Medication Adherence Among Adolescents with Bipolar Disorder

Tina R. Goldstein, PhD,¹ Megan Krantz, BA,¹ John Merranko, MA,¹ Matthew Garcia, BA,¹
Loren Sobel, MD,¹ Carlos Rodriguez, MD,² Antoine Douaihy, MD,¹
David Axelson, MD,³ and Boris Birmaher, MD¹

Abstract

Objective: To examine medication adherence and associated factors among adolescents with bipolar disorder (BP) using both objective and subjective methods.

Method: Participants were 21 adolescents with a primary BP diagnosis recruited from a pediatric specialty clinic. All participants were prescribed at least one psychotropic medication. Self- and parent-reported adherence were assessed monthly over 6 months. Objective data on medication adherence were gathered through an electronic weekly pillbox. Demographic and clinical factors were assessed through self, parent, and physician ratings at baseline, 3, and 6 months.

Results: Objective data indicate 41.5% of doses (58.6% of days) were not taken as prescribed over a mean of 3 months of follow-up. Subjective reports (patient, parent, and physician) significantly overestimated adherence as compared with objective data. Factors from multiple domains were associated with poorer adherence, including more daily doses, higher weight, dose timing (poorer on mornings/afternoons and weekends), less temporal proximity to medication management appointment, greater self-reported cognitive difficulties with adhering to treatment; the most potent predictor of missed doses was greater overall illness severity.

Conclusions: Findings provide further evidence of poor medication adherence among youth with BP, and highlight the limits of subjective report of adherence. Providers should give careful attention to adherence when making decisions regarding treatment response and changes to medication regimen when working with youth with BP.

Keywords: bipolar disorder, adolescent, medication adherence

Introduction

BIPOLAR DISORDER (BP) affects 2% of youth worldwide (Van Meter et al. 2011) and is characterized by high rates of comorbidity, suicidality, and psychosocial impairment (Birmaher et al. 2009; Goldstein et al. 2010, 2012). Treatment of youth with BP in clinical practice commonly includes mood stabilizing and antipsychotic medications (for a review, see Liu et al. 2011); due to the complexity of the disorder and high rates of comorbidity, pharmacotherapy for pediatric BP commonly involves multiple medications (Bhowmik et al. 2013). Yet, the majority of adolescents with BP continue to experience impairing symptoms and recurrences even when prescribed recommended pharmacotherapy (Geller et al. 2010; Pavuluri et al. 2010).

One reason why youth with BP continue to be symptomatic despite adequate treatment may be poor medication adherence, defined as “the extent to which a person’s behavior corresponds with agreed recommendations from a healthcare provider” (World Health Organization 2003). Difficulties with adherence can pres-

ent in a variety of ways. The literature on poor adherence most commonly focuses on missed doses, but may also include other behaviors that deviate from provider recommendations, including incorrect timing of doses and incorrect dosing. Due to the complexity of the phenomenon, experts in the field came to consensus on the following definition of poor adherence: less than 80% of prescribed medication taken or gaps in medication of at least 7 days (Velligan et al. 2009b). Among adult psychiatric populations, individuals with BP rank among the least treatment adherent, with a mean nonadherence rate of 60% (Cramer and Rosenheck 1998).

Few studies have examined rates of medication adherence among youth with BP. Generally, research indicates that adolescents are especially vulnerable to poor adherence with psychotropic medications—even more so than younger children and adults (Hack and Chow 2001). It is, therefore, not surprising that the limited extant data indicate medication adherence among adolescents with BP is particularly problematic. One study of child and adolescent psychiatric inpatients found the most potent predictor of nonadherence after discharge was a mood disorder diagnosis

¹Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

²Hospital of Fuerteventura, Canary Health Service, Canary Islands, Spain.

³Nationwide Children’s Hospital, Columbus, Ohio.

(Yazdi et al. 2008). The few published studies indicate rates of nonadherence among adolescent outpatients with BP from 66% in the prior month through parent report (Coletti et al. 2005), to 44% for antipsychotics, and 47% for mood stabilizers in the prior year through self and clinician report (Patel et al. 2005). DelBello et al. (2007) documented that 65% of adolescents with BP were non-adherent over 1 year posthospitalization for an acute mood episode through self and parent report.

Each of the prior studies are limited by reliance on self, parent, and/or physician report of adherence; such subjective methods are known to overestimate adherence as compared with more objective methods (e.g., medication monitoring devices, pill count, serum levels; Shi et al. 2010). Indeed, studies in adults with BP indicate that self-report data reliably overestimate adherence as compared with objective data from pharmacy claims (Stephenson et al. 2012), serum concentrations (Jonsdottir et al. 2010), and medication event monitoring systems (MEMS; Badiiee et al. 2012). Clinician report failed to identify nearly 50% of adult outpatients classified as nonadherent with antipsychotics through MEMS (Byerly et al. 2005). The only study of youth with BP that employed both subjective and objective methods of adherence showed that both self-report and pill count overestimated adherence compared with serum lithium concentrations (Drotar et al. 2007). As such, the NIMH expert panel on treatment adherence research recommends use of multiple methods to assess medication adherence (Velligan et al. 2009a).

The consequences of poor medication adherence for adolescents with BP are dire. Providers' assessments of treatment response and decisions regarding dosing/regimen changes are predicated on accurate information regarding adherence. Nonadherent youth with BP exhibit higher rates of relapse and longer time to recovery (Gearing and Mian 2005; Gearing et al. 2009), and more frequent and longer hospitalizations (Scott and Pope 2002). Healthcare costs for one nonadherent adult with BP are equal to that of 13 adherent adults (Durrenberger et al. 1999). Other poor outcomes associated with inadequately treated BP in youth include psychosocial impairment, substance abuse (Birmaher et al. 2006), and suicide (Muller-Oerlinghausen et al. 1996). Given that medication adherence is a potentially modifiable behavior (Kane 1985), such negative outcomes may be prevented if better understood and more effectively targeted in treatment.

A substantive body of work indicates that multiple factors affect medication adherence in adults with BP, converging in four domains (Jamison et al. 1979; Velligan et al. 2009b): (1) Illness-specific factors (e.g., symptomatology); (2) Patient factors (e.g., interpersonal conflict); (3) Treatment factors (e.g., dosing schedule); and (4) Treatment provider factors (e.g., collaboration with treatment team). Research indicates that developmental factors represent an additional domain affecting medication nonadherence among adolescents with chronic health conditions. For example, drives for peer acceptance, low acceptability of cosmetic side effects, and incomplete development of reasoning capabilities have potent associations with adherence to medication regimens during adolescence (Shaw 2001; Pogge et al. 2005). The few studies to explore factors associated with medication adherence among youth with BP found that poorer adherence was associated with male sex, poorer family functioning (Drotar et al. 2007), and greater time since diagnosis (Coletti et al. 2005).

We assessed rates of medication adherence through objective and subjective methods among adolescents diagnosed with BP, and examined factors from multiple domains associated with adherence. We hypothesized: (1) objective methods of measuring adherence would indicate lower rates of adherence than subjective methods; and (2) factors from multiple domains would be associated with adherence, specifically illness factors (symptom severity, psychiatric comorbid-

ity), patient factors (male sex, lower SES, family conflict), treatment factors (side effects, regimen complexity), provider factors (distrust of provider), and developmental factors (older age, higher pubertal status).

Methods

Participants

We recruited participants from the Child and Adolescent Bipolar Spectrum Services (CABS) clinic at Western Psychiatric Institute and Clinic at the University of Pittsburgh for a 6-month naturalistic study examining factors associated with medication adherence. Potentially eligible participants were approached by members of their treatment team regarding their interest in the study. Interested youth were referred to the study coordinator.

Inclusion criteria. Eligible adolescents met the following criteria: (1) age 12 years 0 months to 22 years 11 months; (2) DSM-4 diagnosis of bipolar I, II, or not otherwise specified (NOS; see Diagnostic Evaluation) through semistructured interview; (3) prescribed at least one psychotropic medication for BP; (4) no evidence of mental retardation or autism spectrum disorder.

Procedures

The study was approved by the Institutional Review Board at the University of Pittsburgh. Study staff explained all procedures to interested adolescents and parents (for participants <18), and obtained written informed consent before the initiation of study procedures. Participation involved an initial diagnostic evaluation; assessments of adherence and related factors were conducted at intake, 3-, and 6-month time points. Participants used an electronic pillbox (see below) daily to yield objective data on medication adherence.

Diagnostic evaluation. Master's level staff were trained to conduct the diagnostic evaluation. Current and past Axis I disorders were assessed at intake through interview with the adolescent; an interview was also conducted with the parent (for youth <18). Those over 18 were given the option of having a parent participate (of 10 youth >18 at intake, four had a parent participate). Evaluators assessed for non-mood psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School-Aged Children Present and Lifetime Version (K-SADS-PL; Chambers et al. 1985), mood symptoms using the mood disorder sections of the K-SADS-P (Present episode, fourth revision; Chambers et al. 1985), plus items from the K-SADS Mania Rating Scale (KMRS; Axelson et al. 2003) to gather more detailed information on affective symptoms.

A study-affiliated child psychiatrist then interviewed the adolescent and parent, and conferred with the evaluator on the adolescent's final diagnoses. We utilized DSM-4 criteria for the diagnoses of BPI and II, and operationalized research criteria for BP NOS (Axelson et al. 2006). Inter-rater reliability (ICC) for the presence/absence of K-SADS-PL Axis I disorders was good ($\kappa \geq 0.80$).

Pharmacotherapy. All study participants were engaged in pharmacotherapy with a study-affiliated child psychiatrist. Pharmacotherapy consisted of an initial assessment followed by weekly to biweekly visits for the first month of treatment. Assuming adequate treatment response, visits were scheduled monthly thereafter. Treating psychiatrists managed participants' medications according to flexible but standardized best-practice algorithms based on the American Academy of Child and Adolescent Psychiatry treatment guidelines for the management of pediatric BP (Kowatch et al. 2005).

Medication adherence

Self/parent/physician report. Adolescents, parents, and prescribing physicians rated the frequency of missed doses of prescribed psychotropic medications over the prior 2 weeks at each medication management session using the following one to five rating scale: (1) almost never missed (<10% of the time); (2) occasionally missed (10%–25% of the time); (3) often missed (25%–50% of the time); (4) missed most of the time (50%–80% of the time); (5) almost always missed (>80% of the time). Physicians' reports were based on conversations with parents and adolescents at scheduled medication management sessions, as well as any between-session communications.

Objective report: the MedTracker. Upon study entry, each participant was provided a MedTracker (Hayes et al. 2006), an electronic pillbox for objectively monitoring medication adherence. The MedTracker appears similar to a weekly pillbox available at pharmacies with a separate compartment labeled for each day of the week. The MedTracker records the time the user opens and closes a compartment door through a plunger depressed by the lid upon opening that contacts a switch under the box upon closure. The switch sends a signal to the microcontroller that timestamps the data. Bluetooth wireless connectivity sends data from the MedTracker to an electronic data file.

The MedTracker yields data on the date and time the pillbox was loaded for the week, specific door openings (representing pill-taking events), and time of each door-opening event. The MedTracker can, therefore, accommodate any individualized dosing schedule, as well as changes in dosing. Specifically, each MedTracker door-opening event is subjected to that individual's dosing schedule on that day to classify the event (i.e., as adherent, wrong-time, wrong-day, dose omission; see below). Because the data storage capacity of the MedTracker is limited to a maximum number of door-opening events, participants were scheduled to return the MedTracker for data retrieval throughout the 3-month usage period based on their dosing schedule (e.g., once daily dosing 30 days).

Prior studies in controlled environments indicate that the device is reliable and easy to use. We selected this technology due to its mobility, automatic data collection, and the 7-day pillbox interface. Participants were given instructions on MedTracker loading and use, and instructed to call study staff with questions or concerns. In addition, participants were asked to record any extenuating circumstances surrounding MedTracker use and/or adherence (e.g., aberrations, difficulties with the device, travel, reasons for missed doses) on a log that they returned to study staff with their MedTracker.

Operationalized definitions of adherence through MedTracker. Primarily, study staff extracted prescribed medications and dosing schedules for the period of study participation (including all medication and dosing changes) from the participant's electronic medical record to accurately operationalize each participant's MedTracker data. Since no studies had previously analyzed MedTracker data like those yielded from this naturalistic study, few guidelines were available to inform operationalization of study variables. We, therefore, referred to studies utilizing MEMS (Acosta et al. 2013), as follows.

An *adherent medication dose* was characterized by MedTracker data indicating: the correct MedTracker door (e.g., the MedTracker door labeled "Monday" was opened on a date that was a Monday) was opened within the correct dosing timeframe prescribed, operationalized as follows: morning (2:00–11:59 am); afternoon

(12:00–4:59 pm); evening (5:00–1:59 am) (e.g., a participant prescribed a morning dose, opened the MedTracker door at 8:14am). A *wrong-time dose* was defined as a correct MedTracker door opening outside of the correct dosing timeframe. A *wrong-day dose* was defined as an incorrect MedTracker door opening, regardless of dosing timeframe. A *dose omission* was defined as the absence of the correct MedTracker door opening during the timeframe for a prescribed dose.

In the process of cleaning the MedTracker data, we cross-referenced all pillbox data with the participant's written log. All gaps in pillbox dosing data were reviewed by study staff (the first author, study coordinator, and data manager) and compared with the participant's log to determine whether gaps were best characterized as dose omissions (e.g., did not refill prescription in time and therefore missed 2 doses) versus missing data (e.g., did not take the pillbox on vacation for the weekend, but took their pill bottle instead). In the event that there was no log entry for a gap in pillbox use, doses in question were considered dose omissions.

Assessment of factors associated with adherence. Participants and their parents met with a master's level evaluator at intake, 3, and 6 months to complete a clinical interview and self and parent report measures of the following factors:

- (1) **Illness-specific factors.** The evaluator provided a global measure of the adolescent's clinical status over the past two weeks using the Clinical Global Impressions Scale for BP (CGI-BP; Spearing et al. 1997). The evaluator also administered the semistructured K-SADS depression rating scale (DRS) and MRS at each assessment to adolescents and parents separately. Summary ratings incorporate all available information, and reflect the worst week in the month preceding evaluation. ICC between the first author and the evaluator for K-SADS mood items was good (DRS ICC = 0.84; MRS ICC = 0.96).

We monitored the course of affective symptoms over follow-up using the Adolescent Longitudinal Follow-Up Evaluation (ALIFE) semistructured interview (Keller et al. 1987). The ALIFE yields weekly psychiatric status ratings (PSR) on a one to six severity scale (1 = no symptoms, 2–4 = subthreshold symptoms, 5–6 = full threshold DSM-4 criteria) for depression and hypo/mania. We operationalized ALIFE PSR data as follows: depression-free weeks were those for which ALIFE depression PSR ≤ 2; hypo/mania-free weeks were those for which ALIFE hypo/mania PSR ≤ 2; and weeks euthymic were those for which both ALIFE depression and hypo/mania PSR ≤ 2. ICC between the first author and the evaluator for ALIFE PSR ratings of depressive and hypo/manic episodes was ≥ 0.80.

- (2) **Patient factors.** Socioeconomic status was ascertained using the Hollingshead four-factor criteria (Hollingshead 1975). Race was assessed through a standardized demographic form at intake. Weight and height were assessed by the clinician at each visit using a scale and stadiometer. Family environment was assessed using the Family Adaptability and Cohesion Scale-II (FACES-II; Olsen et al. 1985) and the conflict behavior questionnaire (CBQ; Robin and Foster 1995).

Adolescents completed the self-report illness management survey (IMS; Logan et al. 2003), a measure of barriers to adherence among youth with chronic illness. The measure includes 27 items rated on a 1 (strongly disagree) to 5 (strongly agree) scale, and yields a total score and scores of

barriers to adherence in four domains: Negativity, Cognitive Difficulties, Social Influence, and Denial (Rhee et al. 2009). Prior studies support the reliability and validity of the measure in assessing youths' barriers to medication adherence in chronic illness. The Denial domain that assesses the adolescent's desire to deny the presence of illness was examined under patient factors (e.g., "Nothing bad would happen to me if I didn't follow my regimen").

- (3) Treatment factors. Evaluators assessed medication type and dosage for all psychotropic drugs prescribed, noting dates of changes. These data were cross-referenced with electronic medical record progress notes to verify dates and dosing. Medication data were operationalized as number of different psychotropic medications prescribed per day, number of total doses of psychotropic medications prescribed per day, and timing of dosing (morning, afternoon, evening; see above). Percentage of scheduled medication management sessions attended during study participation was extracted from the electronic medical record.
- (4) Treatment provider factors. We measured the patient-provider relationship through the Negativity domain of the IMS that assesses the adolescent's relationship with treatment providers, for example, "I don't always trust the doctors and nurses."
- (5) Developmental factors. Pubertal status was assessed through the Self-Rating Scale for Pubertal Development (Peterson et al. 1988). The Cognitive Difficulties domain of the IMS assessed cognitive capacities ("It's hard for me to stay organized enough to keep track of my medications or other things related to my illness"), and the Social Influence subscale of the IMS yielded ratings of peer and family influence on medication beliefs and behaviors ("I don't want my friends to know about my illness").

Data analysis

To compare the objective MedTracker data on adherence with the subjective reports, Spearman correlation coefficients were computed between each subjective rating (as measured on five percentage intervals) and corresponding MedTracker-measured percent of doses adherent. Because the subjective reports were only collected at participants' scheduled medication management sessions and reflected retrospective report over 2 weeks' time, medication adherence was modeled using only the MedTracker data, which were repeatedly measured every time a participant was due to take a dose.

To identify factors associated with medication adherence, we performed binary logistic regression in which each recorded MedTracker dose over follow-up was categorized dichotomously (adherent vs. nonadherent). Autocorrelation and partial autocorrelation functions were computed to assess the level and nature of autocorrelation between the many within-subject repeated observations. Results indicated that the covariance pattern of these data was expectedly autoregressive, so an ante-dependent covariance pattern was fitted in all logistic models to account for the autoregressive covariance pattern while also allowing for unequal time spacing between MedTracker observations and nonconstant correlation structure, since correlation structure between sequential doses depends on factors such as time of day (Kenward 1987).

Variables theorized to confound the effects of predictor variables on outcome were first univariately analyzed and entered in all subsequent models as covariates (all significant with $p < 0.02$); these variables included days of MedTracker use, days until next

clinical assessment, weekday versus weekend, timing of doses (morning, afternoon, evening; not all subjects had doses prescribed in each time period), number of prescribed doses per day, and number of medications prescribed per day. Because the relationships between adherence and days of MedTracker use, and days until next clinical assessment were quadratic, both were fit quadratically, and in both cases the linear and quadratic coefficient estimates were significant (all $p < 0.005$). Both "number of days" measures were collinear by definition; we included number of days until next clinical assessment as a covariate in subsequent models because it was the stronger predictor of adherence. Likewise, number of doses prescribed per day and number of medications prescribed per day were highly collinear ($r_s = 0.87$), so subsequent models controlled for the stronger predictor—number of doses prescribed per day.

Post hoc statistical power to detect odds ratios (OR) of 1.3 or greater was more than 90% for controlled models regressed on continuous, count, categorical, or ordinal predictor variables (accounting for covariates described above using methods described in Shieh 2005, performed using SAS 9.4). Effect sizes reported by OR reflect unitary change of one standard deviation for continuous variables and are parameterized to reflect the odds of nonadherence.

Results

Demographics/patient illness characteristics

Demographic and clinical characteristics of the sample are presented in Table 1. In brief, the sample includes 21 adolescents (43% males) with an average age of 17.2 (SD = 3.1, Range 12–22). Subjects were, on average, middle class (mean SES = 3.3, SD = 1.2). Thirty-three percent of the sample ($n = 7$) met criteria for BPI, 33% ($n = 7$) BP II, and 33% ($n = 7$) BP NOS. The average age of onset of manic/hypomanic symptoms was 11.9 (SD = 4.1). On average, subjects met criteria for 1.5 (SD = 1.1) current Axis

TABLE 1. DEMOGRAPHIC AND CLINICAL VARIABLES ($N = 21$)

Variable	
Age ($M \pm SD$)	17.2 $\pm$ 3.1
Sex (%male)	9 (43%)
Race	
Caucasian	14 (66.7%)
African American	5 (23.8%)
More than 1 race	2 (9.5%)
Socioeconomic status ^a ($M \pm SD$)	3.3 $\pm$ 1.2
Living situation (% with both parents)	6 (29%)
Bipolar Subtype ^b	
Bipolar I	7 (33%)
Bipolar II	7 (33%)
Bipolar NOS	7 (33%)
Age of first onset manic/hypomanic symptoms ($M \pm SD$)	11.9 $\pm$ 4.1
Mean number of current axis I diagnoses ^{b,c}	1.5 $\pm$ 1.1
Current comorbid axis I diagnoses ^c	
Behavioral disorder	10 (48%)
Anxiety disorder	8 (38%)

^aHollingshead.

^bAssessed through the schedule for affective disorders and schizophrenia for school-aged children present and the lifetime version K-SADS-PL, K-SADS-P depression section, and K-SADS mania rating scale.

^cAssessed through the schedule for affective disorders and schizophrenia for school-aged children present and the lifetime version K-SADS-PL. NOS, not otherwise specified.

I diagnoses through K-SADS, and 18 (85.7%) had at least one comorbid diagnosis.

Medication information

On average, youth were prescribed 2.7 (SD=1.6, Range 1–6) psychotropic medications at study intake from five classes (Table 2); 16 (76.2%) were prescribed >1 medication. Over the 6-month study period, 33.3% of participants experienced at least one medication change (i.e., discontinued a medication or prescribed a new medication), and 61.9% experienced at least one dosing change (dose, time of day, number of doses).

Medication adherence

Self/parent/physician report. Participants, parents, and physicians completed adherence ratings at each medication management session over follow-up (mean number of completed self-reports = 4.7, parent reports = 4.3, physician reports = 4.3) using a one to five rating scale [(1) almost never missed (<10% of the time); (2) occasionally missed (10%–25% of the time); (3) often missed (25%–50% of the time); (4) missed most of the time (50%–80% of the time); and (5) almost always missed (>80% of the time)]. Fourteen percent of participants ($n = 3$), 24% of parents ($n = 5$), and 48% of physicians ($n = 10$) rated the participant's nonadherence as "3" (often) or greater (i.e., >25% of the prior 2 weeks) at any time point over follow-up (test of equal proportions: $\chi^2 = 4.33$, $p = 0.2$).

Of the participants who self-reported nonadherence "3" (often) or greater at any time point, only one had parent and physician ratings also reflecting nonadherence ratings of "3" (often) or

greater. Overall, agreement between participant self-report and parent and physician report was quite weak (all pairwise Kappas and weighted Kappas <0.2).

Objective report: the MedTracker. On average, participants used the MedTracker for 79.9 days (SD = 29.6; Range 28–143), 71.2% of which were weekdays and 28.8% weekend days. The mean percentage of overall adherent days through MedTracker was 41.4%; rate of adherent days was significantly greater on weekdays than weekend days (59.7% vs. 55.7%, $F = 5.41$, $p = 0.02$). Mean percentage of overall adherent medication doses through MedTracker was 58.5%; five subjects (23.8%) met the accepted criteria for adherence (22) at >80% of doses.

Adherence rates significantly differed between morning (53.6%), afternoon (18%), and evening doses (69.5%) ($F = 57.99$, $p < 0.0001$; all pairwise comparisons $p < 0.0001$), however, it is important to note that only two subjects were prescribed an afternoon dose. There was no day-of-week by time-of-day interaction. On average, 41.5% of doses over follow-up were categorized as dose omissions. Of these, 45.7% were morning, 9.8% afternoon, and 36.3% evening. There were 4.3% wrong-time doses. Of these, 20.0% were morning, 69.2% afternoon, and 10.8% evening.

Association between subjective and objective reports of adherence. Medication adherence rates assessed through MedTracker were lower than for all subjective reporters, with low Spearman correlations between the MedTracker and self ($r_s = 0.26$), parent ($r_s = 0.29$), and physician ($r_s = 0.28$) reports.

Factors associated with adherence through MedTracker

Illness-specific factors. Diagnostic factors, including BP subtype, number of comorbid diagnoses, and age of illness onset were not associated with MedTracker dose omissions (all $ps > 0.05$). Similarly, neither presence of a comorbid ADHD/behavioral disorder nor presence of a comorbid anxiety disorder was associated with MedTracker dose omissions. Depression (KDRS) and mania (KMRS) severity scores, and percent of follow-up weeks euthymic, depressed, and hypo/manic on the ALIFE were also not associated with dose omissions (all $ps > 0.05$). However, greater CGI-BP illness severity was significantly associated with more dose omissions (OR = 2.56, $F = 22.56$, $p < 0.0001$).

Patient factors. Race, SES, and living situation were not associated with MedTracker dose omissions. In univariate analyses, being male and having higher BMI were associated with more dose omissions ($ps < 0.05$), however, these variables were no longer statistically significant when controlling for significant covariates (see above). There remained a negative linear relationship between weight and adherence (heavier subjects had more dose omissions; OR = 3.57, $F = 12.45$, $p = 0.0004$). Neither family environment (FACES-II) nor family conflict (CBQ) was associated with dose omissions. Higher total IMS score (i.e., greater self-reported barriers to adherence) was significantly associated with more dose omissions (OR = 1.10, $F = 5.10$, $p = 0.02$). However, this effect was driven primarily by the Cognitive Difficulties subscale (recalculation of total IMS score, excluding the Cognitive Difficulty items yielded a nonsignificant effect; see Developmental Factors, below).

Treatment factors. There was no relationship between medication type and dose omissions. Both number of doses prescribed

TABLE 2. PSYCHOTROPIC MEDICATIONS PRESCRIBED AT STUDY INTAKE ($N = 21$)

	Mean	SD
Number of psychotropic medications	2.7	1.6
Number of daily doses prescribed	2.9	1.6
	Count	%
Morning dose	14	66.7
Afternoon dose	2	9.5
Evening dose	19	90.5
Atypical antipsychotics	11	52.4
Aripiprazole	3	14.3
Risperidone	3	14.3
Quetiapine	6	28.6
Antidepressants	5	23.8
Citalopram	1	4.8
Fluoxetine	1	4.8
Desyrel	1	4.8
Bupropion	3	14.3
Sertraline	1	4.8
Stimulants	7	33.3
Dextroamphetamine	2	9.5
Methylphenidate	4	19.1
Lisdexamfetamine	1	4.8
Mood stabilizers	13	61.9
Lithium	2	9.5
Lamotrigine	13	61.9
Other	4	19.1
Levothyroxine	1	4.8
Metformin	1	4.76
Clonazepam	1	4.76
Guanfacine	1	4.76

TABLE 3. RESULTS OF MULTIVARIATE ANALYSIS

Variable	F	p
Illness-specific factors		
CGI-BP illness severity ^a	14.98	0.0001
Patient factors		
Weight	0.52	0.5
Treatment factors		
Number of daily doses prescribed	5.88	0.02
Dosage time of day	39.26	<0.0001
Day of week (weekend vs. weekday)	7.46	0.006
Proximity to medication management visit (quadratic)	4.03	0.04
Developmental factors		
IMS cognitive difficulties subscale ^b	1.80	0.2

^aClinical Global Impressions Scale for bipolar disorder (Spearing et al. 1997).

^bIllness management survey (Logan et al. 2003).

p-values in bold indicate statistical significance < .05

per day and number of medications prescribed per day were significantly associated with dose omissions in univariate models (i.e., more medicines and more doses were associated with more dose omissions, $ps < 0.05$), however, these two variables were highly correlated ($r = 0.87$), so only the number of doses prescribed per day remained significantly associated with dose omissions when controlling for confounding variables ($OR = 3.54$, $F = 33.12$, $p < 0.0001$). Furthermore, dosage timing was significantly related to dose omissions such that poor adherence was associated with afternoon doses, followed by morning doses and evening doses ($F = 57.99$, $p < 0.0001$). Additionally, participants had more dose omissions on weekend days than weekdays ($F = 5.41$, $p = 0.02$). Change in medication dosing (dose, time of day, number of doses) over follow-up was not associated with adherence.

An interesting pattern emerged in the MedTracker data, whereby participants had fewer dose omissions in the days leading up to, and also in the days immediately following a medication management visit ($F = 18.93$, $p < 0.0001$). However, percentage of medication management sessions attended during study participation was not associated with medication adherence.

Treatment provider factors. Scores on the IMS Negativity domain were not associated with MedTracker dose omissions.

Developmental factors. Of the developmental factors explored, only higher scores on IMS Cognitive Difficulties were associated with more dose omissions ($OR = 1.10$, $F = 4.89$, $p = 0.03$).

Multivariate model. In a final model, including all significant factors from each domain and the aforementioned control variables (presented in Table 3), the only factor that remained significantly associated with adherence in the presence of all other factors was CGI-BP Illness Severity ($OR = 2.24$, $F = 14.98$, $p = 0.0001$).

Discussion

To our knowledge, this is the first study to utilize a daily objective measure of prospective medication adherence among young people with BP, compare it with subjective report, and examine factors associated with adherence. Our findings provide further evidence of poor medication adherence in this population: objec-

tive data indicate 41.5% of doses (58.6% of days) were not taken as prescribed over 3 months of follow-up.

As hypothesized, subjective reports from patients, parents, and physicians overestimated adherence as compared with objective data; agreement between self, parent, and physician report of adherence was poor. Factors from multiple domains were associated with poorer adherence, including more daily doses, higher weight, dose timing (mornings/afternoons, and weekends), less proximity to medication management visit, and greater self-reported cognitive difficulties with adherence; the most potent factor associated with missed medication doses over follow-up was greater overall illness severity.

The overall rate of medication nonadherence we report is in the range of those described in other studies of youth with BP (i.e., 44%–66%; Coletti et al. 2005; Patel et al. 2005). Similar to findings across physical and mental health conditions in adolescents, we found self, parent, and physician report overestimated adherence as compared with monitoring devices (Shi et al. 2010). Factors, including social desirability, memory biases, and limited insight, may limit the accuracy of subjective methods of reporting (Sajatovic et al. 2010).

Greater illness severity emerged as the most potent factor associated with poor adherence. The specific manner in which illness severity is associated with adherence remains unclear, particularly given that no individual symptom(s) specifically accounts for the association. It is possible that the substantial heterogeneity in symptom presentation and comorbidity in this population renders it difficult to identify specific symptoms or symptom presentations that are most associated with poor adherence. Alternatively, it is possible that it is the overall burden of these heterogeneous symptoms together that incrementally contribute to poor adherence. Regardless, illness symptoms can affect judgment, cognition, and daily routines, and impairments in one or more of these processes may lead to missed doses. Additionally, poor adherence can result in greater illness severity. Future studies should aim to identify the specific pathways whereby illness severity impacts adherence to develop targeted interventions.

In keeping with the literature in adults with BP (Goodwin and Jamison 2007), we found that self-reported cognitive difficulties on the IMS were associated with lower adherence. However, it is unclear in our sample to what extent cognitive barriers are symptoms of affective and/or comorbid illnesses (e.g., ADHD) as opposed to incomplete development of reasoning capabilities associated with adolescence (Shaw 2001; Pogge et al. 2005). Regardless, intervention aimed to assist with organization and planning around medication adherence may prove beneficial.

We were surprised that most of the developmental factors examined (age, pubertal status, social influences) were not associated with medication adherence in this sample. Coletti et al. (2005) similarly found that age was not associated with adherence among youth with BP. Perhaps young people with BP experience a delay in emotional development due to their psychiatric disturbance during a sensitive developmental period, such that they experience some normative developmental challenges of adolescence at a later age than their healthy peers. Future studies may also consider additional developmental factors demonstrated to be associated with medication adherence like drives for autonomy and control (Shaw 2001; Pogge et al. 2005).

In contrast with other studies of youth with chronic illnesses (Rhee et al. 2009), other self-reported barriers to medication adherence measured on the IMS (i.e., negativity about treatment/providers, social influences, and denial) were not associated with poorer adherence. Psychoeducational approaches targeting barriers have been shown to enhance adherence among adults with BP

(Goodwin and Jamison 2007), however, no psychotherapy study for youth with BP to date has reported on medication adherence as an outcome (West and Pavuluri 2009).

In the present study, all participants were engaged in ongoing medication management through the specialty outpatient clinic from which they were recruited; some participants also received psychotherapy services at our clinic, some received psychotherapy with community providers, whereas others were not receiving psychotherapy at all. We did not systematically record receipt of psychotherapy services in the present study, which precluded our ability to examine potential relationships between psychosocial intervention and medication adherence. It is possible that ongoing treatment in a specialized clinic may have had an impact on the adolescent's perception of barriers. Regardless, adjunct to psychoeducation, motivational approaches aiming to resolve ambivalence about having a psychiatric illness requiring treatment may be considered (Taddeo et al. 2008). Additionally, providers should strive to build a collaborative relationship with patients by fostering open communication.

Most often, treatment for youth is initiated by parents (de Haan et al. 2013), and, therefore, family characteristics may impact treatment initiation and continuation (Armbruster and Kazdin 1994). However, with respect to patient factors, we did not find a significant association between family environment and medication adherence. Conflictual family environment has been associated with poorer treatment adherence in another study of youth with BP (Drotar et al. 2007), and in some studies of youth with other physical illnesses (Gardiner and Dvorkin 2006), whereas others have found no association between parent-adolescent conflict and adherence (Saletsky et al. 2014). Some posit that adolescents may not take recommended treatments as a means of asserting their independence (Taylor and Eminson 1994), and/or playing out family conflict. Future studies may aim to better understand the role of family factors in medication adherence among adolescents to ensure that interventions targeting adherence consider developmentally relevant family factors.

We found that youth who weighed more were less adherent with medication. We are unable to determine the temporal sequence of weight gain and medication initiation in our study design. Possibly some youth experienced weight gain as an unwanted side effect of their medication and as a result became less adherent; alternatively, youth who were heavier at medication initiation may have been less likely to adhere due to concerns about weight gain. Indeed, others report that adolescents may not adhere to medications with unwanted physical side effects due to heightened concerns with appearance (Pogge et al. 2005). Clinicians should therefore explore potential links between weight and medication adherence throughout the course of medication treatment with these youth.

In keeping with the adult literature (Goodwin and Jamison 2007), we found that greater daily dosing was associated with poorer adherence, suggesting that simpler regimens may enhance adherence. Furthermore, youth missed afternoon doses (only two subjects had afternoon dosing) and morning doses more often than evening doses, and weekend day doses more often than weekday doses. This finding is consistent with the recommendation that doses be tied to specific daily routines (e.g., brushing teeth) to enhance adherence (Velligan et al. 2009a). Systematic assessment of patterns of missed doses and subsequent problem-solving may be considered.

Finally, the finding that youth were more adherent in the days immediately preceding and following a medication management appointment is of note. Youth may change their medication-taking behavior to be in line with provider and/or parent expectations to minimize dissonance or feelings of guilt. Others may have experienced the upcoming/recent appointment as a reminder of the

importance of their medication. It is possible that contact with treatment providers between appointments may enhance adherence during this vulnerable period.

Limitations

The MedTracker records the date and time of each pillbox door opening, and these data serve as a proxy for medication-taking behavior. However, we cannot ensure that the subject ingested the medication. Relatedly, when a participant was prescribed more than one medication during the same timeframe, a MedTracker compartment opening during that particular timeframe does not allow us to detect adherence with one medication, but not another. However, if the compartment was not opened during the said timeframe, we can conclude that none of the medications prescribed for that timeframe was taken. The MedTracker data do not enable us to determine the reason for any dose omission, however, we employed a method of cross-referencing each gap in MedTracker data with a participant's written log to increase the likelihood that gaps in data were accurately classified as true dose omissions versus missing data.

Additionally, the Hawthorne effect suggests that MedTracker data may not represent true adherence rates because participants modify their behavior in response to their awareness of being observed (McCarney et al. 2007). Furthermore, some studies suggest that the use of a medication monitoring device like a pillbox may enhance adherence (Azrin and Teichner 1998). We did not observe an increase in adherence over the course of MedTracker use, however, it remains possible that MedTracker use did modify medication-taking behaviors from the outset. All of these considerations suggest that the MedTracker data may overestimate adherence. Furthermore, we did not obtain collateral information on medication adherence through blood levels. Blood levels are routinely obtained only for certain medications (e.g., lithium, valproate) prescribed at low rates in our sample. Subjective ratings of adherence were retrospective, and therefore introduced methodological variance between the subjective and objective methods used in this study; relatedly, future studies may explore predictors of reliability in subjective reporting.

All participants were engaged in outpatient medication management, and some were receiving psychotherapy. These services varied, and may have differentially impacted observed rates of adherence. The sample size in this study was limited; however, we had adequate statistical power to detect moderate effect sizes. Although all of the youth in the study had a primary BP diagnosis, the sample was heterogeneous in terms of age and psychiatric comorbidity, which may have limited our ability to detect subgroup differences. Furthermore, limited diversity (i.e., largely Caucasian, middle class) may limit generalizability of the findings to more representative samples.

Finally, we did not measure some factors that demonstrated associations with adherence in other populations of chronically ill adolescents, or adults with BP, including parental monitoring of medication, specific symptoms, and side effects (Gardiner and Dvorkin 2006; Goodwin and Jamison 2007; Saletsky et al. 2014). Future studies may consider such factors in larger samples.

Clinical Significance

Young people with BP exhibit poor medication adherence when measured objectively, yet they, their parents, and treating physicians report nonadherence. Providers should thus give careful consideration to the issue of adherence when making decisions about treatment response and subsequent changes to medication regimen for youth

with BP, particularly among those youth with more severe BP illness. Given that factors from multiple domains were associated with adherence, a patient-centered motivational approach to improving adherence that allows flexibility to focus on the unique set of factors relevant in any individual case may hold greatest potential for benefit.

Acknowledgments

This study was supported by grant MH092424 (Goldstein) from NIMH. The authors thank Rachael Fersch-Podrat LCSW, Nina Hotkowski LCSW, and the staff of the child and adolescent bipolar spectrum (CABS) clinic at the University of Pittsburgh Medical Center. Statistical consultant is John Merranko MA.

Disclosures

Dr. Goldstein has received research support from NIMH, NIDA, NICHD, The Fine Foundation, The Ryan Licht Sang Foundation, The Pittsburgh Foundation, and the Brain and Behavior Foundation, and royalties from Guilford Press. Dr. Birmaher receives research support from NIMH, royalties from Random House, Inc., and Lippincott Williams & Wilkins. Dr. Axelson is a consultant for Janssen Research and Development, and receives royalties from Wolters Kluwer. Dr. Douaihy receives research support from NIMH, NIAAA, NIDA, Orexo Pharmaceuticals, Alkermes, and receives royalties from OUP and PESI Publishing and Media. All other authors have no conflicts of interest to disclose.

References

- Acosta F, Ramallo-Farina Y, Boshch C, Caravaca A: Antipsychotic treatment dosing profile in patients with schizophrenia evaluated with electronic monitoring (MEMS). *Schizophr Res* 146:196–200, 2013.
- Armbruster P, Fallon T: Clinical, sociodemographic, and systems risk factors for attrition in a children's mental health clinic. *Am J Orthopsychiatry* 64:577–585, 1994.
- Axelson DA, Birmaher B, Brent D, Wassick S, Hoover C, Bridge J, Ryan N: A preliminary study of the kiddie schedule for affective disorders and schizophrenia for school-age children mania rating scale for children and adolescents. *J Child Adol Psychop* 13:463–470, 2003.
- Axelson DA, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan ND, Leonard H, Iyengar S, Bridge J, Keller M: Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 63:1139–1148, 2006.
- Azrin NH, Teichner G: Evaluation of an instructional program for improving medication adherence for patients with chronic mental illness. *Behav Res Ther* 36:849–861, 1998.
- Badiee J, Riggs PD, Rooney AS, Vaida F, Grant I, Atkinson H, Moore D: Approaches to identifying appropriate medication adherence assessments for HIV infected individuals with comorbid bipolar disorder. *AIDS Patient Care* 26:388–394, 2012.
- Bhowmik D, Aparasu R, Rajan S, Sherer J, Ocoa-Perez M, Chen, H: The utilization of psychopharmacological treatment and medication adherence among medicaid enrolled children and adolescents with bipolar depression. *J Affect Disorders* 150:424–429, 2013.
- Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan ND, Leonard H, Hunt J, Iyengar S, Keller M: Clinical course of children and adolescents with bipolar spectrum disorders. *Arch Gen Psychiatry* 63:175–183, 2006.
- Birmaher B, Axelson DA, Goldstein BI, Strober M, Gill MK, Hunt J, Houck P, Ha W, Iyengar S, Kim E, Yen S, Hower H, Esposito C, Goldstein TR, Ryan ND, Keller M: Four-year longitudinal course

- of children and adolescents with bipolar spectrum disorders: The Course and Outcome of Bipolar Youth (COBY) study. *Am J Psychiatry* 166:795–804, 2009.
- Byerly M, Fisher RK, Whatley K, Holland R, Varghese F, Carmody T, Magouirk B, Rush AJ: A comparison of electronic monitoring vs. clinician rating of antipsychotic adherence in outpatients with schizophrenia. *Psychiatry Res* 133:129–133, 2005.
- Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA, Davies M: The assessment of affective disorders in children and adolescents by semistructured interview: Test-retest reliability of the schedule for affective disorders and schizophrenia for school-age children, present episode version. *Arch Gen Psychiatry* 42:696–702, 1985.
- Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Tabrizi MA, Johnson R: The schedule for affective disorders and schizophrenia for school age children. *Arch Gen Psychiatry* 42:696–702, 1985.
- Coletti DJ, Leigh E, Gallelli KA, Kantafaris V: Patterns of adherence to treatment in adolescents with bipolar disorder. *J Child Adol Psychop* 15:913–917, 2005.
- Cramer JA, Rosenheck R: Compliance with medication regimens for mental and physical disorders. *Psychiatry Serv* 49:196–201, 1998.
- de Haan AM, Boon AE, de Jong JT, Hoeve M, Vermeiren RR: A meta-analytic review on treatment dropout in child and adolescent outpatient mental health care. *Clin Psychol Rev* 33:698–711, 2013.
- DeBello MP, Hanseman D, Adler C, Fleck DE, Strakowski SM: Twelve month outcome of adolescents with bipolar disorder following first-hospitalization for a manic or mixed episode. *Am J Psychiatry* 164:582–590, 2007.
- Drotar D, Greenely RN, Demeter CA: Adherence to pharmacological treatment for juvenile bipolar disorder. *J Am Acad Child Psy* 46:831–839, 2007.
- Durrenberger S, Rogers T, Walker R, deLeon J: Economic grand rounds: The high costs of care for four patients with mania who were not compliant with treatment. *Psychiatry Serv* 50:1539–1542, 1999.
- Gardiner P, Dvorkin L: Promoting adherence in children. 2006 Available at www.aafp.org. Accessed July 14, 2015.
- Gearing RE, Mian IA: An approach to maximizing the treatment adherence of children and adolescents with psychotic disorders and major mood disorders. *Can Child Adolesc Psychiatry Rev* 14:106–113, 2005.
- Gearing RE, Mian IA, Sholonsky A, Barber J, Nicholas D, Lewis R, Solomon L, Williams C, Lightbody S, Steele M, Davidson B, Manchanda R, Joseph L, Handelman K, Ickowicz A: Developing a risk model of time to first-relapse for children and adolescents with a psychotic disorder. *J Nerv Ment Dis* 197:6–14, 2009.
- Geller B, Tillman R, Bolhofner K, Zimmerman B: Pharmacological and non-drug treatment of child bipolar I disorder during prospective eight-year follow-up. *Bipolar Disord* 12:164–171, 2010.
- Goldstein TR, Birmaher B, Axelson DA, Goldstein BI, Gill MK, Smythers C, Ryan ND, Strober M, Hunt J, Keller M: Psychosocial functioning among bipolar youth. *J Affect Disord* 114:174–183, 2010.
- Goldstein TR, Ha W, Axelson DA, Goldstein B I, Liao F, Gill MK, Ryan ND, Yen S, Hunt J, Hower H, Keller M, Strober M, Birmaher B: Predictors of prospectively observed suicide attempts among youth with bipolar disorder. *Arch Gen Psychiatry* 69:1113–1122, 2012.
- Goodwin G, Jamison KR: Medication adherence. In: *Manic-Depressive Illness*. New York, Oxford University Press, 2007 Vol 2, pp. 849–865.
- Goodwin G, Jamison KR: Psychotherapy. In: *Manic-Depressive Illness*. New York, Oxford University Press, 2007 Vol 2, pp. 869–905.
- Hack S, Chow B: Pediatric psychotropic medication compliance: A literature review and research-based suggestions for improving treatment compliance. *J Child Adol Psychop* 11:59–67, 2001.

- Hayes T, Hunt J, Adami A, Kaye J: An Electronic Pillbox for Continuous Monitoring of Medication Adherence. *Conf Proc IEEE Eng Med Biol Sci* 1:6400–6403, 2006.
- Hollingshead A: Four-factor Index of Social Status. New Haven, Yale University, 1975.
- Jamison KR, Gerner RH, Goodwin FK: Patient and physician attitudes toward lithium: Relationship to adherence. *Arch Gen Psychiatry* 36:866–869, 1979.
- Jonsdottir H, Opjordsmoen S, Birkenaes A, Engh JA, Ringen PA, Vaskinn A, Aamo T, Friis S, Andreassen OA: Medication adherence in outpatients with severe mental disorders: Relation between self-reports and serum level. *J Clin Psychop* 30:169–175, 2010.
- Kane JM: Compliance issues in outpatient treatment. *J Clin Psychop* 5:22–27, 1985.
- Keller MB, Lavori PW, Friedman B, Nielsen E, Endicott J, McDonald-Scott P, Andreasen NC: The Longitudinal Interval Follow-Up Evaluation: A comprehensive method for outcome in prospective longitudinal studies. *Arch Gen Psychiatry* 44:540–548, 1987.
- Kenward MG: A method for comparing profiles of repeated measurements. *Appl Statist* 36:296–308, 1987.
- Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M; and the child psychiatric workgroup on bipolar disorder: Treatment guidelines for children and adolescents with bipolar disorder. *J Am Acad Child Psy* 44:213–235, 2005.
- Liu HY, Potter MP, Woodworth KY, Yorks DM, Petty CR, Wozniak JR, Faraone SV, Biederman J: Pharmacologic treatments for pediatric bipolar disorder: A review and meta-analysis. *J Am Acad Child Psy* 50:749–762, 2011.
- Logan D, Zelikovsky N, Labay L, Spergel J: The illness management survey: Identifying adolescents' perceptions of barriers to adherence. *J Pediatr Psychol* 28:383–392, 2003.
- McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P: The Hawthorne effect: A randomised controlled trial. *BMC Med Res Methodol* 7:30, 2007.
- Muller-Oerlinghausen B, Wolf T, Ahrens B, Glaenz T, Schou M, Grof E, Grof P, Lenz G, Simhandi C, Thau K, Vestergaard P, Wolf R: Mortality of patients who dropped out from regular lithium prophylaxis: A collaborative study by the International Group for the Study of Lithium-Treated Patients (IGSLI). *Acta Psychiatry Scand* 94:344–347, 1996.
- Olsen DH, Portner J, Lavee Y: Family Adaptability and Cohension Evaluation Scales (FACES-II). Minneapolis, MN, University of Minnesota Press, 1985.
- Patel NC, DelBello MP, Keck PE, Strakowski SM: Ethnic differences in maintenance antipsychotic prescription among adolescents with bipolar disorder. *J Child Adol Psychop* 15:938–946, 2005.
- Pavuluri MN, Henry DB, Findling RL, Parnes S, Carbray JA, Mohammed T, Janicak PG, Sweeney JA: Double-blind randomized trial of riperidone versus divalproex in pediatric bipolar disorder. *Bipolar Disord* 12:593–605, 2010.
- Peterson AC, Crockett L, Richards M, Boxer A: A self-report measure of pubertal status: Reliability, validity and initial norms. *J Youth Adolescence* 17:133, 1988.
- Pogge D, Singer M, Harvey P: Rates and predictors of adherence with atypical antipsychotic medication: A follow-up study of adolescent inpatients. *J Child Adol Psychop* 15:901–912, 2005.
- Rhee H, Belyea MJ, Ciurzynski S, Brasch J: Barriers to asthma self-management in adolescents: Relationships to psychosocial factors. *Pediatr Pulm* 44:183–191, 2009.
- Robin AL, Foster SL: The conflict behavior questionnaire. In: *Dictionary of Behavioral Assessment Techniques*. Edited by Hersen M, Bellack AS. New York, Pergamon, 1995, pp. 148–150.
- Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G: Measurement of psychiatric treatment adherence. *J Psychosom Res* 69:591–5999, 2010.
- Saletsky RD, Trief PM, Anderson BJ, Rosenbaum P, Weinstock RS: Parenting style, parent-youth conflict, and medication adherence in youth with type 2 diabetes participating in an intensive lifestyle change intervention. *Fam Syst Health* 32:176–185, 2014.
- Scott J, Pope M: Nonadherence with mood stabilizers: Prevalence and predictors. *J Clin Psychiatry* 63:384–390, 2002.
- Shaw RJ: Treatment adherence in adolescents: Development and psychopathology. *Clin Child Psychol Psychiatry* 6:137–150, 2001.
- Shi L, Liu J, Koleva Y, Fonseca V, Kalsekar A, Pawaskar M: Concordance of adherence measurement using self-reported adherence questionnaires and medication monitoring devices. *Pharmacoeconomics* 28:1097–1107, 2010.
- Shieh G: Power and sample size calculations for multivariate linear models with random explanatory variables. *Psychometrika* 70:347–358, 2005.
- Spearing MK, Post RM, Leverich G, Brandt D, Nolen WA: Modification of the Clinical Global Impressions (CGI) Scale for bipolar illness: The CGI-BP. *Psychiatry Res* 73:159–171, 1997.
- Stephenson JJ, Tuncelli O, Gu T, Eisenberg DM, Panish J, Crivera C, Dirani R: Adherence to oral second-generation antipsychotic medications in schizophrenia and bipolar disorder: Physicians' perceptions of adherence vs. pharmacy claims. *Int J Clin Pract* 66:565–573, 2012.
- Taddeo D, Egedy M, Frappier J: Adherence to treatment in adolescents. *Paediatr Child Health*, 13:19–24, 2008.
- Taylor D, Eminson D: Psychological aspects of chronic physical illness. In: *Child and adolescent psychiatry*. Edited by Rutter ME, Taylor L, Hersov L. New York, Oxford Press, 1994, pp. 737–748.
- Van Meter AR, Moreira AL, Youngstrom EA: Meta-analysis of epidemiologic studies of pediatric bipolar disorder. *J Clin Psychiatry* 72:1250–1256, 2011.
- Velligan DI, Weiden P, Sajatovic M, Scott J, Carpenter DJ, Ross R, Docherty JP: The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 70:3–46, 2009a.
- Velligan DI, Weiden P, Sajatovic M, Scott J, Carpenter DJ, Ross R, Docherty JP: Expert consensus panel on adherence problems in persistent mental illness. *J Clin Psychiatry* 70:1–46, 2009b.
- West A, Pavuluri MN: Psychosocial treatments for childhood and adolescent bipolar disorder. *Child Adol Psych Cl* 18:471–482, 2009.
- World Health Organization: Adherence to Long-term Therapies: Evidence for Action. WHO Marketing and Dissemination, Geneva, Switzerland, 2003.
- Yazdi K, Unterlass G, Kemmler G, Kralovec K, Aichorn W: Factors influencing adherence in children and adolescents treated with antipsychotics or antidepressants. *J Clin Psychiatry* 10:160–161, 2008.

Address correspondence to:

Tina Goldstein, PhD
Western Psychiatric Institute and Clinic
University of Pittsburgh Medical Center
3811 O'Hara St, BFT#531
Pittsburgh, PA, 15213

E-mail: goldsteintr@upmc.edu