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## Lithium Versus Other Mood Stabilizing Medications in a Longitudinal Study of Bipolar Youth RH = Lithium in Youth With Bipolar Disorder

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### Abstract

**Objective:** Lithium (LI) is the mainstay for bipolar disorder (BD) treatment in adults, but evidence in youth is limited. We used data from the Course and Outcome of Bipolar Youth (COBY) study to assess whether LI vs. other mood stabilizing medication (OMS) was associated with improved outcomes, including mood symptoms and suicidality.

**Method:** COBY is a naturalistic, longitudinal study of 413 youth, 7–17.11 years old at intake, with BD. At each visit, medication exposure, psychiatric symptoms, and psychosocial function over the preceding follow-up period were assessed using the Adolescent Longitudinal Interval Follow-Up Evaluation. Using mixed models, we determined whether participants taking LI vs. OMS (but not LI) differed regarding mood symptoms, suicidality, psychosocial function, hospitalization, aggression, and substance use.

**Results:** 340 participants contributed 2638 six-month follow-up periods (886 LI, 1752 OMS), over a mean follow-up of ten years. During LI (vs. OMS) follow-up periods, participants were older, less likely to have lifetime anxiety, and less likely to be on antidepressants ( $p$ -values $<.005$ ). After covariate adjustment, the LI group (vs. OMS) had half as many suicide attempts ( $p=.03$ ), fewer depressive symptoms ( $p=.004$ ), less psychosocial impairment ( $p=.003$ ), and less aggression ( $p=.0004$ ). Similar findings were observed in the subgroup of follow-up periods where participants were  $<18$  years old.

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**Conclusion:** Findings are consistent with adult studies, showing that LI is associated with decreased suicidality, less depression, and better psychosocial functioning. Given the paucity of evidence regarding lithium in children and adolescents, these findings have important clinical implications for the pharmacological management of youth with BD.

### Keywords

bipolar disorder; child and adolescent; lithium; mood stabilizers; suicidality

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### Introduction

An impressive body of literature supports lithium as an effective maintenance treatment of bipolar disorder (BD) in adults. Meta-analyses of randomized controlled trials (RCTs) in adults with BD show that lithium (LI) compared to placebo prevents manic episodes, and to a lesser extent, depressive episodes<sup>1-3</sup>. Large observational studies using electronic health records have found lithium to be superior to other mood stabilizing medication (OMS) for the prevention of mood episodes in adults with BD<sup>4,5</sup>. In the United Kingdom, lithium was associated with a longer time to treatment failure (i.e. augmentation or switching medications due to poor response) than olanzapine, quetiapine, or valproate<sup>4</sup>. In a recent study assessing rehospitalization in a study of electronic health records in Finland, lithium was associated with lower rates of rehospitalization compared to other medications, including oral antipsychotics and valproate<sup>5</sup>. A recent systematic review found that observational studies provide real-world evidence that lithium is superior to other maintenance medications in adults with BD, and is associated with less rehospitalization, fewer treatment failures (defined as medication switches or augmentation), and fewer relapses<sup>6</sup>.

Lithium is also one of the few medications in psychiatry that may prevent suicide (in both unipolar and bipolar depression). A meta-analysis of RCTs in adults with bipolar or unipolar depression found that lithium (compared to placebo) was associated with a substantial reduction in suicide deaths (OR=.13; p=.01) and, impressively all-cause mortality (OR=.38; p=.04)<sup>7</sup>. A recent observational study using linked Swedish national registers found that lithium was associated with a 14% reduction in suicide attempts or deaths; valproate was not associated with any change in suicide rates<sup>8</sup>. To our knowledge, only one small study has assessed the relationship between lithium and suicidal ideation. In a group of severely depressed, suicidal adults randomized to lithium+citalopram (n=40) vs. placebo+citalopram (n=40), lithium did not decrease suicidal ideation over a four-week period; however, they did see improvement in the small (n=11) subgroup with therapeutic lithium levels.<sup>9</sup>

However, compared to evidence in adults, support for the use of lithium in children, adolescents, and transitional age adults remains sparse. While a recent systematic review did find evidence for safety and efficacy of lithium in adolescents, sample sizes are small, follow-up times are short, and studies comparing LI to OMS are largely negative<sup>10</sup>. A review of RCTs in children and adolescents with acute mania found only four relevant trials and concluded that, while there is some evidence that LI might be superior to placebo in this population, additional studies with larger samples are needed<sup>11</sup>. The largest study to assess

the anti-manic effects (Treatment of Early Age Mania; TEAM) compared lithium, divalproex, and risperidone in youth 6–15 years old who were currently in a manic episode. This study found that lithium and divalproex were less effective than risperidone in treating mania<sup>12</sup>, but findings differed greatly according to site and comorbidity (e.g. ADHD)<sup>13</sup>. In addition, the mean length of manic episode in this study was almost five years, indicating an absence of episodic mood disturbances that may be more likely to respond to lithium<sup>14</sup>, and the average age of the subjects was only 10.1 years old. More recently, an RCT of lithium in youth 7–17 years old, and in a current manic episode, found that lithium can be effective for mania and/or mixed episodes in youth. Compared to the placebo group, youth treated with lithium showed a five-point greater decrease in the Young Mania Rating Scale (Cohen's  $d=0.53$ ,  $p=.03$ ); there were no differences between the lithium and placebo groups on Children's Depression Rating Scale, though these youth were not selected for depression<sup>15</sup>. There is also some evidence that lithium can be helpful for aggression, particularly in the context of conduct disorder, in children and adolescents<sup>16</sup>; and may improve substance use outcomes in youth with BD<sup>17,18</sup>.

To our knowledge, there have not been studies to assess whether lithium might prevent suicidal behaviors, mood episodes, hospitalizations, or aggression in youth with BD. While adult data are robust, the lack of pediatric data, in conjunction with significant potential side effects, blood draws, and possible toxicity, have led to significant questions about the role for lithium in children and adolescents. Using longitudinal data from the Course and Outcome of Bipolar Youth (COBY) study, we conducted a post-hoc analysis to assess whether exposure to lithium (vs. other mood stabilizing medications) is associated with differences in suicidality, mood symptoms, mood episodes (i.e. recurrences of (hypo)mania or depression), psychosocial function, hospitalizations, and aggression. While RCTs are the gold standard to assess the effects of medication, this rich longitudinal dataset allows a real-world evaluation of the effects of medication over a longer duration of follow-up than would be feasible with an RCT.

## Method

### Study Subjects

Methodology used in the COBY study has previously been described in detail<sup>19</sup>. Briefly, this ongoing, naturalistic study recruited 413 youth 7–17.11 years old who met criteria at intake for DSM-IV bipolar I (BD-I), BD-II, or operationally defined BD not otherwise specified (NOS)<sup>20,21</sup> according to the Schedule for Affective Disorders and Schizophrenia for School-Aged Children–Present and Lifetime Version (K-SADS-PL<sup>22</sup>; see eMethods). Participants were recruited primarily from outpatient clinics (68%), inpatient units (15%), or advertisements (14%) at the three study sites (University of Pittsburgh Medical Center (UPMC), University of California Los Angeles (UCLA), and Brown University). Participants were enrolled regardless of current mood state or treatment status. Participants with schizophrenia, IQ lower than 70, autism, and mood disorders secondary to substances, medications, or medical conditions were excluded.

## Procedures

Each study site's institutional review board approved the study before enrollment of any participant. Youths and their parents or primary caretakers provided written informed assent and consent, respectively, after receiving a complete description of the study procedures.

**Diagnostic Assessment:** At intake, current and lifetime psychiatric disorders were assessed based on youth and parent interviews, using the KSADS-PL. The Mania Rating Scale (MRS) and Depression Rating Scale (DRS) of the KSADS-PL were also administered to better characterize mood symptoms. Trained research staff conducted all assessments; cases were presented to child psychiatrists or psychologists, who confirmed diagnoses. K-SADS-PL kappa coefficients for psychiatric disorders were at least 0.8; intraclass correlation coefficients for the K-MRS and the K-SADS-P depression section were at least 0.95.

**Illness Severity:** During each follow-up (scheduled approximately every six months), the Longitudinal Interval Follow-up Evaluation (LIFE)<sup>23</sup> was used to assess psychiatric symptoms. The LIFE-Psychiatric Status Rating (PSR) scale was used to assess week-by-week fluctuations (since the last follow-up) in mood, anxiety, substance use, and other psychiatric symptoms; hospitalizations were also assessed using a comparable tool. Beginning in August 2005 (approximately five years after study launch), the PSR was also used to assess suicidal ideation. Mood symptoms and suicidal ideation were rated weekly on a scale of "1" (no symptoms) to "6" (extreme symptoms). The LIFE-Psychosocial Functioning (PSF) was used to assess monthly fluctuations in psychosocial functioning, including work/school, interpersonal, recreation, and satisfaction domains. The DRS and MRS were also administered during each follow-up, providing detailed information about mood symptoms and suicidality during the worst week of the past month.

**Medication:** At each follow-up, weekly medication dosage since the previous visit was recorded using the PSR (PSR-medication). The participant reported the medication they took (not what they were prescribed); *average* weekly dosage was also collected, but not information about the number of days that they took the medication or blood levels. Thus, a low average weekly dose could reflect the prescribed dose or be due to poor adherence, possibilities which may have very different implications for prognosis. For the purposes of this analysis, due to difficulties with interpretation of dosage data, we defined exposure according to whether the participant took the medication during each week (yes/no), regardless of dosage.

**Additional Measures:** The Hollingshead measure was utilized to quantify socioeconomic status (SES)<sup>24</sup> at baseline. The Behavior Control Scale (BCS), a parent-report form administered at all follow-ups, was used to assess aggression and other externalizing behaviors over the past week<sup>25</sup>.

## Statistical Analysis

For the current analysis, we included all six-month follow-up periods where the participant reported taking lithium or another mood stabilizing medication >75% of the follow-up weeks. Six-month follow-up periods were classified as "LI blocks" if the participant took

lithium for >75% of the weeks, regardless of other medications. Blocks were classified as “OMS blocks” if participants took other mood stabilizing medication, but not lithium, for >75% of the weeks, i.e. antimanic anticonvulsants, first- and second-generation antipsychotics, and/or lamotrigine (see Table S1, available online, for specific medications). For follow-up periods >6 months (e.g. due to a late or missed assessment), we only included the most recent six months of data. Except where noted, analyses discussed below used six-month blocks as the unit of analysis.

The primary analysis focused on the relationship between LI vs. OMS and the following clinical outcomes: suicide attempts and suicidal ideation (in the absence of an attempt); threshold and subthreshold depression; threshold and subthreshold (hypo)mania; psychosocial functioning; hospitalization; aggression; and substance use disorder. As in previous papers, any self-injurious behavior that included definite intent (intent score of “3” or more) and/or mild lethality (medical threat score “3” or more) was considered a suicide attempt<sup>26</sup>. There has been one suicide death in this cohort study. Suicidal ideation (SI) was considered positive if the SI item on the KDRS and/or the PSR was rated as a “3” (mild) or more at any time during a follow-up interval. (The PSR for SI was collected starting in August 2005; prior to this date, we only had information on SI from the KDRS in the past month.) We used PSR-depression and PSR-mania both to assess for threshold mood episodes (based on DSM-IV criteria) and subthreshold mood symptoms (mean scores across each follow-up period). Because mania scores were heavily right-skewed, these were log transformed. For aggression, we used the 10-item aggression subscale from the BCS (range: 0–30), which included items related to both verbal and physical aggression. Substance use was defined as meeting threshold criteria for abuse or dependence of alcohol or drugs on the PSR.

We implemented a penalized regression (Lasso regression) in R for each outcome to determine which covariates to adjust for in the final model (see Supplement 1, available online, for details). Because of the complexities of longitudinal analysis, particularly in a naturalistic study, many time-varying covariates may be influenced by previous lithium exposure, and adjustment for these covariates can induce bias<sup>27</sup>. To address this, we ran two models for each outcome. First, we adjusted only for variables that clearly preceded (and could not be influenced by) lithium exposure, either prior to or during COBY study follow-up (e.g. age, age at bipolar onset, family history of mania, race, SES, sex, and site). This model avoids over-adjustment, but also may not account for important confounding. Thus, we ran a second model adding time-varying covariates that could, at least theoretically, be influenced by previous exposure to lithium; these include bipolar subtype, lifetime disorders (including anxiety, disruptive behavioral, and substance use disorders up to and including the relevant assessment), lifetime psychosis, and number of previous hospitalizations. In SAS 9.4, mixed models were implemented using selected variables.

To test additional questions of interest, we ran several supplemental analyses. First, we tested observed relationships in youth only (<18 years old). Second, to assess whether effects were specific to lithium, or also found with (and perhaps explained by) other medication classes, we entered other medication classes (antipsychotics, anticonvulsants, lamotrigine, antidepressants) and total number of medications into models that showed a

significant effect of lithium. Third, we conducted sensitivity analyses to test (1) whether observed effects persisted after removing blocks with both LI and OMS exposure (i.e. comparing LI *only* vs. OMS *only*) and (2) whether observed effects differed across BD subtype (i.e. BD I/II vs. BD-NOS). Fourth, while above analyses were primarily *between-subject*, we also tested whether effects remained if only including participants who contributed both LI and OMS blocks over follow-up (a *within-subject* comparison, using participant as the unit of analysis). Fifth, a subset of the sample had never been on lithium at time of intake, defined as no past lithium exposure and no lithium exposure over the first follow-up period. In this subset, we tested which clinical and demographic factors predicted lithium exposure over follow-up (using participant as the level of analysis). We also tested whether associations between lithium and clinical outcomes were found in this subset, after adjusting for the relevant intake clinical variables and Lasso-selected intake covariates.

Finally, we conducted a supplemental analysis to test the relationship between taking LI (vs. OMS) during the three months prior to a mood episode and the severity of the mood episode (e.g. suicidal ideation, suicide attempt, hospitalization, and polarity). Specifically, we tested whether LI vs. OMS for at least five weeks during the eight-week “exposure period” (defined as 12 weeks to 4 weeks prior to episode) was associated with differential severity of the subsequent episode. Comprehensive methods for this analysis are given in the Supplement, available online.

## Results

### Demographics

Over follow-up, 340 participants contributed 2638 follow-up periods (886 LI blocks, 1752 OMS blocks). During 65% (574/886) of LI blocks, participants were also on an additional mood stabilizer (i.e. antipsychotic, lamotrigine, and/or antimanic anticonvulsant) for >75% of follow-up weeks. Participants who took lithium over follow-up reported an older age of bipolar onset ( $p=.05$ ) and had an earlier intake date ( $p=.02$ ) than those who took only non-lithium mood stabilizers (Table 1). Compared to OMS blocks, participants exposed to LI were slightly older ( $p=.003$ ), assessed at an earlier follow-up date ( $p<.0001$ ), less likely to have a history of DBD ( $p=.008$ ) and anxiety ( $p<.0001$ ), and more likely to have a history of psychosis ( $p=.05$ ). During LI blocks (vs. OMS blocks), youth were also less likely to be on antidepressants ( $p=.009$ ) (Table 2). The findings that individuals with lithium had an earlier intake date, and earlier follow-up dates, is consistent with an observed decrease in the prescribing rate of lithium over the course of follow-up (Figure S1, available online).

### Primary Analysis: LI vs. OMS and Clinical Outcomes

Variables selected by the Lasso regression are listed in Table S2 (available online). After adjusting for intake covariates and age, youth in the LI vs. OMS groups were half as likely to have a suicide attempt ( $p=.03$ ), had lower mean PSR-depression score ( $p=.004$ ), better psychosocial function ( $p=.003$ ), and less aggression ( $p=.0004$ ) (Table 3). Adjusting for additional time-varying covariates did not alter the point estimates or conclusions (Table 4). Findings were similar when only considering blocks where the participant was <18 years old. While the inverse relationship between LI and suicide attempts was no longer

significant, the inverse relationship between LI and both SI and threshold depression became significant in this subgroup (Table 4).

### Supplemental Analyses:

#### Sensitivity Analyses:

**Adjustment for specific medications:** Adjustment for specific types of mood stabilizers, antidepressants, and total number of medication classes did not diminish the associations between LI (vs.OMS) and significantly associated clinical outcomes; additionally, the effects of other medications were generally not significant, and if significant, were in the opposite direction of lithium (e.g. associated with more depression, decreased functioning) (Table 5).

**LI-only vs. OMS-only:** This analysis excluded blocks where participants were exposed to LI and OMS. Comparing 256 LI-only blocks (contributed by 60 participants) and 1732 OMS-only blocks (contributed by 265 participants), findings generally remained significant. An exception was suicide attempts, which did not show significant difference between LI-only vs. OMS-only; however, there were only six attempts in the LI-only group, thus limiting inference (Table S3, available online).

**Bipolar Subtype:** The effect of LI vs. OMS was similar in youth with threshold (BD-I/II) vs. subthreshold BD (BD-NOS), with no significant interactions (Table S4, available online).

**Within-subject analysis:** A within-subject analysis, including only individuals who contributed both LI and OMS blocks over follow-up (n=65), yielded similar effect sizes; however, several associations were not significant due to limited power (Table S5, available online).

**Predictors of LI exposure:** To assess the degree to which associations may have been attributable to (or masked by) pre-existing clinical differences between LI vs. OMS (i.e. confounding by indication), we tested whether our outcome variables predicted later lithium exposure. Subgroup for this analysis included 23 individuals who would later be exposed to lithium and 156 who would not. Testing the relationship between later starting lithium and bipolar subtype, we found that no one who had BD-II during the first follow-up period was later started on lithium; thus, we limited the analysis to participants with BD-I or BD-NOS (n=23, n=143). Despite limited power to detect associations, individuals who would later be prescribed lithium were three times more likely to have suicidal ideation during the first six-month follow-up (p=.03) (Table 6). Within this initially lithium-free subset, associations found between lithium and clinical outcomes were similar in magnitude to those found in the entire sample, but not significant due to limited power (Table S5, available online). An exception to this was depressive symptoms, which was not inversely associated with lithium in this subgroup.

**Site by Time Interactions:** From Figure S1, available online, we noticed that, between the years of 2003 and 2010 there was a significant decrease in the percent of participants on LI vs. OMS, driven entirely by the UPMC site. This significant site\*time interaction (p=.006) presented the opportunity to test whether site-specific temporal changes in lithium



prescriptions would be associated with site\*time interactions in the clinical outcomes of interest. Indeed, both psychosocial function and depressive symptoms showed a similar (inverse) pattern (interaction  $p$  values  $<.001$ ), with UPMC worsening over time relative to other sites (Figure S2, Figure S3, available online). The patterns for suicidal ideation and attempt were similar, though interactions were not significant ( $p$  values  $>.2$ ; Figure S4 and Figure S5, available online). There were no site\*time interactions with the aggression outcome (Figure S6, available online).

**Episode Severity:** Finally, we assessed whether LI (vs. OMS) during the three months prior to the onset of a mood episode was associated with indicators of severity within the episode (Table S6, available online). Consistent with the primary analyses, we found that individuals taking LI (vs. OMS) had better psychosocial functioning during episodes ( $p=.006$ ), and a less marked decline in functioning during the episode ( $p<.0001$ ). There was no significant effect on length of episode or hospitalization. Li (vs. OMS) was not significantly related to suicidal ideation or attempts in this analysis, though given rarity of events, there was limited power to detect differences.

## Discussion

In a longitudinal analysis of youth and emerging adults with BD, after controlling for confounders, we found that lithium use (as compared to other, non-lithium mood stabilizers) was associated with fewer suicide attempts, fewer subthreshold depression symptoms, better psychosocial function, and less parent-reported aggression. All findings were of similar magnitude (and most were also significant) when only follow-up periods before age 18 were included in the analysis; in fact, in the subset of youth  $<18$  years old, lithium was also associated with less threshold depression and less suicidal ideation. The finding regarding suicide attempts was especially striking since suicidal ideation during the first follow-up period increased the likelihood of later taking lithium. Results were specific to lithium; other medication classes did not show these positive effects. Comparing LI-*only* vs. OMS-*only* yielded similar effect sizes on most clinical measures, though numbers were insufficient to make inference about suicide attempts in this sensitivity analysis. Associations between lithium and clinical outcomes did not differ in participants with threshold versus subthreshold BD. Our inference was further supported by supplemental site\*time interactions, which indicated that site-dependent changes in prescribing patterns (i.e. decrease in LI prescribing in one site) were mirrored by predicted changes in rates of depressive symptoms and psychosocial function.

Overall, findings are consistent with previous literature, primarily in adults, showing that lithium might improve mood course (including depressive symptoms), prevent suicide attempts, and ameliorate aggression<sup>6,8,16,28</sup>. Interestingly, in our sample, lithium did not appear to be superior to other mood stabilizing medications regarding the (hypo)mania outcomes. This is somewhat inconsistent with the literature in adults, which has generally found lithium to be even more protective for manic episodes than depressive episodes.<sup>2</sup> It is possible that our null finding reflects that the relative benefits of lithium for (hypo)manic symptoms might not be as clear in earlier onset BD. This would be consistent with a previous RCT (TEAM study) that found lithium to be inferior to risperidone regarding the

treatment of mania<sup>12</sup>. However, it is also possible that confounding by indication might explain the lack of observed effect (comparing LI vs. OMS). While not significant, youth with a hypomanic episode during the first follow-up period were almost twice as likely to be prescribed lithium later in follow-up; thus, this observation should be interpreted with caution.

This observational study provides evidence for effectiveness in this population of youth with BD, as opposed to efficacy in a controlled setting (i.e. RCT); while efficacy studies are important, effectiveness studies may be more generalizable to the target clinical population and provide more “real-world” information<sup>29</sup>. In combination with the growing number of large-scale studies in adults that show these effects, these findings provide evidence that lithium should be considered as a viable and important treatment option for youth with BD. When considering optimal treatment for BD in youth, these potential benefits should be weighed against the possible risks of long-term lithium exposure (e.g. effects on kidney and thyroid function) and the fact that it can be lethal in overdose.

This study has limitations that should be considered when interpreting results. First, as discussed above, confounding by indication can be problematic in an observational study. We had the benefit of assessing predictors of lithium exposure in a subset of the sample, and findings from this analysis showed that participants later prescribed lithium had higher levels of clinical symptomatology; thus, it is unlikely that such factors explained observed beneficial effects of lithium, though they could have masked or decreased observed effects. Also, this was just a subset of the sample; participants already on lithium at the beginning of the study might have had different characteristics prior to starting lithium. We also conducted a supplemental within-subject analysis that showed similar results, making between-subject confounding a less likely explanation of observed effects. Of note, the observational nature of this study limits our ability to assess other effects of medication (e.g. the effect of antidepressants or polypharmacy), since it is difficult to tease apart medication effects from confounding by indication.

Second, we only collected medication and symptom data every six months, so temporally fine-grained recall of medication dosage and symptomatology is limited. While we assessed average weekly dose, we did not collect data regarding daily dose or blood levels; thus, it is possible that some individuals were not on therapeutic doses of lithium or other mood stabilizing medications. We also did not collect data about adherence to medication. Third, we did not collect data regarding side-effects or tolerability of medication, so we were not able to compare these outcomes across groups. Fourth, prior to August 2005, suicidal ideation was only assessed during the month prior to follow-up (using the KDRS); thus, some follow-up periods with suicidal ideation were likely misclassified. This measurement error would have most likely led to an underestimate of the negative association between LI (vs. OMS) and suicidal ideation.

Despite these limitations, the COBY study provides a unique opportunity to assess the effect of medications in a larger sample, with much longer follow-up, and arguably more generalizable to our patient population, than an RCT. Using this rich dataset, we have provided evidence, for perhaps the first time, that lithium, compared to other mood

stabilizing medications, may be superior in preventing suicidal attempts, decreasing depressive symptoms, and improving psychosocial function in youth and emerging adults. Future work should focus on (1) elucidating the mechanisms by which LI improves outcomes in BD, so that novel therapeutics can be developed to target these mechanisms with fewer side effects; and (2) identifying who will best respond to LI, to optimize the risk-benefit ratio.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Disclosure:

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**Table 1.**

Demographic Characteristics of Individuals Who Contributed to Lithium Blocks Over Follow-up Compared to Those That Only Contributed to Other Mood Stabilizer Blocks

Variable	LI +/- OMS (n=139)	OMS only (n=201)	Stat	P
Age at intake (y) (SD)	12.6 (3.2)	12.3 (3.3)	t=1.06	.29
Intake date (SD)	14APR2003 (1.3 years)	02AUG2003 (1.1 years)	t=-2.27	.02
Total follow-up (y) (SD)	10.7 (2.9)	10.1 (3.5)	t=1.86	.06
Sex (% female)	70 (50%)	90 (56%)	X <sup>2</sup> =1.03	.31
Site			X <sup>2</sup> =3.73	.16
Brown	35 (25%)	69 (34%)		
UCLA	25 (18%)	37 (18%)		
Pittsburgh	79 (57%)	95 (47%)		
% Non-White	20 (14%)	33 (16%)	X <sup>2</sup> =0.26	.61
SES (SD)	3.5 (1.2)	3.5 (1.1)	t=-.10	.92
Age of Bipolar Onset (SD)	9.5 (4.1)	8.7 (3.9)	t=2.00	.05
Family History of Mania	46/129 (41%)	64/188 (59%)	X <sup>2</sup> =0.09	.77
LI years per participant (SD) [min, max]	3.2 (2.4) [0.5,10]	--	--	--
OMS years per participant (SD) [min, max]	1.2(1.8) [0,8]	3.5 (2.9) [.5, 12]	--	--

Note: LI = Lithium; OMS = Other Mood Stabilizer; UCLA = University of California Los Angeles

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**Table 2**

Time-varying characteristics of youth during Lithium vs. Other Mood Stabilizer blocks

Variable	LI Blocks (n=886)	OMS Blocks (n=1752)	Stat	P
Age (S.D.)	17.4 (4.8)	16.9 (4.7)	t=-2.86	.004
Mean Follow-up Date (S.D.)	16NOV2007 (3.4 years)	29AUG2008 (3.5 years)	t=-4.66	<.0001
Bipolar Type			F=1.25	.29
Bipolar I	722 (82%)	1203 (69%)		
Bipolar II	50 (6%)	195 (11%)		
Bipolar NOS	113 (13%)	353 (20%)		
Lifetime hospitalizations (S.D.)	2.22 (2.98)	2.06 (3.34)	t=-1.61	.20
Lifetime DBD (%)	624 (71%)	1394 (80%)	t=-2.65	.008
Lifetime Anxiety (%)	482 (54%)	1207 (69%)	t=-4.68	<.0001
Lifetime Psychosis (%)	380 (43%)	508 (29%)	t=1.95	.05
Lifetime Substance Abuse (%)	89 (10%)	127 (7%)	t=-1.15	.25
Current Medications (>75% of follow-up period)				
Non-lithium Mood Stabilizer (%)	574 (65%)	1752 (100%)	--	--
Antipsychotics (%)	496 (56%)	1295 (74%)	t=-5.30	<.0001
Antimanic Anticonvulsants (%)	114 (13%)	573 (33%)	t=-5.43	<.0001
Lamotrigine (%)	68 (8%)	390 (22%)	t=-5.61	<.0001
Antidepressants (%)	223 (25%)	527 (30%)	t=-2.61	.009
Stimulants (%)	203 (23%)	627 (36%)	t=-.75	.45

Note: DBD=Disruptive Behavioral Disorder; LI=Lithium; NOS=Not Otherwise Specified; OMS=Other Mood Stabilizer.

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**Table 3:**

Relationship between Lithium vs. Other Mood Stabilizer exposure and outcome variables, adjusting for lasso-selected characteristics.

Outcome Variable	LI	OMS	OR/beta (CI)	P
<i>Suicidal Ideation and Attempts</i>				
Suicide Attempt n (%)	<b>17 (2%)</b>	<b>63 (4%)</b>	<b>.51 (.28, .95)</b>	<b>.03</b>
Suicidal Ideation n (%)	56 (6%)	171 (10%)	.69 (.45, 1.07)	.10
<i>Mood Symptoms</i>				
Threshold Depression n (%)	212 (24%)	497 (28%)	.76 (0.55, 1.05)	.10
Mean PSR Depression Score (S.D.)	<b>2.0 (1.1)</b>	<b>2.3 (1.2)</b>	<b>-.19 (-.32, -.06)</b>	<b>.004</b>
Threshold Mania/Hypomania n (%)	164 (19%)	248 (14%)	1.35 (0.95, 1.91)	.09
Mean PSR (Hypo)mania Score (S.D.)	1.9 (1.8)	1.9 (1.9)	.03 (-.04, .08)	.47
<i>Psychosocial Functioning</i>				
Worst PSF (lower is better)	<b>10.2 (10.0)</b>	<b>11.1 (11.2)</b>	<b>-.55 (-.90, -.19)</b>	<b>.003</b>
<i>Other Outcomes</i>				
Hospitalization n (%)	71 (8%)	139 (8%)	1.03 (.71, 1.51)	.87
Aggression score (BCS)	<b>4.7 (4.7)</b>	<b>5.9 (4.7)</b>	<b>-1.1 (-1.7, -.5)</b>	<b>.0004</b>
Substance Use Disorder n (%)	45 (5%)	105 (6%)	.65 (.33, 1.28)	.21

Note: BCS=Behavior Control Scale; LI=Lithium; OMS=Other Mood Stabilizer; PSR=Psychiatric Status Rating; PSF=Psychosocial Functioning.



**Table 4**

Relationship between Lithium vs. Other Mood Stabilizer and outcome variables where  $p < .10$  in Table 3, adjusted for additional lasso-selected time-varying covariates and in youth <18 years old.

Symptom	Baseline Covariates	+ Time-Varying Covariates	Youth <18 years old
Suicide Attempts	<b>.51 (.28, .95)</b>	<b>.47 (.25, .88)</b>	.54 (.26, 1.1)
Suicidal Ideation	.69 (.45, 1.07)	.66 (.43, 1.01)	<b>.56 (.32, .96)</b>
Threshold Depression	.76 (0.55, 1.05)	.76 (.55, 1.05)	<b>.64 (.44, .93)</b>
Mean PSR Depression	<b>-.19 (-.32, -.06)</b>	<b>-.16 (-.29, -.03)</b>	<b>-.23 (-.39, -.07)</b>
Threshold (Hypo)mania	1.35 (0.95, 1.91)	1.27 (.90, 1.80)	1.31 (0.88, 1.94)
Worst PSF	<b>-.55 (-.90, -.19)</b>	<b>-.46 (-.81, -.11)</b>	<b>-.72 (-1.13, -.31)</b>
Aggression score (BCS)	<b>-1.1 (-1.7, -.5)</b>	<b>-1.0 (-1.6, -.38)</b>	<b>-1.1 (-1.8, -.5)</b>

Note: BCS=Behavior Control Scale; PSR=Psychiatric Status Rating; PSF=Psychosocial Functioning.

**Table 5**

Adjustment for other specific types of mood stabilizers, antidepressants, and total number of medication classes.

	Suicide attempt	Mean PSR Depression	Worst PSF (lower is better)	Aggression (BCS)
Lithium	<b>.51 (.28, .95) *</b>	<b>-.19 (.07) **</b>	<b>-.55 (.18) **</b>	<b>-1.1 (.32) ***</b>
Lithium	.54 (.29, 1.00)	<b>-.19 (.07) **</b>	<b>-.58 (.18) **</b>	<b>-1.1 (.32) ***</b>
Lamotrigine	1.4 (0.8, 2.5)	-.02 (.07)	-.29 (.19)	.37 (.33)
Lithium	<b>.54 (.29, 1.00) *</b>	<b>-.17 (.07) **</b>	<b>-.47 (.18) *</b>	<b>-1.0 (.31) **</b>
Atypical APs	1.4 (0.8, 2.5)	<b>.13 (.06) *</b>	<b>.54 (.16) ***</b>	.66 (.30)
Lithium	<b>.52 (.28, .98) *</b>	<b>-.17 (.07) **</b>	<b>-.49 (.18) **</b>	<b>-1.2 (.32) ***</b>
Anticonvulsants	1.2 (.7, 2.1)	.13 (.07)	.36 (.19)	-.36 (.35)
Lithium	<b>.52 (.28, .97) *</b>	<b>-.17 (.07) **</b>	<b>-.53 (.18) **</b>	<b>-1.2 (.31) ***</b>
Antidepressants	1.4 (0.9, 2.4)	<b>.20 (.06) ***</b>	<b>.33 (.16) *</b>	<b>-.58 (.29) *</b>
Lithium	<b>.49 (.27, .91) *</b>	<b>-.24 (.07) ***</b>	<b>-.66 (.18) ***</b>	<b>-1.0 (.32) **</b>
# Med Classes <sup>a</sup>	<b>2.0 (1.2, 3.4) **</b>	<b>.32 (.05) ***</b>	<b>.68 (.14) ***</b>	<b>-.59 (.23) *</b>

Note:

\*  
p<.05

\*\*  
p<.01

\*\*\*  
p<.001;

<sup>a</sup>Dichotomized at median of 2.1 current medication classes; PSR = Adolescent Longitudinal Interval Follow-Up Evaluation Psychiatric Status Ratings; PSF = Adolescent Longitudinal Interval Follow-Up Evaluation Psychosocial Functioning; BCS = Behavioral Control Scale; APs = Antipsychotics.

**Table 6**

Clinical predictors at intake of lithium exposure (Lithium=23, Other Mood Stabilizer=143), adjusting for demographic predictors in Table 1 (i.e. assessment date, age of bipolar onset)<sup>a</sup>

Variable	OR (CI)	P
<b>Suicidal ideation</b>	<b>3.2(1.1, 9.1)</b>	<b>.03</b>
Suicide attempts	2.1 (0.2, 21.6)	.53
Threshold Depression	1.2 (0.5, 3.0)	.70
Threshold (Hypo)mania	1.8 (0.7, 4.7)	.20
PSF_worst	1.1 (0.9, 1.3)	.37
Aggression (BCS)	1.0 (0.9, 1.1)	.70
Bipolar Type (BD 1 vs BD NOS)	1.2 (0.5, 3.1)	.65
Lifetime hospitalizations	0.8 (0.5, 1.2)	.26
Lifetime DBD	0.5 (0.2, 1.5)	.22
Lifetime Anxiety	2.2 (0.8, 5.9)	.12
Lifetime Psychosis	0.9 (0.3, 2.8)	.83
Antidepressant (during 1 <sup>st</sup> f/u period)	1.4 (0.5, 3.9)	.47
Stimulant (during 1 <sup>st</sup> f/u period)	1.0 (0.4, 2.1)	.96

Note:

<sup>a</sup>Substance abuse could not be assessed due to low frequency of this predictor at baseline (n=11); BCS=Behavior Control Scale; BD=Bipolar Disorder; BD NOS=Bipolar Disorder, Not Otherwise Specified; PSF=Psychosocial Functioning.

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