2019

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R. L. Findling

N. K. McNamara

M. Pavuluri

J. A. Frazier

M. Rynn

See next page for additional authors

HHS Public Access

Author manuscript

J Am Acad Child Adolesc Psychiatry. Author manuscript; available in PMC 2020 February 01.

Published in final edited form as:

J Am Acad Child Adolesc Psychiatry. 2019 February ; 58(2): 287–296.e4. doi:10.1016/j.jaac.2018.07.901.

Lithium for the Maintenance Treatment of Bipolar I Disorder: A Double-Blind, Placebo-Controlled Discontinuation Study

Dr. Robert L. Findling, MD, MBA,
The Johns Hopkins University, Baltimore, MD

Dr. Nora K. McNamara, MD,
Case Western Reserve University, Cleveland, OH

Dr. Mani Pavuluri, MD, PhD,
The Brain and Wellness Institute, Chicago, IL

Dr. Jean A. Frazier, MD,
University of Massachusetts Medical School, Boston

Corresponding Author: Robert L Findling, MD, MBA, The Johns Hopkins University, 1800 Orleans Street Suite 12344A, Baltimore, MD 21287; RFindli1@jhmi.edu.

Ms. Martz served as the statistical expert for this research.

The authors would like to thank the study participants and their families.

Disclosure: Dr. Findling has received research support, acted as a consultant, and/or served on a speaker's bureau for Aevi, Akili, Alcobra, Amerex, the American Academy of Child and Adolescent Psychiatry (AACAP), American Psychiatric Press, Bracket, Epharma Solutions, Forest, Genentech, Ironshore, KemPharm, Lundbeck, the National Institutes of Health (NIH), Neurim, Nuvelution, Otsuka, the Patient-Centered Outcomes Research Institute (PCORI), Pfizer, Physicians Postgraduate Press, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Syneurx, Teva, Tris, TouchPoint, and Validus. Dr. McNamara has received research or travel support from and/or acted a consultant for Acadia Pharmaceuticals, F. Hoffmann-La Roche AG, Forest, Janssen Pharmaceuticals, Lundbeck, NaBen, NIH, Otsuka Pharmaceuticals, Pfizer Inc., Shire, Sunovion Pharmaceuticals, and Tonix Pharmaceuticals. Dr. Pavuluri is the cofounder of the Brain and Wellness Institute and holds shares in Medcircle, Inc. Dr. Frazier has received grant or research support from NIH, the National Institute of Mental Health (NIMH), Fulcrum Therapeutics, Janssen Research and Development, LLC, Neuren Pharmaceuticals, Roche, and SyneuRX International. She has served on the editorial board of the *Harvard Review of Psychiatry* and as associate editor of the *Journal of Child and Adolescent Psychopharmacology.* Dr. Rynn has received grant or research support from NIMH, NICHD, Neurocrine Biosciences, Inc., and Pfizer Inc. She has received royalties from UptoDate. Dr. Robb has received research and/or travel support, has received royalties and/or honoraria, has stock or equity in, acted as a consultant, and/or served on a speaker's bureau for Actavis/Allergan/Forest, Aevi Genomic Medicine, AACAP, American Academy of Pediatrics, Bracket, the Child and Adolescent Psychiatric Society of Greater Washington local branch, Case Western Reserve University, College of Neurologic and Psychiatric Pharmacists, Eli Lilly and Co., GlaxoSmithKline, Guilford Press, Janssen Pharmaceuticals, Inc., Lundbeck, the National Center for Advancing Translational Sciences, Neuronetics, Neuroscience Education Institute, NICHD, NIMH, the National Institute of Neurological Disorders and Stroke, the North American Center for Continuing Medical Education, Otsuka, Pfizer Inc., Shire, Sunovion Pharmaceuticals, Supernus, SyneuRx, and the University of Cambridge. She has also participated in paid speaking engagements at the University of Kansas Medical Center, Our Lady of the Lake Hospital, and the Carle University School of Medicine. Dr. DelBello has received grant or research support from NIMH, the National Institute of Diabetes and Digestive and Kidney Diseases, PCORI, Amarex, Johnson and Johnson, Supernus, Sunovion, Otsuka, Pfizer, Lundbeck, and Shire. She has served as a consultant to, on the advisory boards of, and/or received honoraria from Akili Interactive, CMEology, Johnson and Johnson, Lundbeck, Neuronetics, Pfizer, Sunovion, Supernus, and Takeda. She has served as field editor of *Bipolar Disorders* and associate editor of the *Journal of Child and Adolescent Psychopharmacology*. Dr. Kowatch has served on a Data Safety Monitoring Board for Forest and Pfizer Inc. Drs. Scheffer, Kafantaris, Zhao, Clemons, Anand, and Taylor-Zapata, Ms. Rowles, Mr. Lingler, and Ms. Martz report no biomedical financial interests or potential conflicts of interest.

Clinical trial registration information: Lithium for the Treatment of Pediatric Mania. https://clinicaltrials.gov/: NCT00442039 (CoLT 1).

Safety and Efficacy Study of Lithium for the Treatment of Pediatric Mania. https://clinicaltrials.gov/: NCT01166425 (CoLT 2)

Dr. Moira Rynn, MD,
Duke University, Durham, NC

Dr. Russell Scheffer, MD,
Private practice

Dr. Vivian Kafantaris, MD,
The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY

Dr. Adelaide Robb, MD,
George Washington University School of Medicine & Health Sciences, Washington, DC

Dr. Melissa DelBello, MD,
University of Cincinnati College of Medicine, Cincinnati, OH

Dr. Robert A. Kowatch, MD, PhD,
Ohio State University Wexner Medical Center, Columbus, OH

Ms. Brieana M. Rowles, MA,
The Johns Hopkins University, Baltimore, MD

Mss Jacqui Lingler, BS,
The EMMES Corporation, Rockville, MD.

Dr. Jian Zhao, PhD,
The EMMES Corporation, Rockville, MD.

Dr. Traci Clemons, PhD,
The EMMES Corporation, Rockville, MD.

Mss Karen Martz, MS,
The EMMES Corporation, Rockville, MD.

Dr. Ravinder Anand, PhD, and
The EMMES Corporation, Rockville, MD.

Dr. Perdita Taylor-Zapata, MD
Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD.

Abstract

Objective: This study examined the role of lithium in the maintenance treatment of pediatric patients with bipolar I disorder (BP-I).

Method: Participants, aged 7 to 17 years presenting with a manic or mixed episode, received 24 weeks of lithium treatment in one of two multiphase studies, the Collaborative Lithium Trials (CoLT 1 and CoLT 2). Responders were randomized to continue lithium or to be cross titrated to placebo for up to 28 weeks. The primary outcome measure was relative risk of study discontinuation for any reason.

Results: A Cox regression analysis found that those who continued treatment with lithium (n=17) had a lower hazard ratio compared to those who received placebo [n=14 (p=0.015)]. The

vast majority of discontinuations were due to mood symptom exacerbations, with most of these occurring in the placebo-treated group. Discontinuation for other reasons occurred at similarly low rates across both group. Most adverse events were mild to moderate in severity, and only one study participant was discontinued from the trial owing to a serious adverse event (aggression). There was no statistically significant difference with respect to weight gain in participants receiving lithium compared to those receiving placebo.

Conclusion: This randomized, double-blind, placebo-controlled discontinuation trial builds support for the role of lithium as a maintenance treatment in pediatric patients with bipolar disorder and for the safety and tolerability of 28 weeks of maintenance lithium treatment.

Keywords

lithium; bipolar; treatment; adolescents; children

Introduction

Bipolar disorder in children and adolescents is associated with significant long-term morbidity and disability.[1-4] Owing to the severity and persistence of bipolar disorder into adulthood,[5-9] safe and effective long-term treatments are needed.

Placebo-controlled studies to date suggest that quetiapine, risperidone, olanzapine, aripiprazole, ziprasidone, and asenapine may have a role in the treatment of acute mania in pediatric patients.[10-15] Despite lithium's history as an established benchmark treatment for adults with bipolar disorder in adults,[16-20] double-blind, placebo-controlled data for children have historically been lacking. A recent double-blind, placebo-controlled study from our group showed lithium's efficacy and effect size in the acute treatment of mania in pediatric patients is comparable to what has been reported in adult patients.[21] Recent open-label data that we have published also indicate that lithium may be a safe and effective longer-term treatment for pediatric patients with bipolar disorder who respond to acute treatment with lithium.[22]

There are limited prospective long-term pharmacological treatment data for bipolar disorder in children and adolescents. Previous prospective data in the pediatric age group have generally been restricted to combination pharmacotherapy studies.[23-25] In addition, aripiprazole has been found to be superior to placebo in the post-acute treatment of children and adolescents with bipolar disorder.[26,27] However, only a modest amount of information exists based on double-blind, placebo-controlled data regarding the treatment of pediatric patients with lithium beyond eight weeks.[28] The purpose of this study is to examine the role of lithium in the maintenance treatment of pediatric patients with bipolar I disorder.

Method

This work was sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) "Best Pharmaceuticals for Children Act Pediatric Off-Patent Drug Study (PODS): Lithium in the Treatment of Pediatric Mania" (Contract HHSN275200503406C).

Institutional Review Board (IRB) approval of the protocol, informed consent, advertising and all amendments were obtained prior to implementation at all study locations. Prior to the initiation of any study-related procedures, the informed consent statement was signed by the participant's parent or legal guardian and by the person who was authorized to administer the informed consent. Further, children who could read and understand the assent form were asked to give written assent.

This work was a multi-center, double-blind, placebo-controlled study. All study participants included in this Discontinuation Trial received 24 weeks of open-label lithium prior to study entry. Most participants (n=21) entered from CoLT 1,[22,29] after completing 8 weeks of open-label lithium treatment during which intensive sampling for pharmacokinetic analyses occurred, followed by a 16-week open-label, post-acute stabilization phase[22] for a total pre-randomization lithium treatment period of 24 weeks.

The remaining 10 participants entered from CoLT 2 following an eight-week double-blind, placebo-controlled study[22,30] in which participants were either treated with: (a) eight weeks of double-blind lithium which was followed by 16 weeks of open-label lithium prior to randomization, or (b) eight weeks of double-blind placebo followed by 24 weeks of open label lithium prior to randomization (see Figure 1).

The Discontinuation Trial was 28 weeks long. Study visits occurred at the following time points: Week 1, 2, 3, 4, 6, 8, 10, 12, 16, 20, 24, and 28 / end of treatment (EOT).

Participants

Briefly, eligible study participants were between the ages of 7 and 17 years (inclusive) and met diagnostic criteria for BP-I, manic or mixed. Further, study participants 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 CoLT 1 and CoLT 2, as well as flow charts outlining study participant disposition through both trials, please see Findling et al. [30]

In both CoLT 1 and CoLT 2, in order to be eligible for this Discontinuation Trial, the outpatient participant must have completed at least six of the last eight consecutive weeks (starting at Week 8) of post-acute open-label treatment with a Young Mania Rating Scale (YMRS) < 10 and Children's Depression Rating Scale-Revised (CDRS-R) < 35,[31,32] and a therapeutic lithium level (≥ 0.6 mEq/L). Psychotherapy was allowed during post-acute open-label treatment, and must have been of stable intensity for the last four weeks of the post-acute open-label period prior to entry into the Discontinuation Trial.

Diagnostic Procedures

Eligible study participants underwent a psychiatric interview with a board-certified or board-eligible child and adolescent psychiatrist to establish a clinical diagnosis of BP-I-manic or mixed phase prior to receiving any study-related medication. Additionally, subjects and their parents or guardians 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) [33] to confirm the clinician's diagnosis.

Outcome Measures

At each visit, psychometric outcome measures including the YMRS, CDRS-R, Clinical Global Impressions-Severity (CGI-S),[34] and CGI-I were obtained. In addition, completed at baseline and Weeks 4, 8, 16, and 28/EOT were the Children's Global Assessment Scale (CGAS),[35] and the Parent General Behavior Inventory-10 Item Mania Scale (PGBI-10M).[36] Inter-rater reliability was established and maintained with quarterly assessments across investigative sites for the YMRS and CDRS-R.

Safety Assessments

Side effects were assessed at every study visit by direct, open-ended query of the participants and guardians with ascertainment facilitated using the Side Effects Form for Children and Adolescents (SEFCA),[37] supplemented by specific items from the UKU Side Effect Rating Scale[38] and the Safety Monitoring and Uniform Report Form (SMURF).[39] Neurological side effects were assessed using the Neurological Examination for Lithium (NELi) [30] and the Neurological Rating Scale (NRS).[40] 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 and an electrocardiogram (ECG) were performed at baseline and EOT.

A fasting comprehensive chemistry profile, complete blood count with differential, lipid profile, thyroid profile, urinalysis, and urine toxicology screen were performed at baseline and EOT. These assessments were also performed, non-fasting, at Weeks 8, 16, and 20 (CoLT 1). To monitor renal function, creatinine clearance was measured at baseline and Weeks 16 (CoLT 2) and 28/EOT. Females of childbearing potential received a urine and serum pregnancy test at baseline and Weeks 8, 16, 20 (CoLT 1) and 28/EOT.

Randomization

Using a blinded random assignment and blinded placebo-controlled discontinuation design, approximately half of the responders remained on maintenance lithium treatment and the other half underwent gradual taper of their lithium dose by the substitution of identically appearing placebo capsules for active lithium capsules. The randomization was stratified by age group, stimulant treatment, antipsychotic medication use and gender.

Lithium Dosing

Participants' lithium treatment was optimized during the antecedent Long-Term Effectiveness Phase. The dose was maintained by an unblinded physician 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. To accurately assess trough levels, lithium serum concentration was obtained after a minimum of seven days after a dose change.

In CoLT 1,[22] the Long-Term Effectiveness Phase followed the open-label eight-week pharmacokinetic treatment phase whereas in CoLT 2, it followed the eight-week double-blind placebo-controlled acute efficacy study. Participants who received placebo during the Efficacy Phase had their doses titrated by unblinded study physicians via weekly lithium dose adjustments to maximize efficacy and minimize adverse events. As in CoLT 1, lithium dose was maintained in order to sustain a recommended trough level between 0.8 and 1.2 mEq/L whilst not exceeding 1.4 mEq/L.

Concomitant medication treatment could be initiated prior to entry into this Discontinuation Trial following a standardized algorithm,[22] based on the extant evidence-based literature at the time these series of studies were designed. Briefly, 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 study participant need. To be eligible for entry into this concomitant treatment algorithm, the participant's lithium dose and mood symptoms needed to be stable. No dose changes to adjunctive medications or new adjunctive medications were to be prescribed in the Discontinuation Trial. For additional details, please see Findling et al.[22]

For participants randomized to receive placebo in the Discontinuation Trial., a gradual medication taper was begun. Dependent upon the participant's lithium dose at the end of the Long-Term Effectiveness phase, the daily dosage was gradually reduced by 300 mg or 600 mg increments each week over the course of four weeks.

For those assigned to continue lithium, their lithium dose was not changed, if possible, during this double-blind period as the patient's lithium dose had previously been optimized. However, based on efficacy and tolerability, a participant's lithium dose could be adjusted within a range recommended by the blinded study doctor. The maximum daily dose was not to exceed 40 mg/kg. In addition, an un-blinded physician at each site monitored the serum lithium level for all study participants, regardless of randomization assignment. The un-blinded physician ensured that lithium levels were maintained at the requisite therapeutic levels for participants randomized to remain on lithium treatment, between 0.8 and 1.2 mEq/L.

Discontinuation Criteria

Participants were withdrawn from the double-blind Discontinuation Trial and could have been eligible for subsequent open-label treatment based on any of the following criteria:

(1) study physician discretion; (2) persistent moderate symptoms of depression (assessed by the administration of the CDRS-R) and/or mania (as assessed by the administration of the YMRS) defined by 10 points above the baseline (last visit in the Long-Term Effectiveness Phase) for two consecutive visits, including interim visits, separated by at least 14 days; (3) any of the following symptoms rated at the maximum score for any of the following YMRS items: #2 (continuous hyperactivity-cannot be calmed), #7 (incoherent; communication impossible), #8 (delusions, hallucinations), or #9 (assaultive; destructive); (4) development of a syndromal manic, mixed or depressive episode, according to DSM-IV in the treating physician's opinion; (5) persistent significant exacerbation of symptoms based on having a

CGI-I score indicative of the participant being “much worse” or “very much worse” for two consecutive visits in the Discontinuation Trial, including interim visits, separated by at least 14 days as compared to the final open label treatment assessment.

Statistical Methods

The primary endpoint is the relative risk of discontinuation for any reason, comparing lithium to placebo. Time from randomization to discontinuation for any reason was analyzed using Cox proportional hazards regression models. Participants who did not discontinue were censored at the time of the Week 28 visit. The Cox proportional hazards regression model included treatment group as the independent factor and was stratified by age group. The data are shown graphically using Kaplan-Meier estimates. The analyses are based on the as-treated (AT) population.

Owing to a miscommunication from the coordinating center, three participants from CoLT 1 who were randomized to receive placebo received lithium, instead. Since these three participants received lithium for the entire course of the discontinuation study, had the integrity of their blinded treatment maintained, and received blinded treatment identical to other participants who received lithium, they are being reported and analyzed within the lithium group.

In addition to time to discontinuation for any reason, time to recurrence of mood symptoms also was analyzed using Cox proportional hazards regression models with treatment group as the independent factor and stratified by age strata. Participants with recurrence of mood symptoms are considered to have had an intervention if they received concomitant psychotherapy, concomitant psychotropic medications or if they left the Discontinuation Trial at the time of the recurrence of mood symptoms. Participants were considered to have recurrence of mood symptoms at the time of the intervention and participants not having recurrence of mood symptoms were censored when they left the Discontinuation trial. One participant had a recurrence of mood episode at Week 2 but had no interventions and completed all 28 weeks of the Discontinuation Trial. This participant was censored at Week 28 for this analysis.

For those who were discontinued due to mood symptomatology, failure for meeting remission criteria was based on previously-described thresholds for depressive[41] and manic[22] symptomatology. Patients’ qualitative mood state at relapse was based on the presence of manic, depressive or mixed (both manic and depressive symptomatology) features at either the last patient visit or at the last patient visit where suprathreshold symptomatology was manifest.

Continuous secondary endpoints were analyzed using a linear regression model with the change score as the dependent variable, baseline score as a covariate, and age strata, gender, study (CoLT 1 vs. CoLT 2) and AT treatment group as factors. Endpoints analyzed were YMRS total score CDRS-R, CGAS and PGBI-10M.

Comparison of categorical baseline variables between treatment groups was made using the Chi-square statistic and continuous variables were compared using Kruskal-Wallis Chi-

square statistic. The baseline value is from the last day of the previous phase, last observation carried forward (LOCF). The change score is the difference between the LOCF value and baseline value. All statistical analysis was performed by using the SAS System for Windows, Version 9.2 or higher (SAS Institute, Cary, NC).

Results

Patient Disposition and Demographics

Participant disposition for the Discontinuation Trial is summarized in Figure 1. Enrollment into the trials occurred from December 2006 through April 2009 (CoLT 1) and May 2010 through March 2013 (CoLT 2). For the purposes of this manuscript, analysis of the Discontinuation Trial includes 31 participants: 21 participants from the CoLT 1 study and 10 participants from the CoLT 2 study. There were 17 participants who received lithium and 14 participants who received placebo.

Of the 31 Discontinuation Trial participants, 13 (42%) completed all 28 weeks of the Discontinuation Trial: 11 (65%) lithium and 2 (14%) placebo-treated patients. The remaining 18 (58%) participants discontinued during the discontinuation trial (see Figure 1). Most of the participants (n=13; 72%) discontinued due to emergence of mood symptoms that met or exceeded pre-specified thresholds: lithium treated patients - 3 (17.6%) and placebo-treated patients - 10 (71.4 %). These patients came disproportionately from the placebo-treated group. Five discontinued for reasons other than mood symptoms: 3 (17.6%) in the lithium group and 2 (14.3 %) in the placebo group. These non-mood related discontinuations occurred at similar rates across both treatment groups.

Demographic information is summarized in Table 1. Prior to entry into the Discontinuation Trial, nine of the participants (29%) were prescribed concomitant psychostimulants for ADHD symptoms. Five (16%) were prescribed an additional mood stabilizer and six (19%) were prescribed an adjunctive antipsychotic medication. At the end of the Long-Term Effectiveness Phase (baseline), YMRS, CDRS-R, CGAS, and PGBI-10M scores did not significantly differ among those participants who received lithium compared with those who received placebo.

Dosing

Participants treated with lithium started the Discontinuation Trial at a mean (SD) dose of 1394 (424) mg/day / 30.7 (5.1) mg/kg/day. The mean (SD) dose of placebo-treated patients at the beginning of the Discontinuation Trial was 1736 (529) mg/day / 28.1 (6.3) mg/kg/day. Based upon Kruskal-Wallis p-values, there were no between-group differences with regard to starting lithium dose [dose (mg/day): p=0.064; weight-based dose (mg/kg/day): p=0.250]. The mean (SD) last reported dose of lithium at the end of the phase was 1412 (438) mg/day / 29.8 (7.2) mg/kg/day.

Efficacy

Efficacy data are outlined in Table 2. The results of Cox regression analysis of the primary efficacy endpoint found a statistically significant difference, with the participants receiving

lithium having a lower HR compared to participant receiving placebo: HR=0.28 (compared to placebo), 95% CI 0.10 – 0.78, and p=0.015 after adjustment by age strata (Figure 2).

Discontinuation due to mood symptoms occurred in 5/17 (29%) of participants treated with lithium compared to 10/14 (71%) of participants treated with placebo, HR-0.24 (lithium compared to placebo), 95% CI 0.08 – 0.74 (p=0.013) after adjustment by age strata. Of the five patients who were discontinued during lithium treatment, three had manic symptomatology and two had elevations in both manic and depressive (i.e. mixed) symptoms. Half of the 10 placebo-treated patients who were discontinued had manic symptoms and the other half had mixed features at discontinuation.

The participants receiving lithium completed an average of 20.7 weeks (SD 11.2 weeks), compared to those participants receiving placebo, who completed an average of 8.7 weeks (SD 8.5 weeks). The difference in the length of participation between the two treatment groups was statistically significant (p=0.043).

On the secondary outcome measures participants who were maintained on lithium tended to have better outcomes across all measures. The mean (SD) change in symptom severity from baseline as measured by change in YMRS score was 4.9 (9.6) for participants treated with lithium and 10.1 (10.0) for participants treated with placebo (p=0.053). See Table S1, available online.

For CDRS-R score mean (SD) change from baseline to LOCF was 1.7 (5.9) for lithium treated participants and 5.2 (10.9) for placebo treated participants (p=0.159). See Table S2, available online. The mean (SD) change of the CGAS score was −0.5 (18.9) for lithium treated participants and −10.3 (12.7) for placebo treated participants (p=0.005). The mean (SD) of change from baseline to LOCF in the parent-rated total PGBI-10M score was 1.2 (7.5) for participants treated with lithium and 5.6 (8.5) for participants treated with placebo (p=0.078).

Adverse Events

Adverse event (AE) data are presented in Table 3. Most AEs were mild to moderate in severity. Twenty-four (77 %) of the study participants experienced at least one adverse event during this trial. Of the 17 lithium treated participants, 15 (88%) reported at least one AE; of the 14 placebo treated participants, nine (64%) reported at least one AE.

The most frequent AEs for those participants who received lithium were: headache (35%), upper abdominal pain (29%), enuresis (24%), vomiting (24%), initial insomnia (18%), upper respiratory tract infection (18%), decreased appetite (12%) and nasopharyngitis (12%). For participants who received placebo, the most frequent AEs were: headache (29%), initial insomnia (14%) and decreased appetite (14%).

Of note, increased suicidal ideation was not reported as an AE. There were no deaths or completed suicides. There was one serious AE, aggression, which led to a lithium-treated participant’s study discontinuation. The event (reported on study day 18) was moderate in severity and rated as possibly related to study medication.

There was no statistically significant between-group difference with respect to weight gain. A mean (SD) weight gain of 1.8 (3.5) kg was seen in the lithium-treated participants and a mean (SD) weight gain of 1.7 (4.1) kg was observed in placebo-treated participants. The mean (SD) change in weight Z score for lithium treated participants was −0.03 (0.28) and for placebo treated participants was 0.04 (0.14).

Clinical Laboratory Evaluations

The thyroid stimulating hormone decreased 2.9 (2.4) mIU/L in placebo treated participants from the start of the study to LOCF, with a smaller decrease of 0.6 (1.6) mIU/L in the participants that remained on lithium.

For lithium-treated patients, the mean (SD) white blood count (WBC) was 7.3 (2.1) × 10^3/L and 8.5 (2.1) × 10^3/L for participants treated with placebo at the beginning of the trial. At study's end the WBC was 8.3 (2.2) × 10^3/L for lithium participants and 7.1 (1.3) for participants treated with placebo (using LOCF).

The mean (SD) estimated creatinine clearance at the beginning of the trial for study participants treated with lithium was 135 (36) mL/min and 124 (28) mL/min for study participants treated with placebo. At the end of the phase, the mean estimated creatinine clearance for study participants treated with lithium was 128 (24) mL/min and 123 (25) mL/min for study participants treated with placebo. The mean creatinine concentration was 0.6 (0.1) mg/dL at both baseline and LOCF for lithium treated participants. The placebo group had mean (SD) creatinine measurement of 0.7 (0.1) mg/dL at baseline and a mean of 0.7 (0.1) mg/dL at LOCF.

Safety

No participants discontinued as a result of any clinically significant findings on vital signs, physical examination or electrocardiographic findings.

Discussion

This randomized, blinded, placebo-controlled discontinuation trial supports a role for lithium as a maintenance treatment in pediatric patients with bipolar disorder. These data contribute to the extant medical literature, as little double-blind data for maintenance treatments exists in this population.

The adverse effect profile was consistent with what has been previously reported both in adults and in our previous work.[21] Of note, lithium was not associated with weight gain or concomitant metabolic effects compared to placebo. This observation distinguishes lithium from the antipsychotic agents[10-13,15] which, prior to this study, is the only class of medications with evidence of acute efficacy but with a risk of substantial weight gain and metabolic disturbances. Renal function was closely monitored throughout the study, and no significant changes in creatinine clearance or renal function were found. Also, of note, patients did not experience an increase in thyroid stimulating hormone, a side effect associated with lithium in [42] the acute phase of the CoLT 2 study, but TSH decreased in placebo-treated patients.[21]

The primary strength of this multi-site trial is the placebo-controlled design and the corresponding gradual tapering of lithium prior to discontinuation in the placebo group. Studies in adult patients have found that mood symptoms tend to emerge and increase in severity soon after rapid discontinuation of lithium treatment, compared to a more delayed tendency toward recurrence when lithium is slowly tapered.[43,44]

The relatively small sample size and trial duration are limitations of the current trial. The sample size is commensurate with the unique challenges of enrolling and maintaining acutely manic patients in placebo-controlled studies on an outpatient basis. In addition, the multi-phase “stepped” design of the CoLT studies required that participants complete the previous two study phases before entering this Discontinuation trial.

Most of our sample (67.7%) came from CoLT 1 which had only open-label phases prior to this study. To enter from CoLT 2, participants needed to complete all 8 weeks of the placebo-controlled acute efficacy study before being enrolled in the open-label Long Term Effectiveness phase. Furthermore, the criteria for stability in the LTE phase prior to entering the Discontinuation phase were quite stringent. Not surprisingly for this population, many LTE participants did not attain durable stability and therefore, did not meet the entry criteria for this study phase.

This randomized, blinded, placebo-controlled discontinuation trial builds support for the use of lithium in the maintenance treatment of pediatric bipolar I disorder. Lithium treatment for the study duration demonstrated good tolerability. However, efficacy and safety over a longer period of time is an empiric question that remains unanswered in this patient population. Therefore, additional longer and larger studies that can more definitively evaluate the efficacy of lithium for the long-term treatment of pediatric bipolar disorder are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was sponsored by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) “Best Pharmaceuticals for Children Act Pediatric Off-Patent Drug Study (PODS): Lithium in the Treatment of Pediatric Mania” (contract HHSN275200503406C).

Conflicts of Interest (past 24 months):

Dr. Findling receives or has received research support, acted as a consultant and/or served on a speaker’s bureau for Aevi, Akili, Alcobra, Amerex, American Academy of Child & Adolescent Psychiatry, American Psychiatric Press, Bracket, Epharma Solutions, Forest, Genentech, Ironshore, KemPharm, Lundbeck, NIH, Neurim, Nuvelution, Otsuka, PCORI, Pfizer, Physicians Postgraduate Press, Roche, Sage, Shire, Sunovion, Supernus Pharmaceuticals, Syneurx, Teva, Tris, TouchPoint, and Validus.

Dr. McNamara receives or has received research or travel support from and/or acted a consultant for Acadia Pharmaceuticals, F. Hoffmann-La Roche AG, Forest, Janssen Pharmaceuticals, Lundbeck, NaBen, the National Institutes of Health, Otsuka Pharmaceuticals, Pfizer Inc., Shire, Sunovion Pharmaceuticals, and Tonix Pharmaceuticals.

Dr. Pavuluri is the cofounder of the Brain and Wellness Institute and holds shares in Medcircle. Inc.

Dr. Frazier has received research support from the following: Fulcrum Therapeutics, Janssen Research and Development, Neuren, Roche, Syneu RX International, NIMH, NIH.

Dr. Rynn has received grant or research support from the National Institutes of Mental Health, the National Institute of Child Health and Human Development, Neurocrine Biosciences, Inc, and Pfizer Inc. She receives royalties from UptoDate.

Dr. Scheffer does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

Dr. Kafantaris does not have any financial relationships or conflicts of interest related to this manuscript to disclose

Dr. Robb receives or has received research and/or travel support, receives or has received royalties and/or honoraria, has stock or equity in, acted as a consultant, and/or served on a speaker's bureau for Actavis/Allergan/Forest, Aevi Genomic Medicine, American Academy of Child & Adolescent Psychiatry, American Academy of Pediatrics, Bracket, the Child and Adolescent Psychiatric Society of Greater Washington local branch, Case Western Reserve University, College of Neurologic and Psychiatric Pharmacists, Eli Lilly and Company, GlaxoSmithKline, Guilford Press, Janssen Pharmaceuticals, Inc., Lundbeck, the National Center for Advancing Translational Sciences, Neuronetics, Neuroscience Education Institute, the National Institute of Child Health and Human Development, the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, North American Center for Continuing Medical Education, Otsuka, Pfizer Inc., Shire, Sunovion Pharmaceuticals, Supernus, SyneuRx, and the University of Cambridge. Dr. Robb has also participated in paid speaking engagements at the University of Kansas Medical Center, Our Lady of the Lake Hospital, and the Carle University School of Medicine.

Dr. DelBello has received grant or research support from National Institute of Mental Health, the National Institute of Diabetes and Digestive and Kidney Diseases, the Patient-Centered Outcomes Research Institute, Janssen, Johnson and Johnson, Supernus, Sunovion, Otsuka, Pfizer, Lundbeck, and Shire. She has served on the advisory board of Sunovion, Neuronetics, Akili, Supernus, Lundbeck, and Johnson and Johnson. She has served as a consultant to Johnson and Johnson, Takeda, and Sunovion. She has served on the editorial board of *Bipolar Disorders* (Section Editor, Pediatrics) and the *Journal of Child and Adolescent Psychopharmacology* (Associate Editor, Neuroimaging). She has received honoraria from American Academy of Child and Adolescent Psychiatry Institute, CMEology and Medscape for presentations. She has served on the speakers' bureau of Sunovion and Otsuka. She has received travel expenses from Sunovion, CMEology, Medscape, and Supernus.

Dr. Kowatch serves on a Data Safety Monitoring Board for Forest and Pfizer Inc.

Ms. Rowles does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

Mr. Lingler does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

Dr. Zhao does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

Dr. Clemons does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

Ms. Martz does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

Dr. Anand does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

Dr. Taylor-Zapata does not have any financial relationships or conflicts of interest related to this manuscript to disclose.

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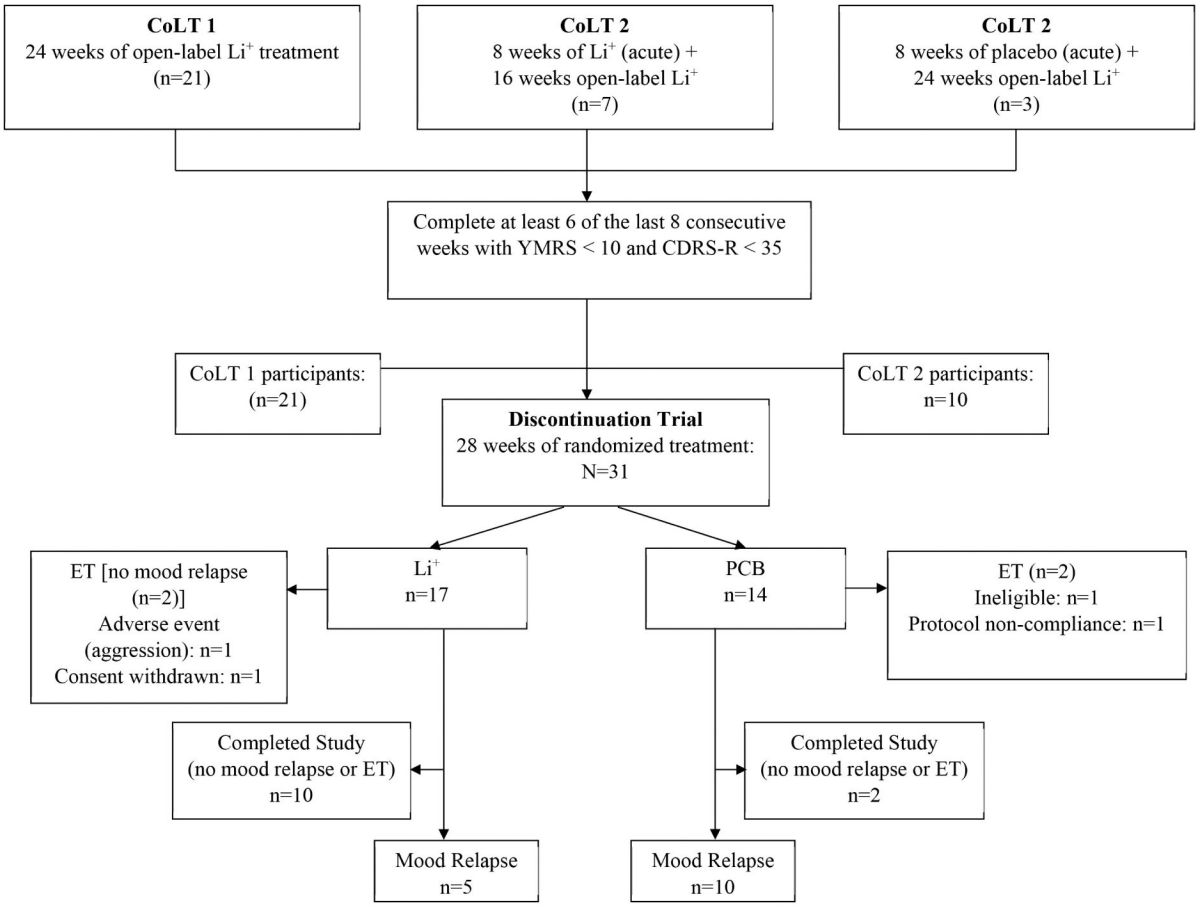

Figure 1:
Participant Disposition As Treated – Discontinuation Trial

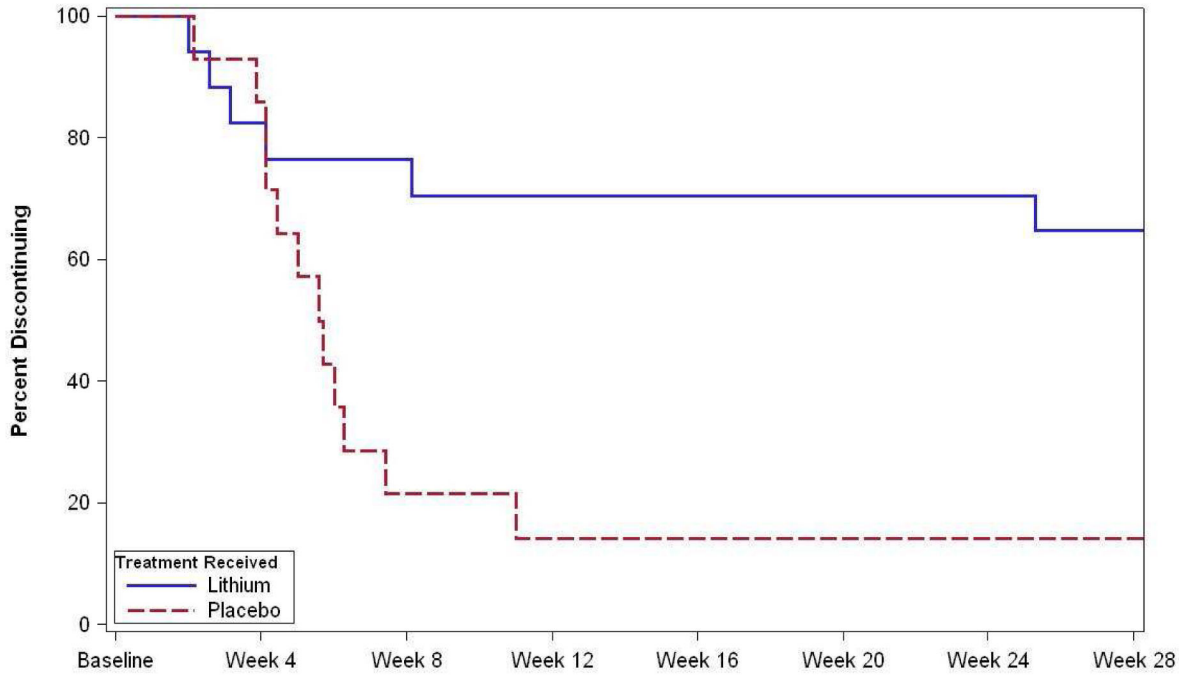

Figure 2.
Risk of Discontinuation for Any Reason (As Treated)

Table 1

Baseline Demographics

Characteristic	Treatment Received		
	Lithium (n=17)	Placebo (n=14)	Total (N=31)
Age at baseline, years Mean (SD)	11.3 (2.2)	12.9 (2.5)	12.0 (2.5)
Gender n (%)			
Male	12 (71%)	9 (64%)	21 (58%)
Female	5 (29%)	5 (36%)	10 (32%)
Race n (%)			
Caucasian	16 (94%)	9 (64%)	25 (81%)
African American	1 (6%)	4 (29%)	5 (16%)
≥ one Race	0 (0%)	1 (7%)	1 (3%)
YMRS Total Score Mean (SD)	4.8 (3.1)	5.9 (2.5)	5.3 (2.8)
CDRS-R Total Score Mean (SD)	20.2 (3.4)	22.4 (6.1)	21.2 (4.9)
CGAS Score Mean (SD)	74.8 (12.5)	71.5 (14.2)	73.3 (13.2)
PGBI-10M Score Mean (SD)	5.1 (4.1)	5.7 (6.9)	5.4 (5.5)
Comorbid Diagnoses			
ADHD	12 (71%)	10 (71%)	22 (71%)
Disruptive Behavior Disorder	2 (12%)	2 (14%%	4 (13%)
Anxiety Disorder	2 (12%)	4 (29%)	6 (19%)
Enuresis	1 (6%)	0 (0%)	1 (3%)
Weight, kg Mean (SD)	45.7 (12.0)	65.7 (27.2)	54.7 (22.3)
Weight Z Score Mean (SD)	0.70 (0.99)	1.32 (1.20)	0.98 (1.12)
Concomitant Medications[a]			
Aripiprazole	0 (0%)	1 (7%)	1 (3%)
Atomoxetine	1 (6%)	0 (0%)	1 (3%)
Guanfacine	0 (0%)	1 (7%)	1 (3%)
Hydroxyzine[b]	3 (18%)	3 (21%)	6 (19%)
Lamotrigine	0 (0%)	1 (7%)	1 (3%)
Methylphenidate	0 (0%)	1 (7%)	1 (3%)
Mixed Amphetamine Salts	3 (18%)	2 (14%)	5 (16%)
Quetiapine	1 (6%)	3 (21%)	4 (13%)
Risperidone	2 (12%)	3 (21%)	5 (16%)
Valproate	0 (0%)	1 (7%)	1 (3%)
Concomitant Psychotherapy n (%)	5 (29.4%)	6 (42.9%)	11 (35.5%)

NOTE: For comorbid diagnoses and concomitant psychotropic medications, *p*-values were not calculated due to small cell size. ADHD = attention-deficit/hyperactivity disorder; CDRS-R = Children's Depression Rating Scale-Revised; YMRS = Young Mania Rating Scale.

[a]Patients could have received more than one concomitant psychotropic medication.

[b]During this study, either lorazepam or hydroxyzine could be prescribed by the treating physician as a rescue medication for sleeplessness and agitation.

Table 2

Risk of Discontinuation for Any Reason

	Treatment Received Group	
	Lithium (n=17)	**Placebo (n=14)**
Participants Status during Discontinuation Trial		
Discontinued	3 (17.6%)	2 (14.3%)
Completed Study	11 (64.7%)	2 (14.3%)
Mood Relapse and Entered Restabilization Phase	3 (17.6%)	10 (71.4%)
Number of Participants		
Completed trial	11 (64.7%)	2 (14.3%)
Discontinued (failed)	6 (35.3%)	12 (85.7%)
Hazard Ratio (Relative to Placebo)	0.28	
(95% CI)	(0.10, 0.78)	
P	0.0150	

Table 3:

Overall Tolerability and Most Frequently Cccurring Adverse Events (In ≥ 10% of the Total Population)

	Discontinuation Phase Treatment Received		
	Lithium (n = 17)	**Placebo (n = 14)**	**Total (N = 31)**
Number of AEs	102	25	127
Number of Participants with at Least One AE *p* > 0.05	15 (88%)	9 (64%)	24 (77%)
Average number of AEs per Participant	6.0	1.8	4.1
Number of SAEs	1 (6%)	0 (0%)	1 (3%)
Highest Severity per Participant			
No reported AEs	2 (12%)	5 (36%)	7 (23%)
Mild	10 (59%)	5 (36%)	15 (48%)
Moderate	3 (18%)	4 (29%)	7 (23%)
Severe	2 (12%)	0 (0%)	2 (6%)
System Organ Class			
Preferred Term			
Nervous system disorders			
Headache	6 (35%)	4 (29%)	10 (32%)
Gastrointestinal disorders			
Abdominal pain upper	5 (29%)	1 (7%)	6 (19%)
Psychiatric disorders			
Initial insomnia	3 (18%)	2 (14%)	5 (16%)
Renal and urinary disorders			
Enuresis	4 (24%)	0 (0%)	4 (13%)
Gastrointestinal disorders			
Vomiting	4 (24%)	0 (0%)	4 (13%)
Metabolism and nutrition disorders			
Decreased appetite	2 (12%)	2 (14%)	4 (13%)
Infections and infestations			
Nasopharyngitis	2 (12%)	1 (7%)	3 (10%)
Upper respiratory tract infection	3 (18%)	0 (0%)	3 (10%)

Note: AE = adverse event; SAE = serious adverse event