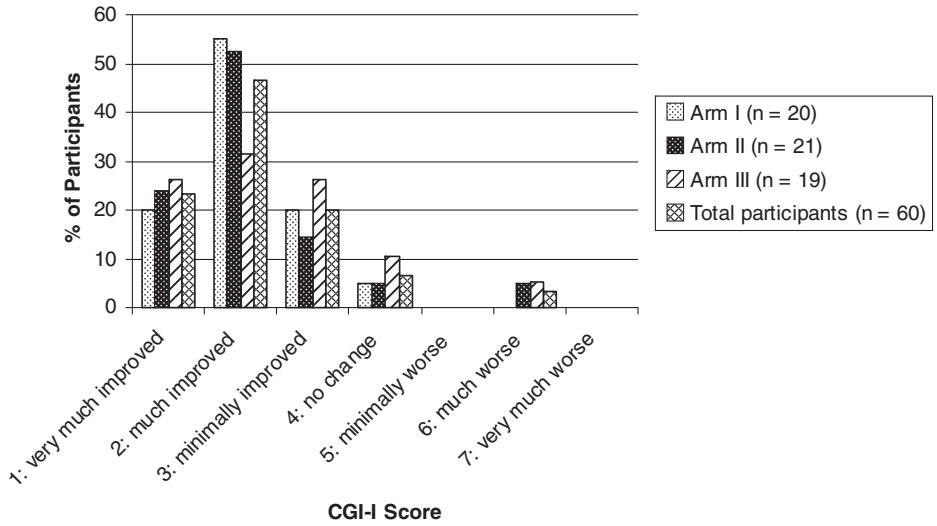

FIG. 2. Clinical Global Impressions-Improvement (CGI-I) Score at Week 8/ET/LOCF. ET = early termination; LOCF = last observation carried forward.

Table 6. Severity of Treatment-Emergent Adverse Events

	Treatment Arm			
TEAE severity	*Arm I (n = 20)*	*Arm II (n = 21)*	*Arm III (n = 19)*	*Total participants (n = 60)*
Number of patients with at least one TEAE	20 (100.0%)	21 (100.0%)	18 (94.7%)	59 (98.3%)
Mild	6 (30.0%)	8 (38.1%)	8 (42.1%)	22 (36.7%)
Moderate	8 (40.0%)	5 (23.8%)	8 (42.1%)	21 (35.0%)
Severe	6 (30.0%)	8 (38.1%)	2 (10.5%)	16 (26.7%)

TEAE = treatment-emergent adverse event.

severity across treatment arms can be found in Table 6. The most commonly experienced AEs reported during the study are listed in Table 7.

Four patients had clinically significant changes in laboratory values during open label treatment with lithium: Increased antithyroglobulin AB and thyroid peroxidase AB ($n = 1$); increased thyrotropin ($n = 2$); decreased hematocrit, hemoglobin, red blood cell count, lymphocyte count, and RDW-CV (TEAE of anemia: $n = 1$); and increased urine specific gravity and leukocyte esterase (TEAE of urinary tract infection: $n = 1$).

Table 7. Most Frequently Occurring (≥10% of Total Patients) Treatment-Emergent Adverse Events

MedDRA system organ class/preferred term	*Total*
Gastrointestinal disorders	
Nausea	40 (66.7%)
Vomiting	33 (55.0%)
Diarrhea	18 (30.0%)
Abdominal pain upper	16 (26.7%)
Abdominal pain	12 (20.0%)
Dry mouth	7 (11.7%)
Nervous system disorders	
Headache	39 (65.0%)
Dizziness	22 (36.7%)
Tremor	16 (26.7%)
Somnolence	11 (18.3%)
Coordination abnormal	6 (10.0%)
General disorders and administration site conditions	
Thirst	11 (18.3%)
Fatigue	10 (16.7%)
Irritability	8 (13.3%)
Pyrexia	6 (10.0%)
Psychiatric disorders	
Initial Insomnia	7 (11.7%)
Metabolism and nutrition disorders	
Decreased appetite	11 (18.3%)
Increased appetite	9 (15.0%)
Renal and urinary disorders	
Pollakiuria	17 (28.3%)
Skin and subcutaneous disorders	
Rash	8 (13.3%)
Respiratory, thoracic and mediastinal disorders	
Nasal congestion	7 (11.7%)
Eye disorders	
Vision blurred	6 (10.0%)
Musculoskeletal and connective tissue disorders	
Back pain	6 (10.0%)

The mean pretreatment thyrotropin concentration was 1.92 (1.05) mIU/L. The mean post-treatment thyrotropin concentration was 5.28 (3.39) mIU/L ($p < 0.0001$). Two patients had a thyrotropin concentration greater than 10 mIU/L at week 4, and at week 8, 4 patients had a thyrotropin concentration greater than 10 mIU/L. There was no overlap between the patients with thyrotropin concentration greater than 10 mIU/L at week 4 and those at week 8. Four patients were described as having a thyroid-related TEAE: Hypothyroidism ($n = 1$); blood TSH increased ($n = 3$). The mean pretreatment white blood cell count was 6.50 (1.69)×10E9/L, and the mean post-treatment white blood cell count was 7.97 (2.08)×10E9/L ($p < 0.0001$). The mean pretreatment neutrophil concentration was 47.2% (14.7) and the mean post-treatment neutrophil concentration was 57.2% (12.9) ($p < 0.0001$).

AEs and study discontinuations in patients with lithium levels above 1.4 mEq/L

To reiterate, the 1.4 mEq/L upper limit for lithium level in the current study was used as a indicator for which dose increases could not occur, rather than a point at which dose was reduced. Owing to concerns regarding lithium toxicity at higher serum concentrations, the proportion of patients whose lithium level at some point exceeded 1.4 mEq/L and the association with more frequent or serious side effects were examined. Neither serious AE frequency nor study discontinuations seemed to rise with lithium serum concentrations above 1.4 mEq/L. These data are shown in Table 8.

Other psychometric measures

Mean (SD) scores at baseline, end of week 4, and end of week 8 for the attention-deficit/hyperactivity disorder Rating Scale-IV, BPRS for Children, Caregiver Strain Questionnaire, Child Mania Rating Scale-Parent, Parent General Behavior Inventory-10 Item Mania Scale, Irritability, Depression, and Anxiety, Nisonger Child Behavior Rating Form-Typical IQ Version, and Pediatric Anxiety Rating Scale are summarized in Table 9. Of note, treatment with lithium was associated with a statistically significant improvement on every subscale except for organicity ($p = 0.56$) on the BPRS for Children. Analyses of the 10 subscales of the Family Environment Scale (data not presented) showed no significant improvement in family functioning after 8 weeks of treatment with lithium. On the Social Adjustment Inventory for Children and Adolescents (data not presented), significant reductions in baseline scores for school behavior problems, spare time problems, problems with siblings, and problems with parents were noted at the end of week 8 (all $p < 0.05$).

Table 8. Adverse Events and Study Discontinuations in Patients with Lithium Level >1.4 mEq/L

	Arm I				Arm II				Arm III				Total			
Lithium level	*N*	*AE*	*SAE*	*ET*	*N*	*AE*	*SAE*	*ET*	*N*	*AE*	*SAE*	*ET*	*N*	*AE*	*SAE*	*ET*
>1.4 mEq/L	8	8	0	1	5	5	0	0	7	6	0	3	20	19	0	4
≤1.4 mEq/L	12	12	5	4	17	16	0	8	12	12	1	4	41	40	6	16
Total	20	20	5	5	22	21	0	8	19	18	1	7	61	59	6	20

AE = adverse event; SAE = serious adverse event; ET = early termination.

Discussion

To develop an empirically based dosing paradigm, three different strategies with increasing starting doses and two different rates of escalation were employed. The more rapid dose escalation paradigm in Arm III was both effective and tolerable. However, despite the substantive proportion (61.1%) of mid-week upward dosing increases that occurred during the first week of treatment, most dosing increases (72.2%) that occurred in the middle of the second week of treatment were not subsequently maintained. For this reason, treating patients in a similar fashion to what was used in Arm III appears, with the exception of having mid-week dosing increases after week 1, to be a relatively effective means by which to achieve therapeutic lithium doses.

This protocol employed a strategy to determine a maximally tolerated lithium dose, rather than treat patients within a therapeutic range based on adult data. Although data from this study help provide information about the upper limits of therapeutic lithium concentrations in youths, this study does not help answer the question of what a minimally effective dose of lithium in youth might be.

The maximum allowable lithium serum concentration, above which further dose increases could not occur in this trial (1.4 mEq/L), is a concentration higher than normally seen in prior pediatric studies (Findling et al. 2003; Kafantaris et al. 2003; Pavuluri et al. 2004; Kowatch et al. 2007). This approach was used to determine whether the upper limits of therapeutic levels reported in adults were tolerable in children and adolescents. In this study, using the 1.4 mEq/L parameter as a stopping criterion for subsequent dose increases appeared to be associated with an appropriate degree of safety.

Overall, lithium was well tolerated. Few patients discontinued treatment as a result of medication-related adverse effects. Further, the most common side effects that were experienced were expected. As it has been reported that treatment with lithium is associated with significant rates of thyrotropin elevation in children and adolescents with bipolar disorder (Gracious et al. 2004), thyrotropin levels were monitored. Overall, mean thyrotropin levels increased after 8 weeks of open-label treatment with lithium. In addition, six patients experienced putatively significant increases (≥10 mIU/L) in thyrotropin levels. Whether or not these elevations would be sustained or magnified if the study was extended beyond 8 weeks remains to be seen.

Data from this relatively large, open-label study of lithium monotherapy in pediatric outpatients adds to the extant literature (Findling and Pavuluri 2008) that suggests that lithium may be useful in the treatment of BP-I in children and adolescents. Lithium monotherapy was generally associated with salutary effects. Regardless of starting dose and dosing strategy, most patients experienced a significant improvement in mood symptoms. In fact, slightly more than half of the patients were considered to be responders after 8 weeks of open-label treatment with lithium.

Table 9. Psychometric Measure Scores

	Baseline	End of week 4		Week 8/ET/LOCF	
Instrument	*Mean (SD)*	*Mean (SD)*	p	*Mean (SD)*	p
ADHD Rating Scale-IV (ARS-IV)					
Total score	34.7 (11.7)	28.3 (12.2)	0.0002	29.4 (11.8)	0.0013
Inattention	18.7 (6.2)	16.0 (6.0)	0.0022	16.7 (5.7)	0.0213
Hyperactivity-Impulsivity	16.0 (6.6)	12.4 (6.9)	0.0003	12.7 (7.2)	0.0001
Brief Psychiatric Rating Scale for Children (BPRS-C)					
Total score	33.9 (9.5)	18.4 (10.3)	<.0001	16.5 (11.0)	<0.0001
Caregiver Strain Questionnaire (CSQ)					
Total score	66.0 (16.6)	N/A	N/A	56.6 (19.8)	0.0029
Child Mania Rating Scale-Parent Report (CMRS-P)					
Total score	27.4 (10.6)	17.7 (10.0)	<0.0001	16.8 (9.8)	<0.0001
Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M)					
Total score	17.6 (6.5)	10.4 (7.7)	<0.0001	10.8 (7.1)	<0.0001
Irritability, depression, and anxiety (IDA)					
Total score	9.9 (1.9)	6.5 (3.4)	<.0001	5.1 (3.7)	<0.0001
Nisonger Child Behavior Rating Form-TIQ (NCBRF-TIQ)					
Conduct Problem	18.3 (9.0)	13.3 (9.6)	0.0001	11.3 (9.9)	<0.0001
ADHD-Total	22.3 (7.3)	17.4 (7.6)	0.0002	16.9 (7.7)	<0.0001
Pediatric Anxiety Rating Scale (PARS)					
Total score with five items	5.9 (7.9)	3.9 (7.2)	0.0091	3.9 (6.1)	0.0031

LOCF = last observation carried forward; ET = early termination.

However, similar to what has been reported in other monotherapy studies in pediatric BP-I (Tohen et al. 2007; Findling et al. 2009; Haas et al. 2009), a majority of the patients did not meet criteria for remission.

This study is primarily limited by its open uncontrolled design, brevity, and relatively small sample size. In fact, the rate of response may be inflated owing to the open nature of this trial. Another limitation is inherent to the fact that this is an outpatient trial. Specifically, the lithium levels that were ascertained may not have been fully accurate, as timing of last dose and medication adherence were based on parent/patient report and not direct clinician observation. Despite this shortcoming, an examination revealed that the daily lithium dose was highly correlated with serum concentration (Pearson correlation coefficient: $n = 361$ pairs, $r = 0.51$, $p < 0.0001$). Finally, because this trial studied only the acute treatment of pediatric mania, conclusions may not be generated as to whether or not lithium has promise as a form of maintenance pharmacotherapy in children and adolescents with BP-I.

Conclusions

Perhaps most notably, the results of this study provide a readily generalizable evidence-based strategy for the dosing of lithium in pediatric patients. Based on these results, a dosing paradigm in which patients begin treatment with lithium at a dose of 300 mg thrice daily, followed by 300 mg weekly increases (with an additional 300 mg increase during the first week) until *a priori* stopping criteria are met, will be used in an upcoming randomized, double-blind, placebo-controlled trial of lithium in pediatric BP-I.

Clinical Significance

This exploratory study obtained data that provide evidence-based dosing strategies for lithium in children and adolescents suffering from BP-I. Lithium was, in general, well-tolerated and associated with significant symptom amelioration in children and adolescents with BP-I. However, as reported with other drug monotherapy studies, remission was not achieved in most patients.

Disclosures

Dr. Findling receives or has received research support, acted as a consultant, and/or served on a speaker's bureau for Abbott, Addrenex, AstraZeneca, Biovail, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Johnson & Johnson, KemPharm Lilly, Lundbeck, Neuropharm, Novartis, Noven, Organon, Otsuka, Pfizer, Sanofi-Aventis, Sepracore, Schering-Plough, Shire, Solvay, Supernus Pharmaceuticals, Validus, and Wyeth.

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Dr. Sikich has a current financial interest in that she receives research funding or participates in clinical trials with Janssen, Pfizer, Bristol Myers-Squibb, Neuropharm, Curemark, and Seaside Pharmaceuticals, and received software for a computer intervention in schizophrenia from Posit Science; in the past, Dr. Sikich received research funding from Eli Lilly, Janssen, Pfizer, Otsuka, and Astra Zeneca, and has served as a consultant for Sanofi Aventis and ABT Associates.

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