

Preliminary Investigation of Lithium for Mood Disorder Symptoms in Children and Adolescents with Autism Spectrum Disorder

Matthew Siegel, MD,^{1,2,3} Carol A. Beresford, MD,^{4,5} Madisun Bunker, BS,² Mary Verdi, MA,²
Donna Vishnevetsky, MD,⁴ Cassie Karlsson, MD,⁴ Olivia Teer, BA,²
Amy Stedman,² and Kahsi A. Smith, PhD³

Abstract

Objective: Children with autism spectrum disorder (ASD) have higher rates of comorbid psychiatric disorders, including mood disorders, than the general child population. Although children with ASD may experience irritability (aggression, self-injury, and tantrums), a portion also experience symptoms that are typical of a mood disorder, such as euphoria/elevated mood, mania, hypersexuality, paranoia, or decreased need for sleep. Despite lithium's established efficacy in controlling mood disorder symptoms in the neurotypical population, lithium has been rarely studied in children with ASD.

Methods: We performed a retrospective chart review of 30 children and adolescents diagnosed with ASD by the, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision (DSM-IV-TR) criteria who were prescribed lithium in order to assess target symptoms, safety, and tolerability. Clinical Global Impressions – Improvement (CGI-I) ratings were performed by two board-certified child psychiatrists with expertise in ASD. CGI-I scores were dichotomized into “improved” (CGI-I score of 1 or 2) or “not improved” (CGI-I score ≥ 3).

Results: Forty-three percent of patients who received lithium were rated as “improved” on the CGI-I. Seventy-one percent of patients who had two or more pretreatment mood disorder symptoms were rated as “improved.” The presence of mania ($p=0.033$) or euphoria/elevated mood ($p=0.041$) were the pretreatment symptoms significantly associated with an “improved” rating. The mean lithium blood level was 0.70 mEq/L (SD=0.26), and the average length of lithium treatment was 29.7 days (SD=23.9). Forty-seven percent of patients were reported to have at least one side effect, most commonly vomiting (13%), tremor (10%), fatigue (10%), irritability (7%), and enuresis (7%).

Conclusions: This preliminary assessment of lithium in children and adolescents with ASD suggests that lithium may be a medication of interest for those who exhibit two or more mood disorder symptoms, particularly mania or euphoria/elevated mood. A relatively high side effect rate merits caution, and these results are limited by the retrospective, uncontrolled study design. Future study of lithium in a prospective trial with treatment-sensitive outcome measures may be indicated.

Introduction

APPROXIMATELY 1% OF CHILDREN IN THE UNITED STATES are diagnosed with an autism spectrum disorder (ASD) (Centers for Disease Control 2012), which include impairments in social communication and the presence of restricted, repetitive, or stereotyped behaviors (American Psychiatric Association 2000). Children with ASD may present with irritability, typically defined as aggression, self-injury, and/or tantrums. Two atypical antipsy-

chotic medications, risperidone and aripiprazole, have established evidence for the treatment of irritability in children with ASD (McPheeters et al. 2011; Siegel and Beaulieu 2012). Some children with ASD, however, present with symptoms of a mood disorder, such as elevated mood/euphoria, mania, paranoia, decreased need for sleep, and/or hypersexuality, which may or may not be accompanied by irritability. Children with ASD have been shown to have higher rates of comorbid psychiatric disorders than the general child population, including mood disorders (Leyfer et al. 2006).

¹Department of Psychiatry, Tufts University School of Medicine, Boston, Massachusetts.

²Spring Harbor Hospital, Westbrook, Maine.

³Maine Medical Center Research Institute, Scarborough, Maine.

⁴University of Colorado, Denver, Colorado.

⁵Childrens Hospital, Colorado.

Statistical Consultant: Kahsi A. Smith.

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Lithium is a psychotropic medication in the mood stabilizer class, with evidence of efficacy in adult and child neurotypical populations; however, lithium has been scarcely studied in the ASD population. To our knowledge, the scientific literature examining use of lithium in children with ASD totals five patients. In 1987 Kerbeshian et al. described two 4-year-old children with ASD who were judged to have a positive response to lithium at serum levels > 1.0 mEq/L. Both children had extreme hyperactivity not responsive to a stimulant; cyclic symptoms, such as sustained laughter, irritability, or giddiness; and a family history of bipolar illness. A separate case report described two individuals with ASD, 7 and 20 years old, with new onset elation, giddiness, and agitation, including self-injurious behavior and aggression toward others, as well as a decreased need for sleep (Steingard and Biederman 1987). In the child, concurrent treatment with lithium (levels close to 1.0 mEq/L) and 200 mg daily of thioridazine produced a positive response. In the young adult, addition of lithium (levels 1.0–1.2 mEq/L) to his existing regimen of chlorpromazine 800 mg per day produced cessation of the seasonal pattern of behavioral deterioration. Finally, Campbell et al. (1972) performed a controlled crossover study of lithium and chlorpromazine in 10 children (8 boys and 2 girls) 3–6 years of age, with hyperactivity or psychosis, 1 of whom had ASD (Campbell et al. 1972). Lithium treatment at 450–900 mg/day was not associated with adverse effects, and the child with ASD showed slight improvement.

As there is such limited information available regarding the use of lithium in children with ASD, we performed an exploratory retrospective chart review of children and adolescents with ASD prescribed lithium for irritability and/or mood disorder symptoms in two specialized inpatient psychiatry units that exclusively serve children with ASD and/or intellectual disability (ID). We sought to evaluate for potential target symptoms, safety, and tolerability of lithium. Based on our clinical experience, we formed an *a priori* hypothesis that a higher number of mood disorder symptoms would be associated with improvement in children with ASD exposed to lithium.

Methods

Participants

After approval by the Institutional Review Boards of Maine Medical Center Research Institute and Children's Hospital Colorado, we identified children and adolescents discharged from two specialized inpatient psychiatry units between August 2008 and March 2013 with a diagnosis of an ASD (autistic disorder, pervasive developmental disorder not otherwise specified [PDD-NOS], or Asperger's syndrome). Each child's discharge summary was then examined for use of lithium during their hospitalization, identifying 48 possible subjects. Each subject's hospital chart was then reviewed by a research assistant for the following inclusion criteria: 1) Age 5–20 years, 2) discharge diagnosis of an ASD (made by the attending child psychiatrist according to American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., Text Revision [DSM-IV-TR] criteria [American Psychiatric Association 2000] and based on a minimum of 7 days of inpatient observation), and 3) initiation of lithium during the hospitalization. Thirty cases met these criteria and detailed data abstraction was performed.

Data abstraction

A data abstraction form was developed that included demographic information; lithium blood levels; duration of lithium

treatment; a checklist of potential side effects; and Axis I, II, and III discharge diagnoses. The form also recorded the presence of pre-lithium symptoms of aggression toward others, self-injurious behavior, hypersexuality, anxiety, euphoria/elevated mood, mania, paranoia, emotional dysregulation, hyperactivity, irritability, and decreased need for sleep (defined as < 5 hours per night of sleep 2 days in a row without observable fatigue the following day). We did not utilize a psychiatric diagnostic instrument, such as the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS), as no instrument has been validated in children with ASD, and we were seeking to explore symptom domains. The expressive language rating was made by reviewing spontaneous language samples recorded in the chart. The abstraction form was tested with two hospital charts at each site, and revised as needed to accurately capture the chart data. The data were then systematically extracted by a research assistant at each site from the charts of all eligible subjects.

Measures

Changes in pre-lithium symptoms after exposure to lithium were measured with the Clinical Global Impressions – Improvement Scale (CGI-I). The CGI-I is a clinician-rated measure of change in mental health status on a seven point scale ranging from 1 (Very much improved) to 7 (Very much worse) (Guy 1976). CGI-I ratings were performed by two board-certified child psychiatrists with expertise in the treatment of children with ASD (MS, CB). The raters were blind to each other's results, and had knowledge of some of the patients from prior care. The CGI-I ratings were based on careful review of recorded changes in the subjects' symptoms while on and off lithium. All relevant data available from the hospital chart, including daily physician progress notes and directly observed behavioral data, were utilized to inform the CGI-I rating.

Analysis

Descriptive statistics (mean, standard deviation) were calculated for continuous data, and frequencies (number, percent) were calculated for categorical data. Independent *t* tests, χ^2 analysis, or Fisher's Exact tests (for cells with $n \leq 5$) were conducted to examine for patient differences between sites, and improvement (CGI score) by pretreatment symptoms. To examine potential differences in CGI scores for therapeutic blood lithium levels (0.51–1.50 mmol/L) compared with subtherapeutic blood levels (≤ 0.50 mmol/L), we conducted χ^2 analysis. All analyses were conducted using SPSS Version 20, and all significance was determined at $p \leq 0.05$.

Results

All 30 subjects had a discharge diagnosis of an ASD (autistic disorder, PDD-NOS or Asperger's syndrome by DSM-IV TR criteria) and were prescribed lithium for mood disorder and/or irritability symptoms. The mean age of the sample was 13.6 years old (SD = 4.1, range 5–21 years), 76% were male and 10% of patients had a seizure disorder. The sample was 96.7% Caucasian and 93.3% non-Hispanic, and 53.3% had ID (full scale intelligence quotient [FSIQ] < 70). Three-quarters (76.7%) of subjects were verbally fluent, 16.7% were minimally verbal (primarily echolalic or scripted speech) and 6.7% were nonverbal (< 10 spoken words). There was no significant difference between the sample populations from each site for the presence of pretreatment mood disorder symptoms, gender, race, or ethnicity ($p > 0.15$ for all) (see Table 1).

TABLE 1. COMPARISON OF PATIENT DEMOGRAPHICS, AND CLINICAL IMPROVEMENT VARIABLES BY SITE

	Site A n = 16	Site B n = 14	Statistic	p value
Age mean (SD)	15.1 (3.9)	11.8 (3.6)	$t=2.43$	0.02*
Sex n (%) male	12 (75%)	11 (78.6%)	FET	1.00
Race n (%) Caucasian	16 (100%)	13 (92.9%)	FET	0.47
Ethnicity n (%) non-Hispanic	16 (100%)	12 (85.7%)	FET	0.21
Weight (kg) mean (SD)	81.6 (28.6)	51.7 (21.5)	$t=3.20$	0.003*
Intellectual disability(FSIQ <70) n (%)	12 (75%)	4 (28.6%)	FET	0.026*
Lithium level (mEq/L) mean (SD)	0.86 (0.20)	0.48 (0.13)	$t=5.79$	0.001*
≥2 mood symptoms n (%)	6/13 (46.2%)	1 (7.1%)	FET	0.03*
Side effects per patient mean (SD)	1.0 (0.89)	0.21 (0.43)	$t=2.99$	0.006*
Length of lithium treatment (days) mean (SD)	43.6 (23.7)	13.9 (10.7)	$t=4.53$	0.001*
CGI Improvement (score of 1 or 2) n (%)	6 (37.5%)	7 (50.0%)	$\chi^2=0.10$	0.75

Chi-square with continuity correction was calculated when cells were >5 for a 2×2 analysis.

*Significance at $p \leq 0.05$.

FET, Fisher's Exact test was calculated when cells were ≤ 5 .

FSIQ, full scale intelligence quotient; CGI, Clinical Global Impressions.

There was a significant difference between sites in subject age, weight, presence of ID, lithium level, length of lithium treatment, mean number of side effects, and number of subjects with two mood symptoms or fewer ($p < 0.05$ for all). There was no significant difference, however, between the proportion of subjects rated as "improved" from each site (37.5% vs. 50%, $p = 0.75$)

Forty-three percent of subjects were rated as "improved" on the CGI-I. Chi Square analysis of the CGI-I score by the proportions of patients with a particular pretreatment symptom revealed, however, that 71% of the subjects with two or more pretreatment mood disorder symptoms were rated as "improved" compared with 40% of the subjects with one (or no) pretreatment mood disorder symptoms. Paired t tests revealed that patients in the "improved" group had a higher average number of pretreatment mood disorder symptoms (mean = 1.38, SD = 1.26) than those in the "not improved" group (mean = 0.57, SD = 0.76), $t = -2.01$, $p = 0.058$. The symptoms most associated with an "improved" rating were mania ($p = 0.033$) or persistent euphoria/elevated mood ($p = 0.041$), (see Table 2).

The mean lithium blood level was 0.70 mEq/L (SD = 0.26, range = 0.30–1.20) and the average length of lithium treatment was 29.7 days (SD = 23.9, range = 4–92). Lithium level was not associated with CGI "improved" status, ($\chi^2 = 0.00$, $p = 1.00$). All

patients had been exposed to an atypical antipsychotic medication prior to lithium treatment, and most were taking concurrent psychotropic medications during the hospitalization. Forty-seven percent of subjects were judged to have a side effect from lithium. The most frequent side effects were vomiting (13%, $n = 4$), tremor (10%, $n = 3$), fatigue (10%, $n = 3$), irritability (7%, $n = 2$) and enuresis (7%, $n = 2$). Other side effects were difficulties in articulation ($n = 1$), motor retardation/excitation ($n = 1$), elevated thyroid-stimulating hormone (TSH) (>5.0 mEq/L) ($n = 1$), polyuria ($n = 1$) and polydipsia ($n = 1$).

Discussion

Despite being a treatment-refractory, hospitalized population, 43% of subjects were judged "improved" on the CGI-I when treated with lithium, and 71% of those with two or more pretreatment mood disorder symptoms were judged "improved." When examined by pretreatment symptom, the presence of mania ($p = 0.033$) or elevated mood/persistent euphoria ($p = 0.041$) were significantly associated with "improved" status. Interestingly, the presence of more typical symptoms of agitation in ASD, such as irritability (aggression, self-injurious behavior, tantrums) or anxiety was not associated with

TABLE 2. CHI-SQUARE OR FISHER'S EXACT TESTS ANALYSIS COMPARING PROPORTION OF PATIENTS WHO "IMPROVED" AND "DID NOT IMPROVE" BY PRETREATMENT SYMPTOM

Pretreatment symptom	Subjects n (%)	CGI 1 or 2 "Improved"	CGI ≥ 3 "Not Improved"	Statistic	p value
Aggression	21 (70%)	10	11	FET	1.000
Persistent irritability	14 (47%)	7	7	$\chi^2 = 0.000$	1.000
Hyperactive-impulsive	14 (47%)	8	6	$\chi^2 = 0.343$	0.558
Emotional dysregulation	24 (80%)	11	13	FET	0.596
Self-injurious behavior	12 (40%)	4	8	FET	0.252
Anxiety	17 (57%)	7	10	FET	0.440
Euphoria/elevated mood ^a	4 (13%)	4	0	FET	0.041*
Mania ^a	7 (23%)	6	1	FET	0.033*
Paranoia ^a	1 (3%)	0	1	FET	1.000
Hypersexuality ^a	8 (27%)	5	3	FET	0.420
Decreased need for sleep ^a	6 (20%)	3	3	FET	1.000

Chi-square with continuity correction and was calculated when cells were >5 for a 2×2 analysis.

^aMood disorder symptom.

*Significance at $p \leq 0.05$.

CGI, Clinical Global Impressions; FET, Fisher's Exact Test and was calculated when cells were ≤ 5 .

“improved” status ($p > 0.25$ for all). The lack of a relationship between lithium level and “improved” status for the overall group is not surprising, given that the majority of the population did not have two or more mood disorder symptoms, and, therefore, may not benefit at any lithium level. These results support our *a priori* hypothesis, based on our inpatient clinical observations as well as the existing case study literature, that lithium may be associated with improvement in children with ASD and mood disorder symptoms.

Almost half the sample (47%) experienced side effects from lithium. Vomiting was the most common (13%) followed by tremor or fatigue (10%) and enuresis or irritability (7%). This rate of side effects is higher than most side effect rates in published clinical trials of psychotropic medicines for ASD, the great majority of which were performed in an outpatient setting. It is possible that reporting of side effects may be increased in inpatient clinical trials, compared with outpatient trials, as hospitalized children are intensively monitored 24 hours a day and all possible physical complaints are noted by nursing staff for further evaluation. Regardless of setting, however, these results suggest caution and careful monitoring of potential side effects in the use of lithium in children with ASD.

Our results must also be interpreted within the context of the sample under study, which was a hospitalized population of children and adolescents with ASD. This sample could be termed refractory to atypical antipsychotic therapy, as 100% of the subjects had had prior exposure to atypical antipsychotics, and still required hospitalization. This was also a more cognitively impaired population on average than the general child and adolescent ASD population, as 53% of the sample had ID. Examination of the sample by study site showed significant differences in a number of variables; however, there was no significant difference between sites in the proportion of patients rated “improved.” Other limitations include the presence of concurrent treatments in the inpatient setting and the use of clinical diagnosis to establish ASD status and record review for ID status, although the ASD diagnosis was made by expert clinical teams based upon extensive inpatient observation and record review. Concurrent medication changes could have occurred, although the typical clinical practice at both sites is to perform one medication trial at a time. Finally, the prevalence of mood disorder symptoms in children with ASD is not well established, potentially limiting the generalizability of the results.

Although we cannot suggest causality based on the retrospective, uncontrolled design of this exploratory study, the association between an increasing number of mood disorder symptoms and an “improved” rating on the CGI-I is an intriguing result. Based on this positive preliminary investigation, prospective, controlled study of lithium in children and adolescents with ASD and symptoms of persistent euphoria/elevated mood, mania, hypersexuality, paranoia, and/or decreased need for sleep may be indicated.

Conclusions

Children with ASD may present with symptoms of a mood disorder, in addition to the irritability symptom cluster. Lithium may be a useful treatment option for children with ASD and two or more mood disorder symptoms, although the possible high rate of side effects indicates that caution is needed. Study of a larger

sample in a prospective controlled trial with treatment-sensitive outcome measures could assess for the efficacy of lithium in this population.

Clinical Significance

A significant portion of children with ASD and irritability do not respond to atypical antipsychotic therapy. Lithium is an understudied agent in the ASD population. Based on this exploratory study, lithium may be a treatment option for children with ASD and mood disorder symptoms.

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Disclosures

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Address correspondence to:

Matthew Siegel, MD
Spring Harbor Hospital
123 Andover Road
Westbrook ME 04092

E-mail: siegem@springharbor.org