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Association of Lithium and Second-Generation Antipsychotics with Neurocognition in Youth with Bipolar Disorder

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Abstract

Objective: Numerous studies have examined the association of antimanic medications with neurocognition in adults with bipolar disorder (BD). However, few studies have examined this topic in youth. Thus, we aimed to examine the association of lithium and second-generation antipsychotics (SGAs), the first-line antimanic medications for youth with BD, with neurocognition in a relatively large sample of youth with BD.

Methods: Participants included 91 youth with BD-I, -II, or -Not Otherwise Specified, aged 13–20 years ($n = 14$ current lithium use, $n = 51$ current SGA use). We examined four tests from the Cambridge Neuropsychological Test Automated Battery: Intra/Extra Dimensional Set-Shifting Task (IED), Rapid Visual Information Processing Task (RVP), Stockings of Cambridge Test (SOC), and Affective Go/No-Go (AGN). Within-sample Z-scores were computed, and a global neurocognitive composite score and *g* factor derived from these tests comprised the primary outcomes. Multivariable analyses controlled for age, sex, and IQ.

Results: Current lithium use was significantly associated with poorer cognitive flexibility/set-shifting (IED). After further controlling for lifetime comorbid attention-deficit/hyperactivity disorder and current depression symptoms in sensitivity analyses, the lithium finding was no longer significant. Current SGA use was significantly associated with greater affective processing bias (AGN). No significant findings survived correction for multiple comparisons. All other cognitive outcomes were not significantly associated with current lithium use, current SGA use, or total number of current medications.

Conclusions: Treatment with lithium or SGAs was associated with minimal neurocognitive impairments, with small effect sizes in primary multivariable analyses. This study adds to the limited body of literature examining medication use in relation to neurocognition in youth with BD. While the current study cannot rule out associations of smaller effect size, present findings suggest that leading mood-stabilizing medications are not associated with frank neurocognitive impairments in youth with BD.

Keywords: bipolar disorder, youth, neurocognition, lithium, second-generation antipsychotics

Introduction

Bipolar disorder (BD) is a severe recurrent mood disorder characterized by episodes of mania and/or hypomania and depression (Birmaher et al. 2009). In addition to the burden of mood symptoms, there is well-established evidence of reduced neurocognitive performance among individuals with BD (Miskowiak et al. 2018). This reduced performance has been observed

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across numerous domains of neurocognition, such as sustained attention, memory, and executive functions (Latalova et al. 2011; Fountoulakis 2020).

While neurocognitive performance is especially poor during mood episodes, deficits are also observed during periods of euthymia (Bourne et al. 2013; Cardenas et al. 2016). Similar to adults, there is evidence among youth with BD of deficits across multiple domains, both during symptomatic intervals and euthymia (Frías et al. 2014; Elias et al. 2017). These deficits may contribute to poorer global, academic, and social functioning (Frías et al. 2017).

In addition to the illness itself, psychiatric medications have also been examined in relation to neurocognition. Lithium and second-generation antipsychotics (SGAs) are leading pharmacological treatment approaches for BD (Torrent et al. 2011; Licht 2012). Patients taking lithium frequently report subjective experience of cognitive side effects, including mental slowing or cognitive dulling, and such perception is likely to precipitate nonadherence (Pachet and Wisniewski 2003; Gitlin 2016). Indeed, lithium use has been associated with neurocognitive impairments in adults with BD, including psychomotor speed, verbal learning, fluency, attention, affective processing, and memory (Pachet and Wisniewski 2003; Holmes et al. 2008; Wingo et al. 2009; Malhi et al. 2016).

However, other studies found no cognitive association of lithium and suggested that it may be beneficial to certain domains of cognition (Bourne et al. 2013; Daglas et al. 2016; Burdick et al. 2020). Antipsychotic use in adults with BD is also associated with impairment across multiple domains, including semantic fluency, verbal learning, verbal memory, attention, processing speed, and recognition memory as well as executive functions related to planning abilities (Donaldson et al. 2003; Jamrozinski et al. 2009; Torrent et al. 2011).

Few studies have investigated the association of pharmacological treatment with neurocognitive performance among youth with BD. A recent meta-analysis of neurocognition among euthymic youth with BD found that both lithium and antipsychotic use are associated with impaired global cognition, whereas antipsychotic use is also linked to impaired attention and vigilance, reasoning, and problem-solving (Elias et al. 2017). Among euthymic youth with BD, lithium use was found to be associated with poorer performance in executive function (Lera-Miguel et al. 2015), while another study found that quetiapine, an SGA, did not affect performance in information processing and memory, which remained comparable to healthy controls over the duration of 48-week treatment (Duffy et al. 2009).

During mood episodes, lithium treatment is associated with reduced performance in domains, such as attention, processing speed, and working memory in youth with BD (Henin et al. 2009; Streicher et al. 2020).

Antipsychotic use appears to be associated with reduced speed of information processing (fluency and visual scanning) among youth with BD during euthymic, depressive, or mixed/manic episode (Bearden et al. 2007), while other studies have found no significant associations between SGA use and neurocognition in symptomatic youth with BD (Henin et al. 2009; Streicher et al. 2020). Specifically, no significant differences in attention were observed after treatment with quetiapine for 6 weeks (Streicher et al. 2020). Finally, treatment with aripiprazole, another SGA, for 24 weeks was associated with improved sustained attention and executive function in adolescents and young adults with BD during active mood episodes, suggesting that even medications of the same class (i.e., SGAs) may have differential impacts on neurocognition (Wang et al. 2012).

Given the importance of lithium and SGAs, the first-line antimanic medications for youth with BD, which are often used as maintenance treatments (Goldstein et al. 2017; Yatham et al. 2018), we set out to add to the current literature by examining the association of these medications with neurocognition in a relatively large sample of youth with BD. We hypothesized that treatment with lithium or SGAs will be associated with reduced global neurocognitive performance, particularly in reversal learning and attentional set-shifting, sustained attention, executive functioning, and visual working memory capacity.

Methods

Participants

Participants were 91 youth (13–20 years old) with BD-I, -II, or -Not Otherwise Specified (NOS; akin to Other Specified Bipolar and Related Disorder). Participants were recruited through a subspecialty clinic at a tertiary academic hospital. The current study is a secondary analysis of participants enrolled in two studies that included neurocognition, blood tests, and imaging measures. Exclusion criteria were as follows: known existing cardiac conditions; autoimmune or inflammatory conditions; taking anti-inflammatory, antiplatelet, antilipidemic, antihypertensive, or hypoglycemic agents; infectious illness in the 14 days before the study; or if unable to provide informed consent. Written informed consent was obtained from all participants, as well as their parent(s) or guardian(s).

Participants received financial compensation or community service involvement hours for participating in the research study. All study procedures were approved by the research ethics board at Sunnybrook Health Sciences Centre.

Diagnostic interview and symptom ratings

The Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime version (K-SADS-PL) (Kaufman et al. 1997) was used to determine BD and comorbid psychiatric diagnoses. The K-SADS-PL is a semi-structured interview with both parent and adolescent that is used to determine present and lifetime history of psychiatric illness in children and adolescents between the ages of 7 and 18 years, according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) (APA, 2000) criteria.

Diagnoses were based on the DSM-IV criteria as participants were enrolled from 2014 to 2019, and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DMS-5) version of the K-SADS-PL was not available until 2016. All interviews were performed by trained study personnel with either bachelor's or master's degree in a health-related field and completed comprehensive K-SADS-PL training under the supervision of the senior author (B.I.G.), a licensed child and adolescent psychiatrist. BD subtypes I and II were defined using the DSM-IV criteria, whereas BD-NOS was defined using operationalized criteria as per the Course and Outcome of Bipolar Youth study (Birmaher et al. 2006).

Mood symptoms were assessed through the K-SADS Mania Rating Scale and the K-SADS Depression Rating Scale (Chambers et al. 1985; Axelson et al. 2003). Participants were also interviewed using Psychiatric Status Rating (PSR) on the Adolescent Longitudinal Interval Follow-Up Evaluation for depression and hypomania, which allowed for symptom assessment on a week-by-week basis for the 12 weeks before the study visit (Birmaher et al. 2006; Miklowitz et al. 2008). Participants were classified as symptomatic if they scored ≥3 on either depression or hypomania ratings in the 4 weeks before the study visit.

The Family History Screen was conducted with the adolescent and parent/s to determine family psychiatric history for all first- and second-degree relatives (Weissman et al. 2000). The Hollingshead Four-Factor Index was used to determine socioeconomic status (Hollingshead 1975, Yale University unpublished manuscript). The Children's Global Assessment Scale was used to measure the adolescent's global functioning over the current period (past month), most severe past, and highest level in the past year (Shaffer et al. 1983). Information regarding psychotropic medication use and tobacco use was collected during the K-SADS-PL interview. All diagnostic and symptom ratings were reviewed and confirmed by a licensed child and adolescent psychiatrist (B.I.G.).

Collection of study data

Study data were collected and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at Sunnybrook Health Sciences Centre and later at the Centre for Addiction and Mental Health (CAMH). REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources (Harris et al. 2009, 2019).

Cognitive testing

The Wechsler Abbreviated Scale of Intelligence was administered to all participants for an estimate of IQ (Wechsler 2011). The Cambridge Neuropsychological Test Automated Battery (CANTAB eclipse version 2.0; Cambridge Cognition, Ltd., 2005), a computerized battery of subtests that utilize a touch screen and high sensitivity trigger buttons to record responses to cognitive tasks, was used to assess specific domains of neurocognition.

The primary outcome measure was global cognition, measured separately by a global composite score and a *g* factor that are derived from Intra/Extra Dimensional Set-Shifting Task (IED) (attentional set-shifting/cognitive flexibility), Rapid Visual Information Processing Task (RVP) (sustained attention), the Stockings of Cambridge Test (SOC) (spatial planning), and the Affective Go/No-Go (AGN) (information processing biases for positive and negative stimuli). Additionally, in exploratory analyses, we examined the aforementioned individual neurocognitive tests as secondary outcomes.

IED was used to examine reversal learning, set-shifting, and cognitive flexibility. Participants are required to discriminate between two visual stimuli and must use the feedback of the program to work out a rule that determines which stimulus is correct. This task consists of nine stages. After six consecutive correct responses, the rule changes and participants progress to the next stage of the task. Participants must flexibly adapt and learn the new rule.

RVP was used to examine sustained attention. Numerical digits are serially presented to the participants, and participants are requested to detect target sequences of digits and must respond every time they see one of three target sequences of digits.

SOC was used to assess spatial planning. Participants must move three colored balls in the bottom display to copy the pattern shown in the top display. Participants are instructed to make as few moves as possible to match the two patterns. The task consists of 12 trials that become progressively more difficult.

AGN was used to examine affective processing bias for positive and negative stimuli. A series of words from two of three different affective categories: positive, negative; neutral are displayed. The participant is given a target category and is asked to press the button whenever they see a word matching the target category. Blocks of 18 words are displayed, with a pause between the blocks.

Z-scores were computed for the following neurocognitive subtest based on current sample norms: IED (Total Errors Adjusted, Pre-extradimensional Errors, Extradimensional Stage Errors, Total Trials Adjusted), RVP (Sensitivity to the Target, Probability of Hit, Total False Alarms, Mean Latency), AGN (Total Commissions, Total Omissions, Mean Correct Latency Positive, Mean Correct Latency Negative), and SOC (Problems Solved in Minimum Moves). Subtest scores denoted as adjusted were corrected for the total number of stages that a participant completed. Subsequently, composite scores were calculated for each neurocognitive test (i.e., IED, RVP, AGN, SOC), which were then averaged to generate a global composite score. In addition, a principal component analyses approach was used to derive a *g* factor from individual composite scores using VARIMAX rotation.

Statistical analysis

IBM SPSS Statistics 25 was used to perform all statistical analyses. Normality of data was determined via Shapiro–Wilks tests. Independent-sample *t*-tests or Mann–Whitney *U* tests were performed for continuous variables among groups, and chi-square tests were utilized for categorical variables. Effect sizes were reported as Cohen's *d* for continuous variables and Cramer's *V* for categorical variables. Multiple linear regression analyses were conducted to determine the relationship between psychiatric medication use (lithium+ or lithium–; SGA+ or SGA–) and neurocognitive outcome variables. All regression models were tested for relevant assumptions. Age, sex, and IQ were included as covariates.

As most participants were concurrently taking other psychotropic medications, the number of current psychotropic classes of medications (stimulants, anticonvulsants, and antidepressants) was calculated for each participant. This variable was included in sensitivity analysis to control for the presence of all other current medication use. In addition, the effect of lifetime diagnosis of attention-deficit/hyperactivity disorder (ADHD), current mood (depression and hypomania, as measured through PSR), BD subtypes, and concurrent use of lithium and SGAs on neurocognitive outcomes were also tested in sensitivity analyses. Statistical significance was set at $\alpha = 0.05$. Correction for multiple comparisons was performed on a family-wise basis, dividing the significance threshold by the number of preselected cognitive domains (i.e., $\alpha = 0.05/5 = 0.01$).

Results

Demographic and clinical characteristics

Of the 91 participants with BD, 14 were currently taking lithium and 51 were currently taking SGA. Of participants taking lithium, 71% ($n = 10$) were also taking SGA. Female participants were significantly less likely than male participants to be taking lithium (36% vs. 70%, $p = 0.01$). There were several between-group differences in clinical characteristics as indicated in Table 1.

Univariate analyses

Associations of current lithium and SGA use with neurocognition are presented in Table 2. Principal component analysis yielded

Table 1. Demographic and Clinical Characteristics of 91 Adolescents with Bipolar Disorder

	Lithium+ (n=14)	*Lithium− (n=77)*	t/U/χ^2	p	*Effect size*	*SGA+ (n=51)*	*SGA− (n=40)*	t/U/χ^2	p	*Effect size*
Demographics characteristics										
Age, years	17.43 ± 1.91	16.81 ± 1.81	429.0	0.22	0.33	16.69 ± 1.84	17.18 ± 1.81	871.0	0.23	0.27
Socioeconomic status	4.36 ± 1.15	4.29 ± 0.79	460.50	0.34	0.07	4.37 ± 0.87	4.20 ± 0.82	874.0	0.20	0.20
Sex (% female)	5 (35.7)	54 (70.1)	6.15	0.01*	0.26	33 (64.7)	26 (65.0)	0.001	0.98	0.003
Race (% Caucasian)	11 (78.6)	60 (77.9)	0.003	0.96	0.01	41 (80.4)	30 (75.0)	0.38	0.54	0.07
BMI	24.65 ± 2.94	23.41 ± 4.15	339.0	0.10	0.35	23.79 ± 3.88	23.36 ± 4.19	831.60	0.51	0.11
Living with both natural parents	7 (53.8)	52 (67.5)	0.92	0.34	0.10	30 (60)	29 (72.5)	1.54	0.22	0.13
Clinical characteristics										
Age of onset	16.34 ± 1.98	14.87 ± 2.49	294.0	0.02*	0.65	15.18 ± 2.36	15.03 ± 2.63	855.50	0.77	0.01
Bipolar subtype										
BD-I	10 (71.4)	18 (23.3)	13.19	0.001*	0.38	19 (37.3)	9 (22.5)	4.22	0.12	0.22
BD-II	1 (7.1)	28 (36.4)				12 (23.5)	17 (42.5)			
BD-NOS	3 (21.4)	31 (31.9)				20 (39.2)	14 (35.0)			
Mood symptom severity and functioning										
Mania—most severe past	36.07 ± 9.04	30.86 ± 8.93	−2.01	0.048*	0.57	32.10 ± 8.68	31.10 ± 9.68	−0.52	0.61	0.11
Mania—past month	6.64 ± 11.23	10.78 ± 11.23	984.0	0.21	0.37	10.65 ± 12.46	9.50 ± 9.67	421.5	0.63	0.11
Depression—most severe past	27.50 ± 13.94	31.41 ± 10.78	1018	0.24	0.35	30.84 ± 12.09	30.77 ± 10.41	430.0	0.98	0.01
Depression—past month	14.86 ± 11.16	16.73 ± 10.42	904.0	0.54	0.18	15.69 ± 11.22	17.40 ± 9.56	451.0	0.44	0.16
PSR hypomania symptom severity	1.43 ± 1.16	1.73 ± 1.17	445.0	0.25	0.26	1.78 ± 1.30	1.55 ± 0.96	971.0	0.03*	0.20
PSR depression symptom severity	2.79 ± 1.48	2.74 ± 1.56	528.0	0.46	0.03	2.76 ± 1.61	2.73 ± 1.47	1006.50	0.40	0.03
CGAS—most severe past	39.64 ± 6.62	43.56 ± 9.30	359.50	0.08	0.49	41.79 ± 9.98	44.28 ± 7.61	767.50	0.14	0.28
CGAS—past year	69.0 ± 10.37	68.78 ± 10.92	−0.07	0.95	0.02	67.26 ± 10.52	70.65 ± 10.91	1.48	0.14	0.32
CGAS—current	64.86 ± 12.19	63.36 ± 11.39	−0.45	0.66	0.13	62.14 ± 12.43	65.38 ± 10.01	1.33	0.19	0.29
Other characteristics										
Lifetime suicide attempt	2 (1.4)	15 (20.0)	0.25	0.62	0.05	13 (26.0)	4 (10.3)	3.51	0.06	0.20
Lifetime suicidal ideation	6 (42.9)	53 (70.7)	4.08	0.04*	0.21	37 (74.0)	22 (56.4)	3.03	0.08	0.19
Lifetime self-injurious behavior	5 (35.7)	45 (60.0)	2.83	0.09	0.18	26 (52.0)	24 (61.5)	0.81	0.37	0.10
Lifetime any abuse	1 (10)	5 (7.7)	0.06	0.80	0.03	3 (7.5)	3 (8.6)	0.03	0.87	0.02
Lifetime sexual abuse or assault	1 (7.1)	10 (13.0)	0.34	0.56	0.06	6 (11.8)	5 (12.5)	0.002	0.96	0.05
Lifetime physical abuse or assault	1 (7.1)	4 (5.2)	0.11	0.74	0.04	2 (3.9)	3 (7.5)	0.49	0.48	0.08
Lifetime psychosis	7 (50)	18 (23.4)	4.21	0.40	0.22	15 (29.4)	10 (25.0)	0.22	0.64	0.05
Lifetime psychiatric hospitalization	10 (71.4)	23 (29.9)	8.85	0.003*	0.31	20 (39.2)	13 (32.5)	0.44	0.51	0.07
IQ	109.36 ± 9.46	105.65 ± 13.66	−0.97	0.33	0.32	104.82 ± 12.55	108.0 ± 13.78	1.15	0.25	0.24
Lifetime tobacco smoking	8 (57.1)	24 (31.2)	3.51	0.06	0.20	15 (29.4)	17 (42.5)	1.68	0.19	0.14
Lifetime comorbid diagnoses										
ADHD	5 (35.7)	35 (45.6)	0.46	0.50	0.07	21 (41.2)	19 (47.5)	0.36	0.55	0.06
Any anxiety disorder	10 (71.4)	67 (87.0)	2.21	0.14	0.16	40 (78.4)	37 (92.5)	3.41	0.07	0.19
SUD	4 (50)	17 (37.0)	0.49	0.49	0.10	14 (53.8)	7 (25.0)	4.72	0.03*	0.30
ODD	1 (7.1)	22 (28.6)	2.88	0.09	0.18	9 (17.6)	14 (35.0)	3.57	0.06	0.20
Conduct disorder	0 (0)	1 (1.3)	0.18	0.67	0.05	0 (0)	1 (2.5)	1.29	0.26	0.12
Medication use—current										
Current any medication	14 (100)	49 (63.6)	7.35	0.007*	0.28	51 (100)	12 (30.0)	51.57	<0.001*	0.75
SGA[a]	10 (71.4)	41 (53.2)	1.59	0.21	0.13	—	—	—	—	—
Lithium	—	—	—	—	—	10 (19.6)	4 (10.0)	1.59	0.21	0.13
SSRI antidepressants[b]	0 (0)	7 (9.1)	1.38	0.24	0.12	5 (9.8)	2 (5.0)	0.73	0.39	0.09
Non-SSRI antidepressants[c]	0 (0)	1 (1.3)	0.18	0.67	0.05	1 (2.0)	0 (0)	0.79	0.37	0.09
Stimulant[d]	2 (14.3)	2 (2.6)	3.85	0.05	0.21	3 (5.9)	1 (2.5)	0.61	0.44	0.08

(*continued*)

Table 1. (Continued)

	Lithium+ (n = 14)	*Lithium− (n = 77)*	t/U/χ^2	p	*Effect size*	*SGA+ (n = 51)*	*SGA− (n = 40)*	t/U/χ^2	p	*Effect size*
Lamotrigine	1 (7.1)	11 (14.3)	0.53	0.47	0.08	7 (13.7)	5 (12.5)	0.03	0.86	0.02
Divalproex	0 (0)	0 (0)	—	—	—	0 (0)	0 (0)	—	—	—
Medication use—lifetime										
Lifetime any medication	14 (100)	71 (92.2)	1.17	0.28	0.11	51 (100)	34 (85.0)	8.19	0.004*	0.60
SGA[a]	13 (92.9)	58 (75.3)	2.12	0.15	0.15	51 (100)	20 (50.0)	32.38	<0.001*	0.48
Lithium	14 (100)	11 (14.3)	43.68	<0.001*	0.69	13 (25.5)	12 (30.0)	0.23	0.63	0.05
SSRI antidepressants[b]	8 (57.1)	34 (44.2)	0.80	0.37	0.09	27 (53.0)	15 (37.5)	2.15	0.14	0.15
Non-SSRI antidepressants[c]	4 (28.6)	14 (18.2)	0.81	0.37	0.09	14 (27.5)	4 (10)	4.30	0.04	0.22
Stimulants[d]	5 (35.7)	15 (19.5)	1.82	0.18	0.14	11 (21.6)	9 (22.5)	0.01	0.92	0.01
Lamotrigine	1 (7.1)	13 (16.9)	0.86	0.35	0.10	6 (11.8)	8 (20)	1.17	0.28	0.11
Divalproex	1 (7.1)	5 (6.5)	0.01	0.93	0.01	2 (3.9)	4 (10.0)	1.35	0.25	0.12

Values for all continuous variables are presented as mean ± standard deviation and categorical variables are presented as *n* (% within group). Effect size = partial η^2 or Cramer's *V*.

*Significant difference.

[a]SGA = risperidone, olanzapine, aripiprazole, ziprasidone, seroquel.

[b]SSRI antidepressants = zoloft, paroxetine, prozac, fluvoxamine, citalopram, lexapro.

[c]Non-SSRI antidepressants = wellbutrin, remeron, effexor, cymbalta.

[d]Stimulants = ritalin, concerta, adderall, dexedrine.

ADHD, attention-deficit/hyperactivity disorder; BD, bipolar disorder; BMI, body mass index; CGAS, Children's Global Assessment Scale; NOS, Not Otherwise Specified; ODD, oppositional defiant disorder; PSR, Psychiatric Status Rating; SGA, second-generation antipsychotics; SSRI, selective serotonin reuptake inhibitor; SUD, substance use disorder.

Table 2. Univariate Analysis of the Association of Current Lithium and Second-Generation Antipsychotic Use with Neurocognitive Performance

	Lithium+ (n = 14)	*Lithium− (n = 77)*	t	p	*Effect size (95% CI)*	*SGA+ (n = 51)*	*SGA− (n = 40)*	t	p	*Effect size (95% CI)*
Global composite score	−0.06 ± 0.41	0.03 ± 0.44	0.64	0.52	0.21 (−0.44 to 0.86)	0.03 ± 0.45	−0.01 ± 0.41	−0.43	0.67	−0.10 (−0.55 to 0.36)
g Factor	0.01 ± 0.84	−0.001 ± 1.03	−0.03	0.98	−0.01 (−0.65 to 0.63)	−0.06 ± 1.00	0.08 ± 1.00	0.62	0.54	0.14 (−0.31 to 0.59)
RVP (composite score)	0.29 ± 0.64	−0.05 ± 0.79	−1.41	0.16	0.44 (−0.18 to 1.06)	−0.02 ± 0.75	0.03 ± 0.75	0.30	0.76	−0.07 (−0.51 to 0.38)
AGN (composite score)	0.01 ± 0.52	−0.01 ± 0.48	−0.11	0.92	0.03 (−0.61 to 0.68)	−0.08 ± 0.45	0.10 ± 0.50	1.69	0.09	−0.38 (−0.82 to 0.07)
IED (composite score)	−0.34 ± 1.01	0.01 ± 0.73	1.63	0.11	−0.51 (−1.13 to 0.11)	0.08 ± 0.72	−0.11 ± 0.86	−1.12	0.27	0.25 (−0.19 to 0.69)
SOC (composite score)	−0.08 ± 1.05	0.01 ± 0.10	0.30	0.76	−0.09 (−0.71 to 0.53)	0.15 ± 1.10	−0.19 ± 0.83	−1.58	0.12	0.35 (−0.09 to 0.79)

AGN, Affective Go/No-Go; CI, confidence interval; IED, Intra-Extra Dimensional Set-Shifting Task; RVP, Rapid Visual Information Processing Task; SGA, second-generation antipsychotics; SOC, Stockings of Cambridge Test.

one *g* factor, which explained 32.6% of the variance. There were no significant differences in global composite score or *g* factor, our primary outcomes, based on the current use of SGA and/or lithium. Furthermore, no significant differences were observed for other neurocognitive outcomes between the groups. Effect sizes were small to medium for all cognitive outcomes, with the 95% confidence interval of the effect size encompassing zero for each cognitive outcome.

Multivariable analyses

Multivariable analysis of the association of current lithium with neurocognitive performance is shown in Table 3. After controlling for age, sex, and IQ, current lithium use was significantly associated with lower IED composite score ($\beta = -0.23$, $p = 0.04$), although this finding did not survive correction for multiple comparisons ($\alpha = 0.01$). Multivariable analysis of the association of current SGA with neurocognitive performance is shown in Table 4. Controlling for covariates, current SGA use was not significantly associated with either global composite score, *g* factor, or any neurocognitive subtest composite scores. Effect sizes of associations with either lithium or SGA, reported as β, were small for all cognitive outcomes.

Sensitivity analyses

Lithium. Current lithium use remained significantly associated with lower IED composite score in sensitivity analyses further controlling for, sequentially (i.e., not concurrently), current hypomania symptom ($\beta = -0.23$, $p = 0.04$), BD subtype ($\beta = -0.23$, $p = 0.048$), and number of current medications ($\beta = -0.32$, $p = 0.01$). However, the association between current lithium use and IED became nonsignificant after controlling for lifetime comorbid ADHD ($\beta = -0.22$, $p = 0.05$) and current depression ($\beta = -0.19$, $p = 0.09$).

Second-generation antipsychotics. Current SGA use was significantly associated with lower AGN composite score in sensitivity analyses controlling for lifetime comorbid ADHD ($\beta = -0.21$, $p = 0.049$). After controlling for current number of medications, the association of current SGA use with AGN composite was no longer significant ($\beta = -0.30$, $p = 0.05$).

No significant findings in the aforementioned sensitivity analyses survived correction for multiple comparisons ($\alpha = 0.01$). Effect sizes of associations with either lithium or SGA use were small to medium for all cognitive outcomes in sensitivity analyses. In additional sensitivity analyses examining concurrent use of both lithium and SGA, there was no significant lithium × SGA interaction effect on any of the neurocognitive composite scores, controlling for age, sex, and IQ.

Table 3. Multivariable Analysis of the Association of Current Lithium Use with Neurocognitive Performance

Cognitive domain	*β (95% CI)*	*B, SE*	p
Global composite	–0.11 (–0.41 to 0.14)	–0.13, 0.14	0.33
g Factor	–0.02 (–0.69 to 0.56)	–0.07, 0.32	0.83
IED composite	–0.23 (–1.0 to –0.02)	–0.51, 0.25	0.04*
AGN composite	–0.02 (–0.28 to 0.34)	0.03, 0.16	0.86
RVP composite	0.10 (–0.27 to 0.68)	0.21, 0.24	0.39
SOC composite	–0.05 (–0.79 to 0.50)	–0.15, 0.32	0.65

*Significant difference.

AGN, Affective Go/No-Go; CI, confidence interval; IED, Intra-Extra Dimensional Set-Shifting Task; RVP, Rapid Visual Information Processing Task; SE, standard error; SOC, Stockings of Cambridge Test.

Table 4. Multivariable Analysis of the Association of Current Second-Generation Antipsychotic Use with Neurocognitive Performance

Cognitive domain	*β (95% CI)*	*B, SE*	p
Global composite	–0.11 (–0.10 to 0.29)	0.10, 0.10	0.32
g Factor	–0.01 (–0.47 to 0.42)	–0.03, 0.22	0.91
IED composite	0.15 (–0.11 to 0.58)	0.14, 0.17	0.18
AGN composite	–0.17 (–0.37 to 0.05)	–0.16, 0.11	0.12
RVP composite	0.03 (–0.29 to 0.37)	0.04, 0.17	0.81
SOC composite	0.20 (–0.05 to 0.83)	0.39, 0.22	0.08

AGN, Affective Go/No-Go; CI, confidence interval; IED, Intra-Extra Dimensional Set-Shifting Task; RVP, Rapid Visual Information Processing Task; SE, standard error; SOC, Stockings of Cambridge Test.

Discussion

This study examined the association of current lithium and SGA use with neurocognitive performance among youth with BD on four individual tests of cognitive flexibility/set-shifting, affective processing, sustained attention, and spatial planning, as well as global cognition, assessed separately by a global composite score and a *g* factor derived from these tests. The current study included one of the largest samples to date to address this topic in youth with BD. Univariate analyses did not yield any significant findings, for either lithium or SGA. After controlling for age, sex, and IQ, current lithium use was significantly associated with poorer performance on the IED task of cognitive flexibility/set-shifting. In sensitivity analyses that controlled for ADHD in addition to age, sex, and IQ, SGA use was associated with significantly greater affective processing bias. No significant findings survived correction for multiple comparisons.

Overall, these findings suggest that treatment with lithium and/or SGAs is associated with minimal neurocognitive decrements, with findings only emerging in secondary analyses and comprising small effect sizes. While this cross-sectional, observational study cannot determine causal associations between these medications and neurocognition, and while the study cannot rule out associations of smaller effect size, present findings are overall reassuring as they do not demonstrate substantial medication-related neurocognitive impairments. This is salient because of the important therapeutic benefits of lithium and SGAs (Derry and Moore 2007; Post 2018), and because subjective attributions of neurocognitive impairment related to medications are associated with nonadherence (Pachet and Wisniewski 2003; Gitlin 2016).

Lithium

In primary analyses, current lithium use was associated with poorer performance on the IED task, a measure of cognitive flexibility/attentional set-shifting, although this finding did not survive correction for multiple comparisons and the effect size was small. This aligns with a previous study in adults with BD where lithium was associated with moderate deficits in cognitive flexibility (Gualtieri and Johnson 2006). Elevated brain lithium levels have previously been associated with poorer set-shifting in older adults with BD (Forester et al. 2009). However, other studies failed to find a significant relationship between lithium use and set-shifting in

youth or adults with BD (Bearden et al. 2007; Henin et al. 2009; McKirdy et al. 2009).

The association between current lithium use and IED performance was reduced to a statistical trend after controlling for lifetime comorbid ADHD and current depression symptoms in sensitivity analysis. As ADHD is associated with compromised cognitive flexibility/set-shifting, it is possible that the observed impairments arise from comorbid ADHD (Bálint et al. 2015; Pievsky and McGrath 2018). Additional studies in euthymic youth with BD are warranted to parse the associations of comorbid ADHD with neurocognitive performance.

No significant association between current lithium use and performance in global cognition, sustained attention, spatial planning, and affective processing bias was found in our primary or sensitivity analyses. Past studies in youth and adults with BD yielded mixed results. A prior study of children with BD found no association between use of mood stabilizers and attentional impairments (Henin et al. 2009), whereas another study reported reduced attention in lithium-treated youth (Streicher et al. 2020). A meta-analysis of 24 studies of euthymic youth with BD found that lithium use was overall associated with impairments in global cognition (Elias et al. 2017). In addition, a cross-sectional and longitudinal study of 88 adults with BD suggested that lithium does not significantly impair cognition when used therapeutically and may be beneficial to neurocognition (Burdick et al. 2020).

Second-generation antipsychotics

Current SGA use was not associated with any of the neurocognitive tasks, nor with global neurocognition, in primary analyses. This is in line with studies of both adolescents and adults with BD that reported no association between SGA use and performance in spatial planning, sustained attention, or set-shifting (Badcock et al. 2005; Henin et al. 2009; Streicher et al. 2020). However, the aforementioned meta-analysis of euthymic youth with BD suggested an association between antipsychotic use and impaired global cognition and attention (Elias et al. 2017), and a 24-week, observational prospective study found that aripiprazole was associated with improved attention and set-shifting in a combined sample of adolescents and adults with BD (Wang et al. 2012).

Sensitivity analyses were only significant for affective processing bias, which was significantly greater (i.e., poorer AGN scores) among participants currently taking SGAs after controlling for lifetime comorbid ADHD. However, the effect size was small to medium, and as with previous findings, did not survive correction. Few studies have examined the association of SGAs with affective processing in youth with BD, although one study of adolescents and adults with BD reported a significant association between current medication use (lithium, antidepressant, antipsychotic, and mood stabilizer) and more positive emotional processing biases (Bilderbeck et al. 2016).

The association between current SGA use and affective processing bias was reduced to a statistical trend after controlling for the total number of current medications. Therefore, it is possible that the association between current SGA use and affective processing bias was confounded by indication (i.e., more severe BD). While the concurrent use of other medications may also have impacted findings, it is noteworthy that the total number of medications was not associated with neurocognition in the current study.

This study should be interpreted in light of several limitations. This is an observational and cross-sectional study, and therefore, we cannot establish the directionality of the observed associations between neurocognitive performance and current lithium and SGA use. While this study is among one of the largest studies examining lithium/SGA-neurocognition associations in youth with BD, the sample size was still modest, particularly the lithium-treated group, which limits potential detection of small effects on neurocognitive performance.

In addition, since 71% of participants taking lithium were concurrently taking SGAs, the observed lithium–neurocognition association may be modulated by concurrent SGA use. Owing to small sample size, analyses were underpowered to assess the effects of each medication individually, and therefore, we opted to control for the total number of current psychotropic medications. As previously mentioned, differences in clinical presentation may result in a greater likelihood of participants receiving lithium or SGAs. These differences may potentially influence neurocognition and confound the observed lithium/SGA–neurocognition association (i.e., confounding by indication).

We did not include a systematic collection of duration of treatment, serum drug levels, and adherence to treatment, which may impact the medication–neurocognition association observed in the current study. Finally, there was meaningful variability in mood symptoms among participants, which was controlled for in sensitivity analyses. Additional future studies with larger samples, ideally using prospective repeated-measures designs, should evaluate the associations between mood severity, psychotropic medications, and neurocognition.

Conclusions

In summary, the findings from this study, one of the largest to date on this topic, suggest that treatment with lithium and/or SGAs is associated with minimal neurocognitive decrements, with generally small effect sizes in primary multivariable analyses. This study adds to the developing body of literature regarding the association of medication with neurocognition among youth with BD. Future randomized controlled clinical trials will assist in elucidating more definitive effects of psychotropic medication use on neurocognitive performance in youth with BD.

Clinical Significance

Neurocognitive impairments are commonly reported in studies of youth with BD. While BD is independently associated with reduced neurocognitive performance, these impairments are often attributed to medications, which in turn contribute to nonadherence. The current study, within the constraints of its acknowledged limitations, presents reassuring data that SGA and lithium use are not meaningfully associated with neurocognitive decrements in youth with BD. This is relevant from a stigma-reduction perspective and may aid in improving messaging around medication side effects and adherence.

Ethics Approval and Consent to Participate

Consent was obtained from all participants and their parent and/or guardian before participating. Ethical approval was granted by Sunnybrook Research Institute Research Ethics Board (REB No. 405/2014 and 347/2011). All data were collected at Sunnybrook Research Institute. However, all data were transferred with the Centre for Youth Bipolar Disorder's relocation to the CAMH. Thus, ethics approval was also granted by the CAMH Research Ethics Board (REB No. 152/2020 and 170/2020).

Availability of Data and Material

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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Disclosures

X.J., M.M., M.K.D., Y.Z., A.A.S., and B.I.G. have no financial relations with any pharmaceutical company and have no conflicts of interest to disclose.

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