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# Adherence Rates and Barriers to Second-Generation Antipsychotic Medication Use in Youth with Bipolar Spectrum Disorders Who Have Overweight/Obesity

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## Abstract

**Objective:** Youth with bipolar spectrum disorders (BSD) are frequently prescribed second-generation antipsychotics (SGAs). Nonadherence to treatment often results in increased mood symptoms and diminished quality of life. We examined SGA adherence rates and adherence barriers among youth who have overweight/obesity and are diagnosed with BSD enrolled in a multisite pragmatic clinical trial.

**Methods:** SGA adherence and adherence barriers at baseline via patient- and caregiver report was assessed. Adherence was defined as taking  $\geq 70\%$  of prescribed SGA doses in the past week. The weighted Kappa statistic was used to measure child-caregiver agreement about adherence rates, barriers, and caregiver assistance. Regression analyses were used to examine associations of caregiver assistance, age, sex, race, insurance status, dosing frequency, and number of concomitant medications with adherence. Barriers to adherence were analyzed separately for youth and their caregivers, using logistic regression to assess associations between informant-reported barriers and informant-reported adherence.

**Results:** Participants included 1485 patients and/or caregivers. At baseline, 88.6% of patients self-reported as adherent; 92.0% of caregivers reported their child was adherent. Concordance between patients and caregivers was moderate ( $k = 0.42$ ). Approximately, 50% of the sample reported no adherence barriers. Frequently endorsed barriers included forgetting, side effects, being embarrassed to take medications, and preferring to do something else. Concordance between informants regarding adherence barriers was weak ( $k = 0.05–0.36$ ). Patients and caregivers who did not endorse adherence barriers reported higher adherence than those who endorsed barriers. Male sex and having once daily dosing of medications were associated with lower adherence.

**Discussion:** One-week patient- and caregiver-reported adherence was high in this sample. Half of the sample reported adherence barriers. Most commonly endorsed barriers were forgetting, side effects, being embarrassed, and preferring to do something else. Caregivers and patients have unique perspectives regarding adherence barriers. Understanding and addressing treatment barriers in clinical practice may facilitate adherence.

**Keywords:** medication adherence, bipolar, youth, antipsychotic, psychiatry

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## Introduction

**B**ipolar spectrum disorders (BSD) affect 2% of youth worldwide (Van Meter et al., 2011). Evidence-based pharmacological treatment strategies to treat youth with BSD include the use of second-generation antipsychotics (SGAs) (Correll et al., 2011; Correll, Sheridan and DelBello, 2010). However, among youth with BSD, adherence to SGAs varies from 44% to 65% (Coletti et al., 2005; DelBello et al., 2007; Yazdi et al., 2008). Adherence can be defined as the extent to which a person's behavior coincides with medical or health advice (Modi et al., 2012). Among youth with BSD, treatment nonadherence is associated with higher risk of relapse, hospitalization, and comorbid psychiatric and medical illnesses (Clatworthy et al., 2007; Edgcomb and Zima, 2018). As such, adherence remains a critical challenge that warrants further attention (Lage and Hassan, 2009).

Although SGAs are effective in reducing symptoms of BSD, several barriers, such as side effects and dosing schedules, negatively influence medication adherence, particularly among adolescents (Correll et al., 2010; Goldstein et al., 2016). Goldstein et al (2016) it was reported that nearly half of youth with BSD did not take their medications as prescribed. A recent study (Klein et al., 2020) examined retrospective patient-centered perspectives of SGA treatment nonadherence among youth with BSD and found only a third of patients reported taking their medications as prescribed. Patients reported unwanted side effects as the top barrier to SGA-medication adherence, and nearly half of patients (45.6%) ranked weight gain as the most concerning barrier. This suggests that patients who have overweight/obesity may be at increased risk of nonadherence. Clatworthy et al (2007) interviewed youth with BSD, and 81% reported some degree of medication nonadherence due to concerns of short- and long-term side effects and doubts that the medication was truly needed. Research on the concordance between child and caregiver reported adherence rates is equivocal. Specifically, O'Brien et al (2013) reported child and caregiver reports of medication adherence among youth with BSD to be similar, whereas Goldstein et al (2016) reported that agreement between patient and caregiver reports was weak.

The Pediatric Self-Management Model postulates that adherence and self-management behaviors in youth occur within the context of individual, family, community, and health care systems (Modi et al., 2012). Individual factors include nonmodifiable traits such as age and sex assigned at birth. Modifiable characteristics include adherence barriers such as forgetting, difficulty swallowing pills, and disliking the taste of medications. Family factors include nonmodifiable aspects, such as family social determinants of health (e.g., family socioeconomic status) and modifiable factors including caregiver involvement (e.g., helping the child take the medication, monitoring the child to assure medication adherence, establishing consistent household routines). Community system factors include involvement of peer, church, and school communities to aid children with health management. Health care system factors include patient-provider communication and access to health care providers. Studies have demonstrated that the creation of a medication tracker and parental oversight with medication regimens improve adherence for youth with BSD (Arlinghaus and Johnston, 2019; Brazendale et al., 2017; Coletti et al., 2005; Dean et al., 2011).

The aim of the current report is to examine adherence rates and barriers to adherence among youth with BSD who have overweight/obesity at baseline of participation in a large pragmatic

study (Welge et al., 2023). We hypothesized that adherence rates as well as concordance between parent and child report would be less than 50%. We also hypothesized that the most frequently endorsed adherence barriers will include side effects, and forgetting medications and these barriers would be associated with worse adherence. Based on prior literature, we hypothesized that older child age (Elhosary et al., 2023; Shetty et al., 2016; Sleath et al., 2017), being male (Goldstein et al., 2016; Sanchez et al., 2021), race/ethnicity minority status (Gutierrez-Colina, et al., 2022; Sleath et al., 2017), greater number of medications (Elhosary et al., 2023), more complex dosing regimen (Goldstein et al., 2016), and more adherence barriers would predict both lower patient- and caregiver-reported adherence. However, it is unknown if youth with BSD who also have overweight/obesity have similar adherence rates and barriers.

## Materials and Methods

### Participants

Study criteria are reported in detail elsewhere (Welge et al., 2023). Briefly, eligible youth were: 1) aged 8–19 years inclusive, 2) sex- and age-adjusted body mass index  $\geq 85$ th percentile, 3) have a lifetime diagnosis of a BSD, and 4) received a new or had an ongoing prescription for an oral regularly dosed SGA. After reviewing study procedures, all participants and their legal guardians or representatives from child services provided informed assent (if 18–19 years old, informed consent) or consent, respectively.

### Setting

Participants were recruited at 64 clinical locations (39 community-based mental health centers and 24 sites in or affiliated with academic health centers). Participating sites are listed at <http://www.mobilitystudy.org>. All study procedures were approved by the Cincinnati Children's Hospital Medical Center (CCHMC) Institutional Review Board (2017-6937C). Patients and their caregivers were asked to complete questionnaires via a REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, TN) survey on a tablet (in-person visits) or via an online link to the REDCap questions sent via email. During the COVID-19 pandemic, most visits transitioned from in-person to telehealth. We were able to continue to collect patient- and caregiver-reported outcomes remotely by sending scales and tape measures to families, as well as allowing for questionnaire completion via a secure REDCap survey sent via email. At baseline, patients and caregivers provided demographic data (age, sex, race/ethnicity, insurance status).

### Questionnaire

**Self- and parent-reported adherence.** Patients and caregivers were asked a question at every study visit regarding their adherence behaviors in the past 7 days. Specifically, they were asked "How many doses of (SGA) have you/this child missed taking in the past week?"

**Adherence barriers.** Adherence barriers were assessed via a checklist of common barriers used in several chronic illness populations, including epilepsy (Gutierrez-Colina et al., 2018), juvenile rheumatoid arthritis (Favier et al., 2018), and kidney transplantation (Varnell et al., 2017). Patients and caregivers were then asked to endorse "yes" or "no" to the following adherence barriers: "forgetting to take them or bring them along," "inconvenient," "dosing

TABLE 1. ADHERENCE BARRIERS ENDORSEMENT AMONG PATIENTS AND CAREGIVERS

<i>Barriers to Medication Adherence</i>	<i>Patients (n = 1452)</i>	<i>Caregivers (n = 1424)</i>	<i>Agreement (k) (n = 1391 dyads)</i>
I forget to take them or bring them with me	21.3%	23.1%	0.36
I don't like the side effects	5.2%	2.1%	0.05
They taste bad	2.9%	2.3%	0.03
Embarrassed to take them	5.0%	2.6%	0.19
Would rather do something else than take medications	1.0%	1.0%	0.13
There were other reasons not listed here	9.5%	16.3%	0.22
Gets in the way of other things I do	4.7%	1.7%	0.29
They don't work	7.0%	4.6%	0.22
Hard to swallow	2.8%	3.7%	0.17
Taking pills at the right time does not match my schedule	0.5%	0.3%	0.16
Ran out of medicine	6.9%	8.7%	0.18
I don't need them	2.5%	2.2%	0.01
They cost too much	8.3%	2.4%	0.16
I could not understand my doctor's instructions about taking them	6.0%	4.8%	0.10
No barriers	49.7%	44.2%	0.30

schedules don't match lifestyle," "they don't work," "too expensive," "side effects," "hard to swallow," "embarrassed to take them," "ran out of medication," "difficulty understanding instructions," "would rather do something else than take medications," "don't need them," "bad taste of medication," and "other reasons."

**Allocation of treatment responsibility.** Based on the valid and reliable measures of allocation of treatment responsibility (Pai et al., 2010; Ryan et al., 2014), a one-item question asked patients and caregivers to indicate if a parent or caregiver gives the patient the medication, reminds the patient to take the medication, or does not help with taking the medication.

#### *Statistical and data analysis*

Adherence was dichotomized into a binary adherence variable (reported missing fewer than 30% of doses in the week prior to the baseline visit) for each informant. A conservative adherence criterion was also computed (patient considered nonadherent if *either* informant reported more than 30% of doses were missed during the prior week). The weighted Kappa statistic was used to measure child-caregiver agreement about adherence rates, barriers, and caregiver assistance. Logistic regression was used to examine associations of caregiver assistance, age, sex, race, insurance status (as a proxy for socioeconomic status), dosing frequency (once/day vs. more than once/day), and number of prescribed psychotropic prescriptions (one vs. more than one) with the conservative adherence criterion. Barriers to adherence were analyzed separately for youth and their caregivers using logistic regression to assess associations between informant-reported barriers and informant-reported adherence.

## **Results**

### *Demographics*

In total, 1565 patients had baseline data. Of these, 1519 were on an orally dosed SGA at baseline; 1485 patients and/or caregivers completed baseline assessments between November 5, 2015 and February 11, 2022, and were included in analyses. Unique respondent data was available for 1452 patients and 1424 caregivers. Dyadic data existed for 1391 patient/caregiver pairs. The mean age of patients at randomization was 13.9 years ( $SD = 2.8$ ).

Approximately, half ( $n = 788$ , 53.1%) were male sex assigned at birth (SaaB); more than half identified as White/Caucasian ( $n = 974$ , 65.6%), 18.4% ( $n = 273$ ) identified as Black/African American; 9.6% of patients ( $n = 142$ ) reported being multiracial, and the remainder ( $n = 36$ , 2.4%) identified as Asian, Native American, or Native Hawaiian/Pacific Islander. A minority of participants ( $n = 191$ , 12.9%) reported Hispanic ethnicity. Most patients ( $n = 1433$ , 96.5%) were prescribed one SGA rather than more than one SGA. Most common dosing was once per day ( $n = 897$ , 64.1%).

### *Patient- and caregiver-reported medication adherence and adherence barriers*

Patients reported 88.6% adherence to SGA medications in the prior week and caregivers reported 92.0% adherence, with a conservative composite rate of 85.5%. The most frequently endorsed barriers among patients included forgetting to take them (21.3%), side effects (9.5%), embarrassed to take medications (7.0%), and wanting to do something other than taking medications (6.9%; Table 1). Among caregivers, the top three reported adherence barriers for their children included forgetting to take them (23.1%), side effects (16.3%), and wanting to do something else other than take medications (8.7%). Nearly half of patients (49.7%) and caregivers (44.2%) reported no adherence barriers.

### *Relationship between adherence, adherence barriers, and sociodemographic and medical factors*

Patients and caregivers who reported no adherence barriers reported higher adherence rates (patient: [ $OR = 5.59$  {3.67, 8.52}]; caregiver: [ $OR = 2.59$  {1.67, 4.02}]). Self-reported adherence was not significantly associated with patient-reported adherence barriers. In contrast, lower caregiver-reported adherence was significantly associated with several adherence barriers, including running out of medications ( $OR = 0.28$  [0.14, 0.55]), not understanding physician instructions regarding medications ( $OR = 0.03$  [0.00, 0.27]), and feeling medications were not needed ( $OR = 0.36$  [0.15, 0.90]). Higher caregiver-reported adherence was significantly associated with reporting that side effects made taking the medication more difficult ( $OR = 1.93$  [1.02, 3.66]).

Male SaaB reported lower adherence rates than female SaaB ( $OR = 1.38$  [95% CI: {1.04, 1.85}]). Black/African American

TABLE 2. ADHERENCE BARRIERS ASSOCIATION WITH PATIENT- AND CAREGIVER-REPORTED ADHERENCE

	Association with Child Adherence				Association with Caregiver Adherence			
	Odds ratio	LCL	UCL	p value	Odds ratio	LCL	UCL	p value
I forget to take them or bring them with me	0.86	0.59	1.26	0.444	1.26	0.78	2.05	0.344
Gets in the way of other things I do	0.71	0.37	1.37	0.307	0.78	0.23	2.60	0.679
Taking pills at the right time does not match my schedule	1.60	0.49	5.24	0.439	0.89	0.27	2.97	0.853
They don't work	0.80	0.40	1.59	0.461	0.95	0.29	3.15	0.935
They cost too much	1.54	0.20	11.90	0.679	na	na	na	0.983
I don't like the side effects	1.28	0.71	2.32	0.417	1.93	1.02	3.66	<b>0.043</b>
Hard to swallow	1.32	0.56	3.10	0.527	0.63	0.19	2.14	0.457
Embarrassed to take them	1.78	0.81	3.90	0.151	1.83	0.57	5.93	0.313
Ran out of medicine	0.72	0.30	1.74	0.463	0.28	0.14	0.55	<b>&lt;0.001</b>
I could not understand my doctor's instructions	0.25	0.05	1.40	0.115	0.03	0.00	0.27	<b>&lt;0.001</b>
Would rather do something else than take medications	0.85	0.46	1.55	0.592	0.65	0.36	1.18	0.157
I don't need them	1.33	0.40	4.41	0.639	0.36	0.15	0.90	<b>0.029</b>
They taste bad	2.13	0.98	4.66	0.058	0.66	0.23	1.91	0.448
No reasons taking this medication(s) is not hard	5.59	3.67	8.52	<b>&lt;0.001</b>	2.59	1.67	4.02	<b>&lt;0.001</b>

Bolded values indicate statistical significance.

LCL, lower confidence limit; na, not applicable; UCL, upper confidence limit.

patients reported lower adherence rates than White/Caucasian patients (81% vs. 87%,  $p = 0.008$ ). Once daily dosing ( $OR = 0.50$  [0.34, 0.72]) and monotherapy ( $OR = 2.5$  [1.6, 3.7]) were associated with poorer patient-reported adherence (78.5% for monotherapy vs. 88.6% for polypharmacy). There was no correlation between child-reported adherence and functioning as measured by the Children's Global Assessment Scale (Shaffer et al., 1983) (CGAS) ( $p = 0.412$ ). The mean CGAS for nonadherent youth was 58.8; the mean CGAS for adherent youth was 58.0.

Patient and caregiver agreement regarding adherence rates was moderate ( $K = 0.48$ ). Agreement between patient- and caregiver-reported barriers to adherence was weak ( $K = 0.05$ – $0.36$ ). Finally, there was a weak-to-moderate but statistically significant correlation between caregiver assistance with taking medication and patient forgetting to take the medication ( $r = 0.22$ ,  $p < 0.001$ ) where patients who received assistance reported forgetting to take their medications less frequently.

## Discussion

This large pragmatic multisite study adds to the understanding of SGA medication adherence rates and barriers to medication adherence in real-world settings for overweight/obese youth with BSD. Previous research reported medication adherence rates among youth with BSD varying from 44% to 65% (Coletti et al., 2005; DelBello et al., 2007; Yazdi et al., 2008). As noted, nonadherence is associated with higher risk of relapse, hospitalization, and comorbid psychiatric and medical illnesses among adults with BSD and among youth with severe mental illness (Clatworthy et al., 2007; Edgcomb and Zima, 2018). Thus, understanding the factors that contribute to nonadherence is critical in improving adherence and self-management behaviors in youth with BSD.

### Patient- and caregiver-reported medication adherence

Our results found higher adherence rates than previously reported. One potential explanation is that we asked patients and caregivers to recall adherence over the past week, a relatively short-time period, which may not be representative of adherence over a longer duration. Of note, most of these patients had been

prescribed an SGA for at least one year prior to the MOBILITY baseline visit. Moreover, patients and caregivers reported adherence rates via tablet computers while in their clinician's office, which could have led to social desirability responding. Finally, it is known that self-reported adherence measures yield over-reporting of adherence, including in youth with BSD (Goldstein et al., 2016).

### Relationship between adherence, adherence barriers, and sociodemographic and medical factors

In this sample, 45%–50% of patients and caregivers reported that there were no barriers to taking their second-generation antipsychotic as prescribed. Not surprisingly, patients and caregivers without endorsed barriers reported greater medication adherence. Interestingly, caregivers who said side effects make taking the medications difficult were more likely to report that their child was adherent to the medication. Those who are adherent are more likely to report side effects. Ultimately, these side effects may then lead to nonadherence. The side effect profile of SGAs is well-established (Correll et al., 2010; Goldstein et al., 2016), as is the impact of side effects on medication adherence among youth with BSD (Clatworthy et al., 2007; Klein et al., 2020).

Consistent with prior studies, male SaaB and Black race were patient-level factors associated with decreased adherence rates (Gutierrez-Colina et al., 2022). Future research might examine if nonadherence is moderated by racial inequities in the health care system, such as continuity of care or clinician competency to implement adherence-related interventions. Prior research suggests younger girls are more adherent than younger boys. In contrast, older boys tend to have higher adherence rates (Bouquembourg et al., 2019). Although we hypothesized that easier-dosing regimens (e.g., once/day, monotherapy) would be associated with better adherence rates, in this sample once-a-day dosing and monotherapy were associated with worse adherence. It may be that clinicians who suspect their patients are nonadherent purposefully prescribe medication to be taken once a day or prescribe fewer medications.

As hypothesized, agreement between patients and caregivers on adherence rates was moderate. Similar studies have demonstrated



low-to-moderate concordance in both adherence and adherence barriers, as each individual has unique self-management experiences (Gutierrez-Colina et al., 2018; Varnell et al., 2017). For example, a caregiver may perceive opposition as an adherence barrier on the part of the child/adolescent, whereas the child/adolescent may report difficulty swallowing the medicine and being embarrassed to take it as adherence barriers, resulting in a mismatch in what is reported (Gutierrez-Colina et al., 2018; Varnell et al., 2017). This can also lead to discrepancies, especially for adolescents who are more independent in their self-management. Understanding the reason for this discrepancy may uncover additional areas for intervention.

Among this sample, caregivers giving their children their medication was associated with better adherence, but reminding the patient to take the medication was not. Notably, odds of adherence nearly tripled when the caregiver gave the patient their SGA dose, suggesting they are an important source of support around adherence and self-management. Consistent with our findings, Coletti et al. (2005) found parental assistance with medication regimens that improve adherence for youth with BSD.

### *Clinical implications*

Understanding adherence barriers that are associated with poor adherence is an initial step to developing targeted and effective interventions to enhance adherence. Clinical interventions such as psychoeducation and motivational interviewing have proven effective in increasing medication adherence among patients with bipolar disorders (Goldstein et al., 2020; Rahmani et al., 2016). Further, behavioral interventions such as pill monitoring and linking medications with established routines have been effective in other chronic pediatric illnesses, but their effectiveness has yet to be established in youth with BSD (Dean et al., 2010). For example, Arlinghaus and Johnston (2019) reported that creating routines increased adherence to medical recommendations. Sajatovic and colleagues (2004) developed a customized adherence intervention for adults with BSD, which is currently being tested in adolescents and young adults.

### **Limitations**

Several limitations should be considered. First, adherence barriers were assessed in general versus being specific to particular SGA medications. Second, respondents could only choose from prelisted barriers and did not have an opportunity to write in other potential barriers. Understanding the other barriers that negatively impact SGA medication adherence is needed. Third, adherence was only measured one-week prior to the clinic appointment. A longer duration of adherence may have yielded different results. Finally, the use of more objective measures of adherence (e.g., electronic monitors) would increase the rigor of adherence monitoring. Self-report is known to be plagued with social desirability and inaccurate reporting. However, this is the most practical form of adherence assessment for a large pragmatic trial across academic and community agencies caring for youth with BSD.

### **Conclusions**

The current study examined SGA adherence rates and barriers, and concordance between patient and caregiver-reported adherence in patients with BSDs. Caregiver assistance with taking medication had a positive effect on patient-reported SGA adherence. Investigations of other modifiable barriers to adherence and interventions to

improve adherence among youth with BSDs, including utilizing pill boxes, employing therapies such as motivational interviewing are warranted. To improve medication adherence among youth with BSDs, future studies to understand variance in reported adherence rates and strategies to overcome perceived barriers are needed.

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### **Authors' Contributions**

M.P.D., C.U.C., J.A.W., and A.C.M. contributed to the study design. Material preparation and analyses were performed by M.P.D., C.C.K., A.C.M., J.A.W., and T.J.B. The first draft of the article was written by C.C.K. and A.C.M. All authors commented on drafts of the article and read and approved the final article.

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