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Pharmacotherapy Adherence for Pediatric Anxiety Disorders: Predictors and Relation to Child Outcomes

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Abstract

Background—Pharmacotherapy is considered an evidenced-based treatment for anxious youth. There is a need to better understand the relation between medication adherence and child outcomes.

Objective—This study prospectively examined:1) baseline predictors of adherence and 2) the relation between medication adherence and clinical outcomes in children and adolescents with anxiety disorders.

Methods—Participants were 349 youth randomized to sertraline, pill placebo, or sertraline plus cognitive behavioral therapy in the Child/Adolescent Anxiety Multimodal Study (CAMS) and followed over 12 weeks. The measure of pharmacotherapy adherence used was pharmacotherapist (PT) ratings of adherence at each session. Four domains of baseline predictors were examined (demographics, child clinical variables, family/parent variables, and treatment variables).

Results—Multiple regression analyses revealed few significant predictors of adherence. The most robust predictors of greater adherence were living with two parents and parents' positive expectations that medication would lead to better outcomes. Pharmacotherapists' ratings of higher adherence predicted higher global functioning at post treatment and treatment responder status.

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Conclusions—In order to increase adherence, improving expectations and instilling hope for positive outcomes and problem solving ways to overcome pragmatic barriers associated with single parent families is recommended.

Keywords

anxiety; adherence; selective serotonin reuptake inhibitors

Suboptimal adherence to medication is viewed as a major treatment obstacle and in some cases the most prominent barrier to treatment effectiveness. Psychiatric medications have been established as an efficacious treatment for pediatric psychopathology (Comer, Olfson, & Mojtabai, 2010). The use of psychotropic medications among children with psychiatric problems can improve not only psychological symptoms, but also quality of life, academic performance, and relationships with friends, family, and others (Hamrin, McCarthy, & Tyson, 2010). Despite these benefits, children generally exhibit lower than optimal rates of medication adherence. Without optimal treatment, these patients are at risk for more severe psychiatric symptoms, declining academic performance, interpersonal problems, suicide, and family stress (Hamrin et al., 2010). Children's medication adherence rates vary between 13.2% and 89.8%, and the majority of studies demonstrating high adherence rates adopt a child or caregiver self-assessment (Adler & Nierenberg, 2010; Hamrin et al., 2010). However, adherence rates assessed through self-report (rather than clinician reports or pill counts), are likely to be higher than actual adherence rates (Pappadopulos et al., 2009; Yang et al., 2012).

Despite the importance of adherence to pharmacotherapy, predictors of adherence in pediatric psychiatry have been inadequately studied and extant studies have reported contradictory findings. Determining predictors of adherence is critical in order to enhance treatment outcomes. The WHO considers general medication adherence to be a 'multi-determined phenomena based on the interplay of several domains (Sabate, 2001). For this reason, and consistent with the WHO model, the current study examined four potential domains of predictors: demographic, child clinical, parent/family, and treatment-related predictors.

With respect to child clinical and demographic variables, youth with milder symptoms at baseline and without comorbid externalizing disorders show higher adherence (Hamrin, McCarthy, & Tyson, 2010). Adolescents differ from their parents in their beliefs and their attitude about medication use (Charch, Yeung, Volpe, Goodale, & dosReis, 2014), and adolescents are less willing to use medications than their parents (Bussing et al., 2012).

In terms of family variables, family dysfunction and poor parent–child communication, and lack of parental involvement in medication routines have been associated with poor adherence (Brinkman et al., 2012). Finally, several treatment variables have been associated with poorer adherence, including short and infrequent doctor appointments, dissatisfaction with the provider, and children's lack of understanding of the reasons for taking medication (Charach & Gajaria, 2008; Hamrin et al., 2010).

In addition to understanding predictors of adherence, another critical question is whether higher adherence to psychiatric medication is associated with better clinical outcomes. Again, data addressing this issue are scant. In the Treatment of Resistant Depression in Adolescents study (TORDIA) medication adherence (defined based on clinician-rated pill counts) was related to a higher response rate (Woldu et al., 2011). Similarly, the Research Unit on Pediatric Psychopharmacology Anxiety study group (RUPP) found that better adherence to active medication (measured by total number of days on medication) was associated with greater improvement, suggesting that longer exposure to fluvoxamine may predict better outcomes (Walkup et al., 2003).

The current study extends this literature by examining these issues using participants randomized in the Child/Adolescent Anxiety Multimodal Study (Walkup et al., 2008). CAMS was a multi-site, randomized, placebo-controlled study comparing 12 weeks of sertraline (SRT), CBT (Coping Cat), their combination (COMB), and pill placebo (PBO) in 488 children and adolescents diagnosed with separation anxiety disorder (SAD), generalized anxiety disorder (GAD), and/or social phobia (SoP). A separate report explores predictors of adherence to CBT (Lee et. al., 2017). Specifically, this study examined: 1) baseline predictors of medication adherence and 2) the relation between medication adherence and child clinical outcomes. Consistent with previous research in other fields, it was hypothesized that lower adherence would be associated with: a) older, compared to younger age, b) higher youth anxiety symptoms and comorbid disorders, c) poorer family interactions and d) lower treatment expectancy.

METHOD

Participants

Participants were 349 youth ages 7 to 17 years old (mean 10.7 years) who met DSM-IV TR (American Psychiatric Association, 2000) criteria for one or more of the following disorders: SAD, GAD, or SoP and were randomized in CAMS to the medication only (Sertraline, SRT), placebo (PBO), and combined treatment (COMB) groups. Table 1 presents the baseline characteristics. For additional details on the CAMS methods see Compton et al. (2010).

Procedures

Participants and at least one parent provided written informed consent and then completed a baseline evaluation which included the measures below (including anxiety severity and functioning). Eligible youth (N = 488) were randomized into one of the following four treatment conditions: CBT (n = 139), SRT (n= 133), COMB (n=140), or PBO (n =76) and those randomized to SRT, COMB, or PBO were included in this study. At each treatment session, the pharmacotherapist (PT) filled out a session summary form regarding adherence. With respect to dosing, the maximum target dose of SRT was 200mg per day. Pharmacotherapy visits were scheduled at weeks 1–4, 6, 8, 10, 12 during the acute 12- week treatment phase. Compliance rating and pill count was obtained at each pharmacotherapy visit. Interim phone visits were scheduled at weeks 5, 7, 9, and 11. Pharmacotherapy (SRT) consisted of eight 30–60-minute sessions involving discussing anxiety symptoms,

functioning, treatment response, and adverse events within supportive clinical care. Providers were psychiatrists and psychiatric nurses. Medication was administered daily using a "fixed-flexible" dosing strategy that was linked to clinical response and side effects (Compton et al., 2010; Walkup et al., 2008).

At 12 weeks (post-treatment), independent evaluators (IEs) conducted a semi-structured diagnostic interview and rated symptom severity and functioning. Three different measures of youth treatment outcomes were used, which were assessed by IEs at baseline and 12 weeks post randomization. Families were compensated for their participation. The protocol was approved and monitored by institutional review boards at each university site.

Measures

Medication Adherence—Using a 7 point Likert scale (1= poor adherence; 7 = good adherence), the PT rated the child's overall adherence each week. The definition of adherence was "*Considering the child's overall adherence, defined as the extent to which the child complied with treatment recommendations or instructions from the previous session, independent of improvement or adverse events. Consider: A) how appropriately did the child take the medication (e.g. percentage of doses taken, evasive or vague about how medication is taken) and B) How engaged the child was in the treatment process (e.g. can be engaged in the sessions, resists or dismisses therapists suggestions).*" The mean across all PT sessions was used as the measure of adherence.

Predictor Measures—Four domains of predictors (assessed at baseline) were examined: *Demographic predictors* included child age, sex, race, ethnicity, socioeconomic status (measured by the Hollingshead Index; Hollingshead, 1971), and whom the child was living with. *Baseline child clinical variables* included principal diagnosis, number of other internalizing (other than SAD, SoP, or GAD) and externalizing (attention deficit hyperactivity disorder, oppositional defiant disorder, ODD, or conduct disorder, CD) diagnoses for each participant based on the Anxiety Disorders Interview Schedule for DSM-IV-Child and Parent Versions (ADIS-IV-C/P; Silverman & Albano, 1996). In CAMS, 10% of IE evaluations were assessed for inter-rater reliability, calculated as intraclass correlation coefficients, which ranged from .82 to .88 (Compton et al., 2010). IEs also completed the *Clinical Global Impressions Scale – Severity* (Guy, 1976). The CGI-S ranges from 1 to 7, with higher scores indicating greater anxiety severity and the *Children's Global Assessment Scale* (CGAS; Shaffer et al., 1983) to assess global functioning (scores ranged from 0 to 100; lower scores represent lower overall functioning).

Family/Parental factors included: a) the *Brief Symptom Inventory* (BSI; Derogatis, 1993), a widely used 53-item measure of parent psychopathology, rated on a 5-point Likert scale from 0 (not at all) to 4 (extremely). The BSI Global Severity Index (BSI-GSI) provides a single score of current psychological distress and symptoms (higher values indicate greater severity). In this sample, the alpha for the BSI-GSI was .95 at baseline. b) the *Burden Assessment Scale* (BAS; Reinhard, Gubman, Horwitz, & Minsky, 1994), a 21-item measure completed by parents assessing how much their child's anxiety disrupts family life. Items are scored from 1 (not at all) to 5 (very much) and higher scores indicate greater burden; the

alpha was .92 at baseline. c) *Brief Family Assessment Measure-III* (BFAM-III, Skinner, Steinhauer, & Santa-Barbara, 1995) provides an assessment of global family functioning. Parents and children/adolescents responded to 14 items using a 5-point scale, higher scores represent greater levels of perceived family dysfunction and the alpha was .85 for parent report and .76 for youth report at baseline. *Treatment -Related factors* included a treatment expectancy scale developed by the CAMS team. Prior to randomization, treatment expectancy was assessed by asking each child and parent to indicate how much improvement they expected under each of the treatments (COMB, SRT, CBT, PBO). Possible ratings were 1 (very much worse) to 7 (very much improvement). Treatment expectancy ratings for the treatment to which the child was randomly assigned were used in the current analyses. Expectations for improvement with SRT were also used for those participants assigned to PBO.

Treatment Outcome Measures—Three measures of post-treatment outcomes (assessed 12 weeks after randomization) were used: 1) the Clinical Global Impressions -Improvement (CGI-I; Guy, 1976) scale assessed by IEs and dichotomized as "responder" defined as a score of 1 (very much improved) or 2 (much improved) or "non-responder" (CGI-I or 3 or higher). 2) The CGAS (Shaffer et al., 1983) described above and 3) the Pediatric Anxiety Rating Scale (PARS; Research Units on Pediatric Psychopharmacology Anxiety Study Group, 2002) an IE-rated instrument assessing the severity of anxiety symptoms. The PARS total score was computed by summing six items assessing anxiety severity, frequency, distress, avoidance, and interference during the previous week. PARS total scores can range between 0 to 30 with higher scores indicating greater impairment and severity.

Data Analyses

To explore predictors of adherence, multiple regressions were conducted for each predictor domain (demographic, child clinical, family/parental factors, treatment -related) to identify significant predictors of adherence. In all analyses treatment condition and site were entered as control variables. To address the second aim, regressions were conducted to examine the relation between adherence and treatment outcomes, controlling for child age, sex, race, family SES, treatment condition, site and baseline anxiety severity and functioning. Linear regressions were used for continuous outcomes (PARS, CGAS) and logistic regression was used for CGI-I response status. Missing data was imputed using Multiple Imputation in SPSS 23. After examining the missing data (10% missing on outcome variable; .03–6.5% missing on other variables) 30 datasets were imputed (Graham, Olchowski, & Gilreath, 2007).

RESULTS

Mean PT rated adherence for the entire sample and by treatment condition was high (see Table 1). No differences were found in adherence rates based on treatment condition (PBO, SRT, or COMBO).

Predictors of Adherence

Results of regressions, provided in Table 2, revealed that only three variables predicted higher adherence: children living with two parents, higher parent pretreatment expectancy (i.e., beliefs that their children would improve with assigned treatment), and higher youth-report of pretreatment expectancy. No other variables predicted adherence.

Adherence and Child Anxiety Outcomes

In multiple regressions examining the relation between adherence and PARS outcomes (Table 3), control variables accounted for up to 21% ($p < .01$) of the variance in post-treatment anxiety symptom severity; PT rated adherence accounted for an additional 2% ($p < .05$) of the variance in post-treatment anxiety symptom severity as measured by the PARS. In terms of post-treatment global functioning (CGAS), the control variables and baseline global functioning accounted for 18% of the variance in global functioning at 12 weeks ($p < .01$), and an additional 3% ($p < .01$) of variance was accounted for by PT-rated adherence. PT-rated adherence also predicted treatment response at 12 weeks (OR = .65, (95% CI = . 43, .98), $p < .04$].

DISCUSSION

This study explored pharmacotherapy adherence, its predictors and relation to treatment outcome in a sample of youth randomly assigned to receive sertraline, pill placebo, or sertraline plus CBT for a primary anxiety disorder (i.e., GAD, SOP, SAD). Overall, findings indicated that few baseline variables predicted adherence and although higher adherence was associated with better post-treatment child outcomes, the effects were modest.

With respect to predictors of medication adherence, youth living with two parents were more adherent than youth living with a single parent. This finding suggests that two parent families may have extra logistical support in the household to drive to appointments, refill prescriptions, and help with reminders to follow through on taking medications and other PTs treatment recommendations. In contrast to hypotheses, no other demographic variable were associated with adherence.

Among baseline child clinical characteristics, such as initial anxiety severity and comorbidity, none were associated with medication adherence. The absence of a relation between child clinical characteristics and adherence was unexpected and in contrast to published studies. This may be due to the restrictive inclusion criteria in CAMS (e.g., depression was an exclusion criterion) or the use of broad classification of internalizing versus externalizing disorders rather than examining specific comorbid disorders individually. One positive interpretation of these finding is that in contrast to other disorders, initial anxiety severity may not lower medication adherence.

With respect to family factors, while the literature has shown that parental psychopathology and other family factors can influence adherence (Bartlett et al., 2004), parental and family factors were not associated with adherence for anxious youth in the current study. One possible explanation is that this sample of parents had low levels of psychopathology (parents mean BSI score was 24.7 on a scale with a range from 0-111) and these families

may not have been experiencing high levels of family dysfunction. It may also be that specific forms of parental psychopathology (e.g., depression), rather than global distress, or other aspects of family functioning might have a stronger impact on adherence, an issue that would be important for future studies to examine.

Finally, with respect to treatment-related factors, findings revealed that parents who expected their children to improve with medication treatment were more adherent. This finding highlights how hope and belief in the positive outcomes of treatment may motivate parents to bring youth to sessions and ensure that they take the prescribed medication. Similarly, youth who strongly believed that the medication treatment would be helpful were rated as more adherent by their PTs. Youth's positive treatment beliefs may have translated into higher levels of treatment engagement. This too highlights the importance of psychoeducation provided by PTs and suggests that when families understand why they are taking medicine and the potential benefits of medication, the more likely they will be to adhere to treatment requirements. Thus, a careful and thorough discussion of the benefits of medication and how it will improve patient's daily life is essential.

Another aim of this study was to examine the relation between medication adherence and treatment outcomes. The general pattern of findings indicated that higher clinician rated adherence was associated with better child outcomes at post-treatment. Specifically, youths whose PT rated them higher in adherence were more likely to show clinically meaningful improvement and higher global functioning. Not all studies report an association between medication adherence and child outcomes. The inconsistent findings may be due to methodological issues in the definition of adherence. For instance, in the one study when adherence was defined using physiological measures, it was positively associated with clinical outcome but not when defined by parental report (Pappadopulos et al., 2009). Intriguingly, in the TORDIA study, researchers found a modest dose response relationship with clinical outcome when adherence was measured using self-report but not drug plasma levels (Woldu et al., 2011). This counter-intuitive finding whereby an objective (physiological) measure of adherence fared less well than a subjective rating (self-report) suggests that others factors than the medication itself may be at play. This appears to also be relevant for interpreting the current findings which revealed that medication adherence (defined by PT ratings) only accounted for a small percent of variance in child outcomes. Personal, family or environmental factors which facilitate a person's readiness or ability to adhere may be the factors associated with better outcome, rather that the medication itself. This is particularly true if treatment outcomes are defined in broad terms, such as quality of life, improved peer or family relationships and better grades in school, which may have less to do with immediate treatment (medication) effects and more to do with environmental, behavioral, or cognitive changes (or a combination).

Findings of this study should be interpreted in the context of several limitations. The CAMS sample, while representative of treatment-seeking youth, may not be representative of non-volunteers in community populations. In addition, only a select number of predictors were examined. Other relevant predictors (e.g., medication ambivalence, readiness for treatment, therapeutic relationship) may be more predictive of medication adherence. The role of unexpected or undesirable medication side effects that have been reported to decrease

adherence to medications was not explored. Another limitation was the definition of adherence used in this study and the restricted range on the adherence measure. Specifically, this study found that PT-ratings of adherence were high, 92.4 % of youth were rated as adherent with treatment (i.e., scored 5 or higher on PT adherence scale of 1–7). Although these rates of adherence suggest that participants were largely compliant with pharmacotherapy, the rates are also likely to be inflated as these participants were enrolled in a clinical trial with resources to assist monitoring and motivating participants (even assisting with transportation). Moreover, PT adherence ratings may be inflated as part of this judgment is based on attending the session. Such high adherence rates are rarely seen in community settings, also raising questions about the generalizability of the current findings. Future research should include additional measures of adherence including objective measures of adherence (e.g. serum concentrations, or MEMS® Medication Events Monitoring System-neither of which were available in CAMS) to determine the "gold standard" definition of adherence. Finally, adherence is not static but varies during treatment alongside other variables (e.g., side effects, child symptoms); examining these time-varying variables may clarify the relations between predictors, adherence, and outcomes.

Summary and Conclusions

In light of the efficacy of medications for pediatric anxiety disorders, studies examining predictors of medication adherence and the relation between medication adherence and outcomes are needed. This study found that while more adherent youth had better outcomes (e.g., higher global functioning, greater clinical improvement) this relation was modest. More robust was the finding that in the management of youth with anxiety disorders special attention to the expectations and beliefs of the youth and the parent about the treatment appear to be important factors to be considered in order to improve adherence. Indeed, these factors hold particular promise for targeting, as they are modifiable.

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Table 1

Means, Standard Deviations, and Ranges for all Variables

Adherence	**Mean (SD)**	**Range**
PT rated adherence (total sample)	6.4 (0.95)	1.00–7.00
SRT	6.4 (0.99)	1.00–7.00
PBO	6.4 (1.00)	1.00–7.00
COMBO	6.4 (0.91)	2.86–7.00
Predictors		
BL Demographic		
Age (years)	10.69 (2.82)	7 – 17
Sex	48.7 % female, 51.3% male	
Race	79.9% white, 8.6% black, 3.2% Asian, 0.9% American Indian, 0.6% Native Hawaiian/Pacific Islander, 6.9% other	
Ethnicity	10.9% Hispanic, 89.1% non-Hispanic	
SES	22.1% SES 1–3, 77.9 % SES 4–5	
Whom child living with	73.1% both natural parents, 26.9% not living with both natural parents	
BL Clinical		
CGI-S	5.03 (.72)	3 – 7
Comorbid internalizing disorders	45.3% internalizing disorders	
Comorbid externalizing disorders	18.4% have externalizing disorders	
Principal diagnosis	22.1% SAD, 40.1% SoP, 37.8% GAD	
Treatment related factors		
Child pretreatment expectancy	2.46 (1.28)	1 – 7
Parent pretreatment expectancy	2.17 (.94)	1 – 6
Family/parental factors		
BSI total	24.7 (22.3)	0 – 111
BAS total	46.9 (13.8)	21 – 93
BFAMG child total	14.2 (5.58)	2 – 30
BFAMG parent total	11.0 (5.40)	0 – 30
Outcomes		
PARS total 12 week	9.12 (6.63)	0 – 27
CGAS 12 week	66.2 (11.8)	31 – 92
CGI-I responder	65.9 % responder, 34.1 % non –responder[1]	

Note: BL = baseline; BSI = Brief Symptom Inventory; BAS = Burden Assessment Scale;

BFAMG =Brief Family Assessment Measure General;

PARS =Pediatric Anxiety Rating Scale; CGI-I Clinical Global Impressions- Improvement

CGAS = Clinical Global Assessment Scale.

[1]Current rates of treatment response are based on raw data at 12 weeks and exhibit slight difference with Walkup et al., 2008, which used Last Observation Carried Forward to account for missing data in reporting treatment response.

Table 2

Predictors of Medication Adherence

	PT-rated adherence		
	F	**R^2**	**β**
Step 1 control variables	1.4	.01	
BL Demographic	1.7	.03	
Age (years)			.01
Sex			−.05
Race			−.01
Ethnicity			−.06
SES			.01
Whom child living w/			.15*
BL Clinical	.88	.01	
CGI-S			.07
CGAS			−.02
Internalizing dx			−.04
Externalizing dx			.06
Principal diagnosis			.05
BL Treatment-related factors	6.4**	.06**	
Child expectancy			.21**
Parent expectancy			.15*
Family/parental psychopathology	1.4	.02	
BSI total			−.11
BAS total			−.04
BFAMG child			−.02
BFAMG parent			.00

Note: Analyses control for treatment condition and site.

* $p < .05$;

** $p < .01$

Table 3

Multiple Regressions Medication Adherence and Child Outcomes

	PARS total			CGAS		
	F	**ΔR²**	**β**	**F**	**ΔR²**	**β**
Step 1 Control variables	12.6**	.21**		9.87**	.18*	
Step 2 Clinician-rated adherence	12.0**	.02*	−.12*	10.6**	.03**	.16*
Logistic Regressions	CGI-I Response					
	B	P	Odds Ratio	95% CI		
Clinician-rated adherence	−.43**	.04	.65	[.48, .98]		

Note: Analyses control for baseline score on the adjustment outcome, child age, sex, race, family SES, treatment condition, and site.

* $p < .05$;

** $p < .01$