A Comparison of Various Methods of Measuring Antidepressant Medication Adherence Among Children and Adolescents with Major Depressive Disorder in a 12-Week Open Trial of Fluoxetine

Paul A. Nakonezny, Ph.D.,^{1,2} Carroll W. Hughes, Ph.D.,² Taryn L. Mayes, M.S.,²
Kathryn H. Sternweis-Yang, Ph.D.,² Betsy D. Kennard, Psy.D.,²
Matthew J. Byerly, M.D.,² and Graham J. Emslie, M.D.²

Abstract

Objective: In this study, we examined antidepressant (fluoxetine) medication adherence in children and adolescents with major depressive disorder (MDD). Using electronic monitoring (EM) as the “reference standard,” we compared various methods of measuring antidepressant medication adherence (including EM, pill counts, and medication diaries) among children and adolescents with MDD and examined the relationship between EM medication adherence and depression severity across time. We then suggested recommendations for clinical researchers and practicing clinicians regarding medication adherence assessment.

Method: Thirty-one child and adolescent outpatients with MDD who enrolled in a 12-week open trial of fluoxetine had their antidepressant medication adherence assessed at each visit, using EM, pill counts, and parent and patient medication diaries. Depression severity was assessed by the Children’s Depression Rating Scales—Revised at each visit.

Results: Twelve-week least squares mean estimates of medication adherence for the entire sample was high, regardless of the adherence assessment method, although the overall adherence among the four methods (EM, pill, parent diary, patient diary) was significantly different (87.5% vs. 90.6% vs. 93.1% vs. 93.3%, respectively, $p = 0.0002$). Adjusted mean symptom severity was significantly lower for the EM “adherent” group than for the EM “nonadherent” group over the 12 weeks of treatment (35.6 vs. 43.8, $p = 0.008$).

Conclusion: Overall, EM medication adherence for the depressed youth in this study is high. Compared with EM, there is a tendency of pill counts and medication diaries to overestimate medication adherence. However, pill count adherence better approximates EM adherence, and compliance with returning medication diaries is poor. Youth who are adherent to fluoxetine treatment have lower symptom severity over the course of treatment. Recommendations are provided.

Introduction

MAJOR DEPRESSIVE DISORDER (MDD) is a common disorder that affects up to 2% of children and 8% of adolescents (Birmaher et al. 2007). This prevalence rate is especially significant given the increased risks of suicidal behavior, substance abuse and dependence, and depressive episodes into adulthood associated with early-onset MDD (Birmaher et al. 2007).

Fortunately, for those who do seek treatment, there have been three randomized controlled trials that have demonstrated the efficacy of fluoxetine in early-onset MDD (Emslie et al. 1997, 2002; March et al. 2004), as well as a meta-analysis that has shown

the efficacy of other pediatric antidepressant treatments (Bridge et al. 2007). Despite the evidence of efficacy, there is a high percentage of medication nonadherence associated with antidepressants (Cramer and Rosenheck 1998; Osterberg and Blaschke 2005), at least among adults treated for depression. In a systematic review by Cramer and Rosenheck (1998), the mean medication adherence among those with adult depression was about 65%. Unfortunately, no studies to date have systematically assessed medication adherence in youth with depression.

Clinical researchers have used various adherence assessment methods, including pill counts, medication diaries, self-reports, clinician rating, chart review, prescription renewal/pharmacy

¹Division of Biostatistics, Department of Clinical Sciences, UT Southwestern Medical Center, Dallas, Texas.

²Department of Psychiatry, UT Southwestern Medical Center, Dallas, Texas.

This study was supported by two grants from the National Institute of Mental Health: Childhood Depression: Remission and Relapse (R01 MH39188 to Dr. G.J. Emslie) and Continuation CBT for Youth with MDD (R34 MH072737 to Dr. B.D. Kennard).

records, and urine or blood analysis. These various methods have been extensively reviewed (Farmer 1999; Osterberg and Blaschke 2005; Velligan et al. 2006), and each method has its own critical shortcomings (Osterberg and Blaschke 2005). Although indirect methods of adherence (e.g., pill counts, medication diaries, and physician and clinician ratings) are commonly used to track medication adherence, they have historically been problematic because they are subject to manipulation and overestimation (Farmer 1999; Osterberg and Blaschke 2005; Byerly et al. 2007b).

Electronic monitoring (EM) has become increasingly used to assess medication adherence in general medical and schizophrenia populations (Diaz et al. 2004; Byerly et al. 2005, 2007a; Osterberg and Blaschke 2005; Nakonezny, et al. 2008). The reliability and validity of EM devices now provides a reasonable "objective reference standard" to evaluate medication adherence and a standard by which other indirect adherence assessment methods can be evaluated (Byerly et al. 2007b; Nakonezny et al. 2008). The most commonly employed EM device consists of a medication vial cap that electronically records the date and time of bottle opening.

Although EM of medication adherence of outpatients in schizophrenia (Byerly et al. 2007b; Nakonezny et al. 2008) and in other patient populations such as HIV (Liu et al. 2001) and hypertension (Burnier et al. 2001) has been previously studied, little research has been devoted to studying medication adherence in children and adolescents with MDD. Indeed, to our knowledge, EM has never been previously used to examine medication adherence in a study involving early-onset pediatric depression.

In the present study, using EM as the reference standard, we compared various methods of measuring antidepressant medication adherence (including EM, pill counts, and medication diaries) among children and adolescents with MDD and examined whether mean adherence changed over time during the 12-week open-label trial of fluoxetine. We also examined the relationship between EM medication adherence and depression severity across time. Finally, we suggested recommendations for clinical researchers and practicing clinicians regarding medication adherence assessment among children and adolescents with MDD.

Methods

Participants

The 31 participants of the present study represent a subsample from two studies of relapse prevention (Emslie et al. 2008; Kennard et al. 2008). Specifically, participants were outpatients from our study of Relapse and Remission in Children and Adolescents with MDD (R01 MH39188) (Emslie et al. 2008) and our study of Relapse Prevention (R34 MH72737) (Kennard et al. 2008). In both studies, participants were treated openly with fluoxetine for 12 weeks. Both treatment studies were approved by the Institutional Review Board (IRB) of the University of Texas Southwestern Medical Center at Dallas, and written informed consent and assent were obtained from all participants and their parent/guardian. The present adherence study was also approved by the IRB. The 31 participants in the present adherence study were consecutively enrolled subjects who entered acute treatment in the above treatment studies from September 2004 through February 2006. (Note: There were two temporary pauses in recruitment for IRB modifications [to include the Kennard study and to add monitoring caps].)

Participants were aged 7–18 years (7–18 years for the Emslie trial; 11–18 years for the Kennard trial). For both treatment studies, participants had to have a primary diagnosis of nonpsychotic MDD, with a Clinical Global Impressions-Severity (CGI-S) ≥ 4 for de-

pression and Children's Depression Rating Scales—Revised (CDRS-R) ≥ 40 . They also had to be in good general medical health and of normal intelligence. Participants were excluded if they had any lifetime history of a psychotic disorder, bipolar I or II disorder, or anorexia nervosa or bulimia and alcohol or substance abuse or dependence within the past 6 months. Pregnant or lactating females and sexually active females not using medically acceptable means of contraception (intrauterine device, birth control pills, or barrier devices) were excluded. Youth on medication(s) with psychotropic effects (other than attention-deficit/hyperactivity disorder (ADHD) medications), prior failure of adequate treatment with fluoxetine, chronic and unstable medical conditions contraindicating study treatments, and patients with first-degree relatives with bipolar I disorder were also excluded.

Procedures

Antidepressant treatment. Study procedures have been previously detailed (Emslie et al. 2008; Kennard et al. 2008; Tao et al. 2009). The 12-week, open-label treatment with fluoxetine was part of larger studies of relapse prevention: the Emslie study compared 6 months of continued fluoxetine versus placebo in responders to 12 weeks of fluoxetine (Emslie et al. 2008), whereas the Kennard study compared 6 months of continued medication alone versus continued medication plus cognitive behavioral therapy designed to prevent relapse (Kennard et al. 2008).

For both treatment studies, participants completed a 2-week, three-visit diagnostic evaluation using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime (Kaufman et al. 1997), and eligible participants were then treated openly during acute phase treatment with fluoxetine for 12 weeks (Emslie et al. 2008; Kennard et al. 2008). Following 1 week at 10 mg, dose was increased to 20 mg, with optional increase to 30–40 mg at week 6. Treatment visits occurred weekly for the first 4 weeks and then biweekly through week 12.

Measures of medication adherence. Medication adherence was evaluated at each subsequent visit using EM, pill counts, and medication diaries. Child psychiatrists conducted all clinical visits, during which symptom severity ratings, safety, and adherence were assessed.

EM and adherence. The reference medication adherence (or reference standard) was assessed with the Medication Event Monitoring System (MEMS[®]), which is a medication vial cap that electronically records the date and time of bottle opening. The MEMS caps used in this study had no cueing mechanisms and their appearance was similar to any other medication bottle, although the cap was slightly larger than a regular pill bottle cap. The company that makes the MEMS caps provided no support for the study.

Prior to initiating fluoxetine for the treatment studies, participants were informed of the purpose and function of the MEMS. However, they did not have access to EM-generated adherence results (EM adherence results were not shared with the patient) at any time during the trial.

For a given patient, EM adherence was operationally defined as the proportion of medication vial caps openings in a given week relative to the prescribed doses for that week. Excessive bottle openings (i.e., openings that exceeded the number of prescribed doses for that week), however, did not count toward overall adherence.

Pill counts and medication diaries. Pill counts and medication diaries were assessed at each study visit. Returned pills were counted to assess the number of pills remaining in relation to the

number of pills prescribed. Both patients and parents were asked to keep separate medication diaries to detail the number of missed doses, and families were reminded to bring in their medication diaries at each visit.

Measures of depression severity. Depression severity was measured by the CDRS-R (Poznanski and Mokros 1996), which is a 17-item clinician-rated instrument assessing depression symptom severity. The CDRS-R total score ranges from 17 to 113, with a score of ≥ 40 considered to be compatible with a diagnosis of MDD. CDRS-R ratings were completed at each visit by the treating child psychiatrists (who were blind to all medication adherence assessment results).

Data analysis

Comparison of EM, pill counts, and medication diaries. Using EM as the reference standard, we compared various methods of measuring medication adherence including EM, pill counts, and medication diaries (across the 12-week, open-trial treatment period—weeks 1, 2, 3, 4, 6, 8, 10, 12) using a mixed linear model analysis of repeated measures. Restricted maximum likelihood estimation and Type 3 tests of fixed effects were used, with the Kenward–Roger correction (Kenward and Roger 1997) applied to the Kronecker product covariance structure (unstructured covariance model @compound symmetry). The main effects of adherence method (EM vs. pill counts vs. medication diaries) and time (mean adherence across the 12-week trial) and the “method” $\times$ “time point (weeks)” interaction effect were examined. Simple method effects (and least squares means) at each time point were also assessed. To examine the pattern of medication adherence over the 12 weeks of treatment by age group (children, adolescents), the mixed model analysis similar to that described above was also carried out separately for children (≤ 11 years old) and adolescents (> 11 years old).

Cross-method agreement. The simple Kappa coefficient was used to assess the magnitude of agreement between EM adherence and each of the other methods of adherence (pill counts and medication diaries). To estimate the Kappa coefficient, we operationally defined adherence as a binomial variable: youth who had a 12-week mean adherence of $< 80\%$ (“nonadherent”) and youth who had a 12-week mean adherence of $\geq 80\%$ (“adherent”). The $< 80\%$ adherence cutoff was selected because it was both conservative in detecting nonadherence of youth who were treated with fluoxetine (and who were parentally supervised) and in line with definitions from prior published research (Lacro et al. 2002; Byerly et al. 2005, 2007b; Osterberg and Blaschke 2005; Velligan et al. 2006, 2007). Spearman rank-order correlation coefficient (r_s) was also used to assess the magnitude of the linear relationship between continuously measured 12-week mean EM adherence and each of the other methods of continuously measured 12-week mean adherence (pill counts and medication diaries). The Spearman correlation analysis was also carried out separately for children and adolescents.

EM adherence and CDRS-R total score. Using EM adherence (the reference standard) and the binomial definition of adherence described above ($< 80\%$ adherence cutoff), a “two adherence groups (EM adherent, EM nonadherent)” $\times$ “eight time points (weeks 1, 2, 3, 4, 6, 8, 10, 12)” mixed linear model analysis of repeated measures, with the ante-dependence covariance

structure, was used to assess the pattern of depressive symptoms (as measured by CDRS-R total score) between “EM adherers” versus “EM nonadherers” across the 12-week acute phase of open-label fluoxetine treatment. Age and baseline CDRS-R total score were included as covariates in the mixed model analysis. The main effects of adherence group (EM adherent vs. EM nonadherent) and time (mean adherence across the 12-week trial) and the “adherence group” $\times$ “time point (weeks)” interaction effect were examined. As a *post-hoc* analysis, a similar mixed model was also carried out for pill count adherence and CDRS-R total scores.

We performed all of the statistical analyses using SAS software, Version 9.2 (SAS Institute, Cary, NC). The level of significance for all tests was set at $\alpha = 0.05$ (two-tailed), and to address any multiple testing (where applicable), p values were adjusted using the false discover rate (Benjamini et al. 1995).

Results

Participant characteristics

The study sample included 14 males (45.2%) and 17 females (54.8%), with an average age of 12.8 ± 2.9 years (range: 7–17 years). Of the 31 participants, there were 10 (32.3%) children (≤ 11 years) and 21 (67.7%) adolescents (> 11 years). Participants included 23 (74.2%) Caucasians, 4 (12.9%) African Americans, 3 (9.7%) Hispanics, and 1 (3.2%) other (not specified). Just over half of the participants (58.1%) were in their first episode of depression. The average age of illness onset was 11.5 ± 2.9 years, and the average duration of the current depressive episode was 1.3 ± 1.2 years. Mean CDRS-R total score at baseline was 56.4 ± 10.1 .

Most participants (70.9%) completed the full 12 weeks of treatment; an additional two participants completed 10 weeks, and three participants completed 8 weeks. Only four youth (12.9%) completed fewer than 6 weeks of treatment.

Comparison of EM, pill counts, and medication diaries

We found a significant main effect of adherence method (EM vs. pill counts vs. medication diaries: $F = 8.00$, degrees of freedom [df] = 3, 56.5, $p = 0.0002$) and a significant time effect (mean change in adherence across the 12-week trial: $F = 2.62$, $df = 7$, 160, $p = 0.01$), but no overall significant “method” $\times$ “time” interaction effect ($F = 0.98$, $df = 21$, 222, $p = 0.48$). Twelve-week least squares mean estimates of medication adherence for the entire sample was high, regardless of the adherence assessment method, although the overall adherence among the four methods (EM, pill, parent diary, patient diary) was significantly different (87.51% vs. 90.55% vs. 93.14% vs. 93.28%, respectively; $p = 0.0002$).

Further, we found a significant within-subjects time effect (over the 12 weeks of treatment) on mean adherence for EM ($p = 0.03$), pill counts ($p = 0.03$), parent medication diary ($p = 0.04$), and patient medication diary ($p = 0.03$). In other words, mean adherence decreased significantly across the 12 weeks of treatment for each of the four methods of adherence, with lower mean adherence observed at later visits. Least squares means and standard errors for adherence by each method (EM, pill counts, and medication diaries) at the eight study periods are shown in Table 1 and Figure 1. When we examined the pattern of adherence by age group (children, adolescents), we found that the overall mean adherence (across the 12 weeks of treatment) was significantly different among the four methods (EM, pill, parent diary, patient diary) for adolescents (85.7% vs. 90.1% vs. 94.0% vs. 94.0%, respectively; $F = 7.48$, $df = 3$, 31.5, $p = 0.0006$),

TABLE 1. OVERALL MAIN EFFECT OF METHOD AND THE “METHOD” × “TIME PERIOD” SIMPLE EFFECTS FOR MEAN LEVEL OF ELECTRONIC MONITORING, PILL COUNT, AND DIARY ADHERENCE

Time period and method	Adherence (%)				F	p
	M	SE	95% CI for M	n		
Week 1 and method					0.19	0.91
EM	95.44	2.58	90.34–99.55	29		
Pill count	96.50	2.47	91.59–99.38	28		
Parent diary	96.83	1.85	93.15–99.51	25		
Patient diary	96.90	1.86	93.22–99.59	20		
Week 2 and method					1.86	0.20
EM	90.34	2.77	84.87–95.81	25		
Pill count	93.64	2.66	89.11–99.64	24		
Parent diary	94.05	2.07	89.95–98.16	18		
Patient diary	94.38	2.08	90.26–98.49	15		
Week 3 and method					3.49	0.04
EM	87.77	2.72	82.39–93.13	26		
Pill count	89.98	2.61	84.82–95.15	25		
Parent diary	94.46	1.98	90.51–98.39	20		
Patient diary	94.59	1.99	90.65–98.54	17		
Week 4 and method					1.71	0.21
EM	83.45	2.82	77.86–89.02	24		
Pill count	85.03	2.73	79.63–90.43	22		
Parent diary	87.98	2.12	83.77–92.18	16		
Patient diary	88.31	2.13	84.11–92.52	15		
Week 6 and method					1.66	0.21
EM	85.11	2.85	79.48–90.73	23		
Pill count	87.10	2.72	81.72–92.47	23		
Parent diary	89.08	2.10	84.92–93.25	16		
Patient diary	89.65	2.11	85.47–93.83	13		
Week 8 and method					2.66	0.05
EM	87.01	2.87	81.33–92.68	22		
Pill count	91.13	2.74	85.71–96.55	22		
Parent diary	93.70	2.19	89.35–98.04	15		
Patient diary	93.96	2.20	89.61–98.32	11		
Week 10 and method					3.74	0.04
EM	86.20	3.17	79.93–92.46	16		
Pill count	91.57	2.89	85.86–97.27	20		
Parent diary	94.53	2.43	89.73–99.34	11		
Patient diary	93.74	2.42	88.94–98.54	9		
Week 12 and method					4.36	0.04
EM	84.77	3.06	78.71–90.82	19		
Pill count	88.76	2.93	82.98–94.54	19		
Parent diary	94.47	2.44	89.63–99.31	11		
Patient diary	94.68	2.45	89.83–99.53	8		
Overall (weeks 1–12)					8.00	0.0002
EM	87.51	1.40	84.71–90.31	30		
Pill count	90.55	1.34	87.88–93.23	29		
Parent diary	93.14	1.04	91.05–95.22	26		
Patient diary	93.28	1.04	91.19–95.37	22		

Overall = 12-week average and represents the overall main effect of method across the entire 12 weeks of treatment; n = sample size; F statistic was used to test for omnibus mean adherence differences among the four adherence methods; $p = p$ value, and the eight simple effect p values were adjusted using the false discovery rate described by Benjamini and Hochberg (1995).

Abbreviations: EM = electronic monitoring; M = least squares mean; SE = standard error; 95% CI = 95% confidence interval for the expected mean value.

but not for children (90.6% vs. 91.5% vs. 92.5% vs. 92.7%, respectively; $F = 1.07$, $df = 3, 20.6$, $p = 0.38$).

Cross-method agreement

“Adherence” was operationally defined as a binomial variable (12-week mean adherence of <80% [nonadherent] and 12-week mean adherence of ≥80% [adherent]). Pill count adherence agreed

with EM adherence in 23 of 31 cases (74.19%, $Kappa = 0.46$, $p = 0.05$), parent’s diary of adherence agreed with EM adherence in 22 of 31 cases (70.97%, $Kappa = 0.38$, $p = 0.09$), and patient’s diary of adherence agreed with EM adherence in 18 of 31 cases (58.06%, $Kappa = 0.16$, $p = 0.64$). When adherence was left as a continuously measured outcome, the Spearman rank-order correlation (r_s) revealed a significant positive linear relationship between EM adherence and pill counts ($r_s = 0.67$, $p = 0.0003$, $n = 29$), but a

FIG. 1. "Adherence method" $\times$ "time period" simple effects for mean level of EM, pill count, and diary adherence. The estimates reported in this figure represent the same least squares means reported in Table 1. The least squares means showed that the overall adherence (over the 12 weeks of treatment) among the four methods (EM, pill, parent diary, patient diary) was significantly different ($p=0.0002$). Further, mean adherence decreased significantly over the 12 weeks of treatment for each of the four methods of adherence (p 's < 0.01). There was, however, no overall significant adherence method $\times$ time interaction effect ($p=0.48$). EM = electronic monitoring.

nonsignificant relationship between EM adherence and parent diary ($r_s = 0.36$, $p = 0.09$, $n = 26$) or patient diary ($r_s = 0.30$, $p = 0.16$, $n = 22$) across the average of the 12 weeks of treatment. Table 2 presents the Kappa coefficient and Spearman correlation results of the proportion of depressed youth who were adherent and non-adherent by each method.

For children, the Spearman correlation revealed a significant positive linear relationship between EM adherence and pill counts ($r_s = 0.92$, $p = 0.0002$, $n = 10$), between EM adherence and parent diary ($r_s = 0.92$, $p = 0.0002$, $n = 10$), and between EM adherence and patient diary ($r_s = 0.83$, $p = 0.002$, $n = 10$) across the average of the 2 weeks of treatment. For adolescents, the Spearman correlation revealed a significant positive linear relationship between EM adherence and pill counts ($r_s = 0.60$, $p = 0.01$, $n = 19$), but a nonsignificant relationship between EM adherence and parent diary ($r_s = 0.09$, $p = 0.72$, $n = 16$) or patient diary ($r_s = 0.007$, $p = 0.98$, $n = 12$) across the average of the 12 weeks of treatment.

EM adherence and CDRS-R total score

We found that, while controlling for age and baseline CDRS-R total score, the adjusted least squares means for depression severity ratings (CDRS-R total scores) were significantly different between the EM adherent and EM nonadherent groups ($F = 8.23$, $df = 1$, 26.7 $p = 0.008$) over the 12 weeks of acute treatment (Fig. 2). In addition, a significant time effect (mean change in CDRS-R total scores across the 12-week trial: $F = 11.23$, $df = 7$, 44 , $p < 0.0001$) was found; "adherence group" $\times$ "time" interaction effect was not significant ($F = 1.92$, $df = 7$, 44.2 , $p = 0.08$). The pattern of the adjusted least squares means showed that CDRS-R total scores decreased significantly across the 12 weeks of treatment within both the EM adherent and EM nonadherent groups ($F = 14.74$, $df = 7$, 41.7 , $p < 0.0001$ and $F = 4.78$, $df = 7$, 44.5 , $p = 0.0005$, respectively), although the adjusted least squares means for CDRS-R total scores were significantly lower for the EM adherent group than for the EM nonadherent group over the 12 weeks of treatment (35.59 vs. 43.81, $p = 0.008$; Fig. 2).

TABLE 2. CROSS-METHOD AGREEMENT OF PILL COUNT AND MEDICATION DIARIES WITH ELECTRONIC MONITORING ADHERENCE

EM	Other method	EM		Other method		EM Adherence		Other method Adherence		Kappa coefficient		Spearman correlation	
		Nonadherence		Nonadherence		Adherence		Adherence		Kappa		r _s	
		n	%	n	%	n	%	n	%	Kappa	p Value ^a	n	p Value ^b
EM	Pill count	31	22.58	4	12.90	24	77.42	27	87.10	0.46 ^c	0.05	29	0.67 ^c
EM	Parent's diary	31	22.58	5	16.13	24	77.42	26	83.87	0.38 ^d	0.09	26	0.36 ^d
EM	Patient's diary	31	22.58	9	29.03	24	77.42	22	70.97	0.16 ^e	0.64	22	0.30 ^e

p Values were adjusted using the false discovery rate (Benjamini and Hochberg, 1995). Nonadherence was operationalized as $< 80\%$ adherence (across the average of the 12-week trial). Spearman rho was assessed between continuously measured 12-week mean EM adherence and each of the other methods of continuously measured 12-week mean adherence (pill counts and medication diaries). *n* = number of participants who were adherent or nonadherent by method of adherence or cross-method comparison of adherence agreement, vis-à-vis the operationalization (or measurement) of adherence (binomial or continuous).

^aExact two-sided.

^bTwo-tailed test.

^cAdherence agreement between pill count and EM.

^dAdherence agreement between parent's diary and EM.

^eAdherence agreement between patient's diary and EM.

FIG. 2. “Adherence group” $\times$ “time period” simple effects for mean level of CDRS-R total score. Least squares means for CDRS-R total score are adjusted for age and baseline CDRS-R total score. Adjusted least squares means for CDRS-R total scores were significantly lower for the EM “adherent” group than for the EM “nonadherent” group over the 12 weeks of treatment ($p = 0.008$). Further, adjusted mean CDRS-R total scores decreased significantly over the 12 weeks of treatment within both the EM adherent and EM nonadherent groups (p 's < 0.0005). There was a marginally significant “adherence group” $\times$ “time” interaction effect ($p = 0.08$). Note: EM adherence was operationally defined as a binomial variable: Youth who had a 12-week mean EM adherence of $< 80\%$ (EM nonadherent) and youth who had a 12-week mean EM adherence of $\geq 80\%$ (EM adherent). CDRS-R = Children's Depression Rating Scales—Revised.

Pill count adherence and CDRS-R total score

As a *post-hoc* analysis, we also carried out a similar analysis for pill count adherence and CDRS-R total scores. We found that, while controlling for age and baseline CDRS-R total score, the adjusted least squares means for depression severity ratings (CDRS-R total scores) were significantly different between the pill count adherent and nonadherent groups ($F = 3.82$, $df = 1$, 31.5 $p = 0.05$) over the 12 weeks of acute treatment. In addition, a significant time effect (mean change in CDRS-R total scores across the 12-week trial: $F = 4.15$, $df = 7$, 46.9 , $p = 0.001$) was found; “pill count adherence group” $\times$ “time” interaction effect was not significant ($F = 1.01$, $df = 7$, 47.1 , $p = 0.44$). The pattern of the adjusted least squares means showed that the adjusted least squares means for CDRS-R total scores were significantly lower for the pill count adherent group than for the pill count nonadherent group over the 12 weeks of treatment (36.54 [SE = 1.33; $n = 27$] vs. 45.05 [SE = 4.14; $n = 4$], $p = 0.05$).

Discussion

The present study examined antidepressant (fluoxetine) medication adherence in children and adolescents with MDD. The results suggest that, with EM as the reference standard, the 12-week mean estimate of EM medication adherence for the sample of depressed youth is high (87.5%). The mean EM medication adherence found in the present study for depressed youth is much higher than that found in adult depression, which is about 65% (Cramer and Rosenheck 1998). Nakonezny et al. (2008) similarly found a mean EM medication adherence of about 67% over a 6-month study among 61 adult outpatients with schizophrenia or schizoaffective disorder. The high medication adherence among the depressed youth in the present study may be due to the frequency of follow-up visits coupled with parental involvement/supervision. In addition, all participants received psychoeducation about the importance of medication adherence.

In this study, mean EM adherence is high for both children and adolescents, but is slightly higher for children (90.5%) than for

adolescents (85.7%). Also, children tend to have consistently high medication adherence ($> 90\%$ mean adherence) regardless of the method of adherence measurement. This finding that children tend to have higher medication adherence than adolescents is in line with previous research (Fotheringham and Sawyer 1995) and is consistent with the role that greater parental involvement/supervision plays in monitoring children's medication behavior.

In the present study, using EM as the reference standard, we also compared various methods of measuring medication adherence over time and examined the relationship between EM of medication adherence and treatment outcome (severity of depressive symptoms). Compared with EM, pill counts and parent and patient medication diaries overestimate medication adherence (by about 3.5% and 6.5%, respectively, in this study), which is consistent with prior reports (Cramer and Rosenheck 1998; Farmer 1999; Osterberg and Blaschke 2005). However, in the present study, the magnitude of adherence agreement between pill counts and EM is a bit stronger than the magnitude of adherence agreement between medication diaries and EM.

As expected, medication adherence decreased significantly across the 12-week study period, although it should be noted that the overall mean adherence was still markedly high. One possible explanation of this finding is that patients may have felt that they were better and no longer needed medication (Cramer et al. 2003). This is a common trend among children and adolescents with depression (Fotheringham and Sawyer 1995), as well as other patient populations (Nakonezny and Byerly 2006; Nakonezny et al. 2008).

Also, as expected, youth who were considered adherent had significantly lower severity of depressive symptoms (as measured by the CDRS-R total score) than youth who were considered nonadherent, which is consistent with previous studies that found an association between greater EM of medication adherence and improved clinical outcomes in schizophrenia patients (Nakonezny et al. 2008), HIV patients (Liu et al. 2001; Wagner et al. 2002), and hypertensive patients (Burnier et al. 2001). It should be noted that adherent youth had an overall high mean EM adherence of 90.6%, whereas the overall mean EM adherence for nonadherent youth was still fairly high (75.2%).

Finally, although sufficient efforts were made to collect all adherence data across the eight study visits, there were many situations in which medication diaries were unreturned. Indeed, compliance with returning the parent and patient diaries ranged from about 80% and 65% at week 1, respectively, to about 50% and 36% by week 12, respectively. Although uncollected EM and pill count data resulted mostly from early discontinuation of participants, EM adherence data from three individual MEMS caps were unavailable because two caps were lost and one cap was damaged. Nonetheless, compliance with returning EM (MEMS) caps and pill counts ranged from about 93% and 90% at week 1, respectively, to about 86% by week 12 and was much better than the compliance with returning medication diaries.

The present study may be tempered by a few limitations. The study had a relatively brief study period and small sample size. In addition, using a small sample within a university (research) medical setting might have limited the generalizability of the study results. In particular, the volunteers (youth) used in the present study may be more adherent than the general, real-world outpatient population of youth with depression, because of the relatively intensive medication management employed in the present study setting (e.g., visit schedule, assessment of symptoms). Thus, findings for the present study may have overestimated the adherence of

what might be expected in the general, real-world outpatient population of depressed youth where physician office visits tend to be less frequent and of briefer duration. Further, EM may overestimate adherence because the events captured by EM (date/time of bottle opening) does not ensure medication ingestion (Farmer 1999; Riekert and Frotar 2002; Osterberg and Blaschke 2005). A period documenting a lack of medication bottle opening, however, most likely represents nonadherence (Osterberg and Blaschke 2005).

In addition, the medication used in this study, fluoxetine, has a long half-life, which may have impacted adherence and symptom change. For example, patients who were nonadherent would have continued to have fluoxetine in their system for several weeks. In fact, it is possible that there would have been greater differences in symptom severity by week 12 if the medication had not had such a long half-life.

It is beyond the scope of this study to broadly generalize our results. As noted above, we recognize and emphasize that the volunteers (youth) who participated in the present study may be more adherent than the general, real-world outpatient population of youth with depression. Thus, the breadth of our results is limited to medication adherence and symptom severity among children and adolescents with MDD with similar clinical characteristics treated with similar methodology within a university (research) medical setting. It is this context in which our results should be interpreted.

To our knowledge, this is the first study to use EM as an objective reference standard, to examine antidepressant (fluoxetine) medication adherence in children and adolescents with MDD, to compare various methods of measuring antidepressant medication adherence among youth with MDD, and to examine the relationship between EM of medication adherence and severity of depressive symptoms. Overall, EM medication adherence for the depressed youth in this study is high (87.5%); thus, depressed youth in the present study appear to be adherent to their antidepressant medication (fluoxetine). Youth who are adherent to fluoxetine had lower severity of depressive symptoms over the course of treatment. Compared with EM, there is a tendency of pill counts and parent and patient medication diaries to overestimate medication adherence. However, pill count adherence better approximates EM adherence, and pill count is more consistently obtained than medication diaries (and compliance with returning medication diaries is poor). Thus, pill count might be an acceptable proxy for evaluating medication adherence in depressed youth (if EM cannot be used), but parent and patient medication diaries do not appear to be an acceptable proxy.

Nonetheless, future research with a larger sample size, a more representative sample of youth with MDD from the real-world outpatient clinic setting, and, perhaps, with other types of selective serotonin re-uptake inhibitors (SSRIs) is needed to further clarify antidepressant medication adherence among children and adolescents with MDD. But the present study is a first step at empirically evaluating medication adherence in depressed youth using EM.

Finally, based on the findings of the present study and that from previous adherence research, we offer the following (adherence assessment) recommendations for future studies in child/adolescent MDD research as well as recommendations/implications for clinicians who treat children/adolescents in community practice settings.

Recommendations for Future Studies in Child/Adolescent MDD Research

1. The use of electronic monitors seems to be a feasible, objective, unobtrusive method of monitoring medication

adherence among depressed youth (with parental involvement) in a medical research setting. A recently published *New England Journal of Medicine* review of adherence assessment stated that EM “provides the most accurate and valuable data on adherence in difficult clinical situations and in the setting of clinical trials and adherence research” (Osterberg and Blaschke 2005).

In the present study, EM effectively assessed and tracked medication adherence of depressed youth across the 12-week study period and youth who were adherent to fluoxetine had lower symptom severity over the course of treatment. Approximately 93% and 86% of the planned EM data were collected at week 1 and 12, respectively. In addition to its feasibility as an adherence assessment method, EM was well accepted by patients (youth) and parents in the present study.

EM (MEMS) caps cost about \$90 for each cap, and they can capture continuous data for up to 36 months. The hardware and software necessary to record and manage adherence data from the MEMS caps has a one-time cost of ~\$500 and is easy to set up and learn. Overall, the implementation of electronic monitors (MEMS caps) in a medical research setting is fairly straightforward.

2. Although we are recommending EM as the first-line method of objectively and unobtrusively assessing medication adherence of depressed youth in a medical research setting, in the event that EM cannot be used (for whatever reason), we are also recommending pill counts as an acceptable proxy for evaluating overall medication adherence of depressed youth with parental/familial involvement. In the present study, pill count adherence better approximates EM adherence, and compliance with returning medication diaries is poor. Although not addressed in the present study, clinical researchers might consider the use of a pill minder box (as a systematic way of accounting for medication usage/adherence).
3. Replication of this research with a larger, more representative sample size is needed to further clarify if children and adolescents with MDD in the real-world community practice setting (who also have parental/familial involvement) are as adherent to their antidepressant medication as those studied in the present study (in a university medical research setting).

Recommendations/Implications of Our Findings for Practicing Clinicians

1. Clinicians should understand that medication adherence directly relates to the course of treatment and to patient outcomes, and efficacy depends on adherence, so patients and their families should be educated about the importance of adherence. In the present study, youth who were considered adherent had significantly lower severity of depressive symptoms than youth who were considered nonadherent.
2. The clinician should undertake formal monitoring efforts or assessment to ascertain if the patient is taking the prescribed medication, because adherence problems make it very difficult, if not impossible, for the prescribing clinician to evaluate treatment response and determine if dosing is appropriate, if concomitant medication is needed, or if a medication switch is warranted (Byerly et al. 2007; Velligan et al. 2009).
3. The use of electronic monitors might not be a practical means of monitoring medication adherence in real-world community practice/clinic settings.

4. Patient/parent self-reports (medication diaries) and/or physician judgment/report might seem appealing as simple and inexpensive ways of assessing medication adherence in the community practice setting. Unfortunately, as found in the present study with depressed youth and in previous research using other psychiatric patient populations (Glazer and Byerly 2008; Velligan et al. 2009), these subjective assessment methods are likely to overestimate levels of medication adherence, and compliance with returning medication diaries is poor.
5. Thus, given the findings of the present study, pill counts in the office (real-world clinic/practice) setting should be considered as an acceptable proxy for evaluating overall medication adherence of depressed youth with parental/familial involvement. Although not addressed in the present study, clinicians might consider the use of a pill minder box (as a systematic way of accounting for medication usage/adherence). Clinicians must stress to patients (youth) and parents the importance of bringing in all bottles of medication (new and old) for evaluation and assessment (Glazer and Byerly 2008).
6. Clinicians should encourage the importance of the therapeutic alliance. Although the overall 12-week mean EM adherence was high (87.5%) among depressed youth in the present study (in a controlled university medical research setting), adherence did decline over the 12-week study period. Thus, to promote consistent medication adherence behavior in the real-world community practice setting, clinicians should encourage familial involvement/support (which is an important component in medication adherence behavior) and make medication/medication adherence discussions a routine part of each office visit with the patient (youth) and parent (Byerly et al. 2007; Glazer and Byerly 2008).
7. Clinicians need to stress to the patient (youth) and parent(s) the importance of not discontinuing medication usage, even if the patient is feeling better, so as to mitigate relapse.
8. If nonadherence is suspected during the course of treatment, then the clinician should try to identify the core barrier(s) or reason(s) behind the nonadherence so as to mitigate relapse (Glazer and Byerly 2008; Velligan et al. 2009).

In summary, the reader is referred to the works of Glazer and Byerly (2008) and Velligan et al. (2009) for a detailed presentation and discussion of medication adherence in patients with mental illness, including adherence assessment, barriers, guidelines, recommendations, and strategies/interventions for addressing medication adherence problems.

Disclosures

Dr. C.W. Hughes has had recent research support from the National Institute of Mental Health (NIMH) and Glaxo Smith Kline and has a consulting contract with BioBehavioral Diagnostics. Dr. B.D. Kennard has received research grant or unrestricted grant support funding from NIMH. Dr. M.J. Byerly has had recent research grant support from the NIMH and AstraZeneca and from Bristol-Myers Squibb, Janssen, and Pfizer for speaking honoraria. Dr. G.J. Emslie receives research support from the NIMH, Biobehavioral Diagnostics, Forest Laboratories, Shire, and Somerset and is a consultant for Biobehavioral Diagnostics, Eli Lilly, Forest Laboratories, Pfizer (as a member of a Data Safety Monitoring Board for a clinical trial), Shire, Validus Pharmaceuticals, and Wyeth Pharmaceuticals. Drs. P.A. Nakonezny and K.H. Sternweis-

Yang and Ms. T.L. Mayes report no financial relationships with or financial interests in pharmaceutical companies. Eli Lilly provided the medication for the Emslie study (R01 MH39188 to Dr. G.J. Emslie), but had no role in the study design or implementation, analysis of data, or authorship of this manuscript. Dr. P.A. Nakonezny performed the statistical analysis in this study.

Clinical Trials Registries

Dr. G.J. Emslie: Determining Optimal Continuation Treatment Duration for Depressed Children and Adolescents (NCT00332787; www.clinicaltrials.gov). Dr. B.D. Kennard: Cognitive Behavioral Therapy for Depression Relapse Prevention in Children and Adolescents (NCT00158301; www.clinicaltrials.gov).

References

- Benjamini Y, Hochberg Y: Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J Roy Stat Soc* 57:289–300, 1995.
- Birmaher B, Brent D, Bernet W, Bukstein O, Walter H, Benson R, Chrisman A, Farchione T, Greenhill L, Hamilton J, Keable H, Kinlan J, Schoettle U, Stock S, Ptakowski K, Medicus J: Practice parameters for the assessment and treatment of children and adolescents with depressive disorders. *J Am Acad Child Adolesc Psychiatry* 46:1503–1526, 2007.
- Bridge J, Iyengar S, Salary C, Barbe R, Birmaher B, Pincus, H, Ren L, Brent D: Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: A meta-analysis of randomized controlled trials. *JAMA* 297:1683–1696, 2007.
- Burnier M, Schneider M, Chiolerio A, Stubi C, Brunner H: Electronic compliance monitoring in resistant hypertension: The basis for rational therapeutic decisions. *J Hypertens* 19:335–341, 2001.
- Byerly M, Fisher R, 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.
- Byerly M, Nakonezny PA, Lescouffair E: Antipsychotic medication adherence in schizophrenia. *Psychiatr Clin North Am* 30:437–452, 2007a.
- Byerly MJ, Thompson A, Carmody T, Bugno R, Erwin T, Kashner M, Rush AJ: Validity of electronically monitored medication adherence and conventional adherence measures in schizophrenia. *Psychiatr Serv* 58:844–847, 2007b.
- Cramer J, Rosenheck R: Adherence with medication regimens for mental and physical disorders. *Psychiatr Serv* 49:196–201, 1998.
- Cramer J, Rosenheck R, Kirk G, Krol W, Krystal J: Medication adherence feedback and monitoring in a clinical trial: Predictions and outcomes. *Value Health* 6:566–573, 2003.
- Diaz E, Neuse E, Sullivan MC, Pearsall HR, Woods, SW: Adherence to conventional and atypical antipsychotics after hospital discharge. *J Clin Psychiatry* 65:354–360, 2004.
- Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, Nilsson M, Jacobson, JG: Fluoxetine for acute treatment of depression in children and adolescents: A placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 41:1205–1215, 2002.
- Emslie GJ, Kennard BD, Mayes TL, Nightingale-Teresi J, Carmody T, Hughes CW, Rush AJ, Tao R, Rintelmann JW: Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. *Am J Psychiatry* 165:459–467, 2008.
- Emslie GJ, Rush AJ, Weinberg WA, Kowatch RA, Hughes CW, Carmody T, Rintelmann J: A double-blind, randomized, placebo-controlled trial of fluoxetine in children and adolescents with depression. *Arch Gen Psychiatry* 54:1031–1037, 1997.

- Farmer KC: Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. *Clin Ther* 21:1074–1090, 1999.
- Fotheringham MJ, Sawyer MG: Adherence to recommended medical regimens in childhood and adolescence. *J Paediatr Child Health* 31:72–78, 1995.
- Glazer WM, Byerly MJ: Tactics and technologies to manage non-adherence in patients with schizophrenia. *Curr Psychiatry Rep* 10:359–369, 2008.
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N: Schedule for affective disorders and schizophrenia for school-age children—present and lifetime version (K-SADS-PL): Initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 36:980–988, 1997.
- Kennard BD, Emslie GJ, Mayes TL, Nightingale-Teresi J, Nakonezny PA, Hughes JL, Jones J M., Tao R, Stewart SM, Jarrett RB: Cognitive-behavioral therapy to prevent relapse in pediatric responders to pharmacotherapy for major depressive disorder. *J Am Acad Child Adolesc Psychiatry* 47:1395–1404, 2008.
- Kenward MG, Roger JH: Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics* 53:983–997, 1997.
- Lacro J, Dunn L, Dolder C, Leckband S, Jeste D: Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: A comprehensive review of recent literature. *J Clin Psychiatry* 63:892–909, 2002.
- Liu H, Golin CE, Miller LG, Hays RD, Beck CK, Sanandaji S, Christian J, Maldonado T, Duran D, Kaplan AH, Wenger NS: A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med* 134:968–977, 2001.
- March J, Silva S, Petrycki S, Curry J, Wells K, Fairbank J, Burns B, Domino M, McNulty S, Vitiello B, Severe J: Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for adolescents with depression study (TADS) randomized controlled trial. *JAMA* 292:807–820, 2004.
- Nakonezny PA, Byerly MJ: Electronically monitored adherence in outpatients with schizophrenia or schizoaffective disorder: A comparison of first- vs. second-generation antipsychotics. *Schizophr Res* 82:107–114, 2006.
- Nakonezny PA, Byerly MJ, Rush AJ: Electronic monitoring of antipsychotic medication adherence in outpatients with schizophrenia or schizoaffective disorder: An empirical evaluation of its reliability and predictive validity. *Psychiatry Res* 157:259–263, 2008.
- Osterberg L, Blaschke T: Adherence to medication. *N Engl J Med* 353:487–497, 2005.
- Poznanski E, Mokros H: Children's Depression Rating Scale—Revised (CDRS-R). Los Angeles: WPS; 1996.
- Riekert KA, Froter D: The beliefs about medication scale: Development, reliability, and validity. *J Clin Psychol Med Settings* 9:177–184, 2002.
- SAS Institute Inc: SAS 9.2 (TS1M0). SAS/STAT. Cary, NC: SAS Institute Inc., 2002–2008.
- Tao R, Emslie G, Mayes T, Nakonezny P, Kennard B, Hughes C: Early prediction of acute antidepressant treatment response and remission in pediatric major depressive disorder. *J Am Acad Child Adolesc Psychiatry* 48:71–78, 2009.
- Velligan DI, Lam YW, Glahn DC, Barrett JA, Maples NJ, Ereshefsky L, Miller AL: Defining and assessing adherence to oral antipsychotics: A review of the literature. *Schizophr Bull* 32:724–742, 2006.
- Velligan DI, Wang M, Diamond P, Glahn DC, Castillo D, Bendle S, Lam YW, Ereshefsky L, Miller AL: Relationships among subjective and objective measures of adherence to oral antipsychotic medications. *Psychiatr Serv* 58:1187–1192, 2007.
- Velligan DI, Weiden PJ, Sajatovic M, Scott J, Carpenter D, Ross R, Docherty JP: The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness. *J Clin Psychiatry* 70(Suppl 4):1–46, 2009.
- Wagner GJ, Remien RH, Carballo-Diequez A, Dolezal C: Correlates of adherence to combination antiretroviral therapy among members of HIV-positive mixed status couples. *AIDS Care* 14:105–109, 2002.

Address correspondence to:
Paul A. Nakonezny, Ph.D.
Division of Biostatistics
Department of Clinical Sciences
UT Southwestern Medical Center
6363 Forest Park Road
Suite 651
Dallas, TX 75390-8828

E-mail: paul.nakonezny@utsouthwestern.edu