Medication Adherence and Quality of Life in Pediatric Inflammatory Bowel Disease

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Objective To examine the relationship between medication adherence and quality of life (QOL) in adolescent patients with inflammatory bowel disease (IBD) utilizing a multimethod adherence assessment approach. **Methods** Medication adherence in 36 adolescents with IBD was assessed via interviews, pill counts, and biological assays. QOL was assessed via patient and parent report. Pediatric gastroenterologists provided disease severity assessments. **Results** Hierarchical multiple regression analyses revealed that adherence contributed significant variance to patient-reported QOL but not parent-reported QOL. Nonadherence to 6-MP/azathioprine was related to poorer patient-reported physical health QOL. Greater self-reported 5-ASA adherence was related to poorer overall psychological health QOL, and particularly social functioning QOL. **Conclusions** Results provide preliminary support for the negative effects of 6-MP/azathioprine nonadherence on QOL and an inverse relationship between 5-ASA adherence and QOL in this population. Adherence burden in patients and the utility of multimethod adherence assessment in research are discussed.

Key words adherence; compliance; inflammatory bowel disease; quality of life.

Inflammatory bowel disease (IBD), which encompasses Crohn's disease and ulcerative colitis, affects approximately nine in 100,000 children and adolescents (Lindberg, Lindquist, Holmquist, & Hildebrand, 2000). It is characterized by chronic, intermittent, and unpredictable inflammation of the gastrointestinal tract resulting in symptoms such as recurrent diarrhea, abdominal pain, fatigue, arthritis, growth delay, delayed puberty, and perianal disease (Drossman & Ringel 2003; Mackner & Crandall, 2006). Depending on presenting symptoms, severity of illness, and individual patient's disease course, treatment can involve multiple medications with varying regimens, infusions, dietary changes, and surgery. Medications used in this population may produce undesirable side effects including weight gain, cushingoid appearance, osteopenia/osteoporosis, pancreatitis, immune suppression, and increased risk of cancer (Mackner, Sisson, & Crandall, 2004). IBD patients are often prescribed immunomodulators such as 6-mercaptopurine (6-MP; or azathioprine, which is cleaved to 6-MP) and/or anti-inflammatory agents such as 5-aminosalicylic acid (5-ASA), which have considerably different dosing schedules. Whereas 6-MP/azathioprine dosing is usually once daily with ~1–2 pills, 5-ASA dosing is often three times daily with up to ~4–6 pills each dose. Patients may also experience changes in dosing depending on their response to treatment. Given the complex treatment regimens these patients are often prescribed, it is plausible that this population experiences difficulty adhering to treatment regimens.

Nonadherence is a pervasive and significant behavioral health issue in pediatric chronic illness populations (Berg, Dischler, Wagner, Raia, & Palmer-Shevlin, 1993; Lemanek, 1990; Rapoff, 1999; Sly, 1988), with prevalence rates of ~50% in children (Rapoff & Barnard, 1991) and 65–75% in adolescents (Logan, Zelikovsky, Labay, & Spergel, 2003; Rapoff & Barnard, 1991). Yet, research on medication adherence in pediatric IBD is scant. In a pediatric IBD sample, Mackner and Crandall (2005) reported medication adherence rates of 38–48% according

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to parent and adolescent reports, respectively; family dysfunction and poor patient coping were also associated with nonadherence. Oliva-Hemker and colleagues (Oliva-Hemker, Abadom, Cuffari, & Thompson, 2007) reported adherence rates of 50% for immunomodulators and 34% for mesalamine using pharmacy refill record data, and adherence was related to greater health care utilization. These two studies provide initial adherence data in this population; however, both studies utilized a unimodal assessment of adherence, and neither examined the direct relationship between adherence and disease outcome. Across populations, studies examining disease outcome related to adherence have focused primarily on symptom reduction, with results varying across treatment and assessment methodology. However, the relationship between adherence and global assessments of well-being used to inform treatment recommendations such as quality of life (QOL) has largely been unexamined. Although research indicates that emotional dysfunction (e.g., depression) contributes to poor QOL (Felder-Puig et al., 2006; Goldbeck, Koffmane, Lecheler, Thiessen, & Fegert, 2007), the extent to which disease management behavior is related to patient QOL is unknown. Indeed, Rapoff (1999) indicated that, across pediatric populations, the impact of adherence on QOL is poorly understood and understudied. Moreover, QOL is a particularly important outcome to examine since children might not readily notice gradual reduction in symptoms, but are likely to notice improved physical, emotional, scholastic, and social function.

In an effort to address the aforementioned limitations in the extant research, this cross-sectional study was designed to examine the relationship between medication adherence and both patient and parent ratings of QOL in pediatric IBD, using data from an ongoing longitudinal study. Additionally, this study provides preliminary data on adherence rates in this population using a multimodal adherence assessment method. This assessment approach was chosen because no one measure has been shown to accurately assess adherence in IBD. It was hypothesized that adherence to medication would predict higher patient- and parent-reported QOL and, conversely, nonadherence would predict lower patient- and parent-reported QOL after statistically controlling demographic and behavioral parameters on QOL.

Method

Participants

Inclusion criteria were: (a) diagnosis of Crohn's disease or ulcerative colitis, (b) 13–17 years of age, (c) prescribed 6-MP/azatinoprine and 5-ASA, (d) 6-TGN assay during the previous month, and (e) English fluency; exclusion criteria were: (a) developmental delay, (b) prescribed >1 mg/kg/d corticosteroids, and (c) comorbid chronic illness. Two hundred seventy-one patients were screened for eligibility, and 48 patients met criteria; eight were never reached for recruitment; and four declined participation. A convenience sample of 36 adolescents (22 male, 14 female; M age $= 15.69$ years, $SD = 1.37$ years) with IBD and their parents served as participants. Families were recruited from a gastroenterology clinic in a large children's hospital in the northeastern United States. Average income was \$120,056 ($SD =$ \$61,727.86). The sample was 85% Caucasian, 11% African American, and 4% Hispanic. Demographics of this sample were representative of the clinic population with respect to race, gender, and income.

Measures

A demographic questionnaire assessing family income, parental age, marital status, parental education, and number of family members in the home was completed by parents.

6-thioguanine Nucleotide (6-TGN) Assay

6-TGN (i.e., 6-MP metabolite) assays measure 6-TGN concentration in blood; this served as a biological proxy measure of adherence to 6-MP/azathioprine. 6-TGN levels have been used in prior research to measure adherence to 6-MP/azathioprine in IBD patients (Belaiche, Desager, Horsmans, & Louis, 2001; Cuffari, Seidman, Latour, & Theoret, 1996). Thiopurine methyltransferase (TPMT), which is an enzyme that catalyzes 6-MP/azathioprine to production of methylated mercaptopurines (6-MMP), was tested for each patient prior to treatment initiation to determine appropriate dosing. Therapeutic 6-TGN levels range from 230 to 400 pmol; values below 230 pmol were considered indicative of nonadherence for this study.

Medical Adherence Measure (MAM)

The MAM (Zelikovsky, in press) is a semi-structured interview conducted with patients and parents that quantifies medication adherence. Adherence scores range from 0 to 100%; $<80\%$ of medications taken was used as the cutoff for nonadherence in this study. Patients and parents were interviewed together in this study, and percentage of doses taken was used as the measure of adherence to both 6-MP/azathioprine and 5-ASA. The MAM has demonstrated adequate convergent validity ($r = -.40$, $p < .05$) and test–retest reliability ($r = .89$, $p < .05$; Zelikovsky, 2007).

Pill Counts
Pill counts of all medication prescribed to each patient were conducted. Patients and parents reported number of pills remaining in bottles and other containers (e.g., pill boxes) for each medication, prescription instructions, date prescription was filled, and quantity filled. Adherence to both 6-MP/azathioprine and 5-ASA was calculated as percentage of doses removed/doses prescribed × 100.

Pediatric Crohn's Disease Activity Index (PCDAI)
The PCDAI (Hyams et al., 1991) is a well-validated assessment of disease activity in pediatric patients with Crohn's disease. The scale is scored 0–100 based on subjective criteria (e.g., pain), objective criteria (e.g., physical exam), laboratory findings, and growth parameters. Scores <15, inactive disease; 15–30, mild to moderate disease; and >30, severe disease activity (Otley et al., 1999). Internal consistency (Cronbach, 1951) was .83 in this sample.

Lichtiger Colitis Activity Index (CAI)
The CAI (Lichtiger et al., 1994) is scored 0–21, with higher scores representing more severe disease. It is assessed across eight ulcerative colitis symptoms. Internal consistency was .87 in this sample.

Pediatric Quality of Life Inventory (PedsQL 4.0)
The PedsQL 4.0 (Varni, Seid, & Rode, 1999) is a 23-item measure that evaluates children's QOL across four areas of functioning: physical, emotional, social, and school. Items are reverse scored and transformed to a 0–100 scale, with higher scores representing better QOL. The PedsQL 4.0 has both child- and parent-report forms and is used in children ages 2–18 years. Respondents rate how much of a problem each item has been during the past month on an anchored Likert scale. This measure yields a Total QOL score, two summary scores (i.e., Physical Health Summary Score and Psychological Health Summary Score), and three subscale scores (i.e., Emotional, Social, and School Functioning). The PedsQL 4.0 is a reliable (α child = .88, α parent = .90; Varni, Seid, & Kurtin, 2001) and valid measure of QOL. Internal consistency was .92 for Parent Report and .92 for Teen Report in this sample.

Children's Depression Inventory (CDI)
The CDI (Kovacs, 1992) is a 27-item self-report measure used to assess the severity of major depression symptomatology in children. Each item on the CDI is a group of three statements that combine to measure the severity of a single depressive symptom on a 0–2 scale. The CDI is a reliable (α from .71 to .89) and valid measure of depressive symptomatology in children (Kovacs, 1992). Internal consistency for this sample was .92.

Procedure

This study was approved by the hospital Institutional Review Board. All recruitment and data collection was conducted by the principal investigator or a trained master's level research coordinator who were not members of the treatment team. Eligible patients and their parents were recruited via telephone. A thorough description of the study was provided and informed consent was obtained. Patients and parents provided information for pill counts, and the MAM interview was conducted via telephone; participants were told their responses would not be shared with the treatment team. Disease and medication regimen information and 6-TGN data were obtained via medical chart review. Demographic and behavioral measures were mailed to participants. Each patient's gastroenterologist provided information for disease severity assessments in patients' chart notes, and this data was obtained and recorded by study personnel. Participants were mailed $25 gift cards for compensation.

Data Analyses

PCDAI and CAI scores were combined into one variable representing disease severity. The rationale for this was that the majority of the sample demonstrated mild to moderate or better disease severity and both measures yield continuous scores appropriate for correlational analyses. Descriptive statistics (i.e., *M*, *SD*, percentages) were conducted on demographic, disease related, and behavioral study variables. Subsequently, independent samples *t*-test and bivariate correlations were performed to identify potential covariates for primary analyses. Finally, hierarchical multiple regression analyses examining the contribution of adherence to patient QOL were conducted in order to test the primary hypothesis.

Results

Preliminary Analyses

Disease related and behavioral descriptive data are presented in Table I. Based on a raw score cutoff of 13 or higher on the CDI (Timbremont, Braet, & Dreessen, 2004), 18.5% of the sample demonstrated clinically elevated levels of depression. Independent samples *t*-tests and bivariate correlations were conducted to identify potential covariates for the primary regression analyses. Results revealed no significant differences between male

and female participants on 5-ASA/6-MP-azathioprine pill count, 5-ASA/6-MP MAM, or 6-TGN measures of adherence ($p > .05$) or on PedsQL 4.0 Teen or Parent Report ($p > .05$). Significant correlations between PedsQL 4.0 Parent Report and both CDI depressive symptoms ($r = -.75$, $p < .01$) and patient age ($r = -.48$, $p < .05$) were observed. There was also a significant correlation between PedsQL 4.0 Teen Report and CDI depressive symptoms ($r = -.77$, $p < .01$), 6-TGN adherence ($r = .40$, $p < .05$) and 5-ASA MAM adherence ($r = -.56$, $p < .01$). Pill count adherence scores for 6-MP and 5-ASA were not significantly correlated with Parent or Teen reported QOL. No significant correlations were observed between measures of adherence and depressive symptomatology, age, or disease severity, and disease severity was not significantly correlated with QOL. Variables significantly correlated (i.e., age and CDI depressive symptoms) with either Parent or Teen Report QOL were entered into the primary regression analyses; variables not significantly correlated with Parent or Teen Report QOL were not entered.

Primary Analyses

Two hierarchical multiple regression equations were constructed to test the primary hypothesis. On Step 1 of each equation, age and CDI total score were entered, followed by 6-TGN adherence, 6-MP MAM adherence, and 5-ASA MAM adherence on Step 2. Parent Report Total QOL and Teen Report Total QOL served as the dependent variables for the two regression equations. Results of the first regression revealed that 6-TGN adherence, 6-MP MAM adherence, and 5-ASA MAM adherence contributed nonsignificant variance to Parent Report Total QOL (F change $= .76$, $p > .05$). In contrast, the second regression revealed that these three measures of adherence contributed a significant 19% of unique variance to Teen Report Total QOL after statistically controlling the significant variance accounted for by age and CDI depressive symptomatology (F change $= 5.06$, $p < .01$; see Table II).

Exploratory Analyses

In order to gain a better understanding of how adherence might be specifically related to different aspects of patient-reported QOL in this population, subsequent regression analyses were performed to examine the relationship between adherence and Teen Report PedsQL 4.0 subscale and summary scores. Regression equations were constructed in the same manner as for the primary analyses. Results revealed nonsignificant contributions of 6-TGN adherence, 6-MP MAM adherence, and 5-ASA MAM adherence to variance in the School and Emotional Functioning subscales (F change $= 2.42$ and 0.63, respectively, p's $> .05$). In contrast, 6-TGN adherence significantly predicted

Table I. Descriptive Data for Disease Related and Behavioral Variables

Variable	*M*	Mdn	*SD*	Percentage
IBD diagnosis				
Crohn's disease				86.1%
Ulcerative colitis				13.9%
CAI score	4.20	0	5.85	
PCDAI score	11.37	10.00	9.83	
Inactive disease (<15)				71.0%
Mild to moderate disease (15–30)				22.5%
Severe disease (>30)				6.5%
6-MP				
Prescribed daily dose	1.49	1.50	0.74	
Pill count adherence	62.62%	64.20%	23.42%	
MAM adherence	93.17%	100%	12.57%	
6-TGN level	163.22[a]	151.00[a]	107.54	
5-ASA				
Prescribed daily dose	9.11	9.00	2.76	
Pill count adherence	51.56%	51.39%	25.24%	
MAM adherence	96.99%	98.31%	4.88%	
PedsQL 4.0 Parent Report for Teens				
Total Score	82.69	86.96	13.48	
Physical Health Summary Score	86.23	93.75	12.92	
Emotional Functioning Subscale	77.41	75.00	20.40	
Social Functioning Subscale	86.67	95.00	15.99	
School Functioning Subscale	78.33	85.00	17.87	
Psychological Health Summary Score	80.80	88.33	15.56	
PedsQL 4.0 Teen Report				
Total Score	79.59	79.35	14.32	
Physical Health Summary Score	82.75	84.38	13.10	
Emotional Functioning Subscale	76.30	85.00	19.34	
Social Functioning Subscale	84.26	85.00	16.74	
School Functioning Subscale	73.15	80.00	21.40	
Psychological Health Summary Score	77.90	81.67	17.02	
CDI Total Score	6.70	4.00	7.43	

[a]80.56% of sample at sub-therapeutic level.

Table II. Multiple Regression Analyses Examining the Contribution of Adherence to QOL

Analyses	Step	Variables	β	*t* for within step predictors	R^2 change for step	*F* Change
Primary						
Equation 1 (DV = PedsQL 4.0 Parent Report Total Score)						
	1	Age	−.35	−2.82*	.65	21.16**
		CDI Total Score	−.67	−5.32**		
	2	6-TGN Adherence	.05	.36	.04	.76
		6-MP MAM Adherence	.21	1.33		
		5-ASA MAM Adherence	−.20	−1.22		
Equation 2 (DV = PedsQL 4.0 Teen Report Total Score)						
	1	Age	.02	.16	.55	14.18**
		CDI Total Score	−.75	−5.28**		
	2	6-TGN Adherence	.22	1.81	.19	5.06*
		6-MP MAM Adherence	.03	.22		
		5-ASA MAM Adherence	−.37	−2.49*		
Exploratory						
Equation 3 (DV = PedsQL 4.0 Physical Health Summary Score)						
	1	Age	−.18	−.91	.14	1.80
		CDI Total Score	−.29	−1.49		
	2	6-TGN Adherence	.41	2.27*	.30	3.48*
		6-MP MAM Adherence	−.08	−.36		
		5-ASA MAM Adherence	−.25	−1.11		
Equation 4 (DV = PedsQL 4.0 Emotional Functioning Subscale Score)						
	1	Age	.05	.35	.64	20.17**
		CDI Total Score	−.80	−6.31**		
	2	6-TGN Adherence	.01	.05	.03	.63
		6-MP MAM Adherence	.12	.74		
		5-ASA MAM Adherence	−.23	−1.34		
Equation 5 (DV = PedsQL 4.0 Social Functioning Subscale Score)						
	1	Age	.18	1.25	.54	13.29**
		CDI Total Score	−.74	−5.14**		
	2	6-TGN Adherence	.12	1.01	.21	5.43**
		6-MP MAM Adherence	.09	.62		
		5-ASA MAM Adherence	−.48	−3.22**		
Equation 6 (DV = PedsQL 4.0 School Functioning Subscale Score)						
	1	Age	.06	.41	.48	10.54**
		CDI Total Score	−.70	−4.58**		
	2	6-TGN Adherence	.16	1.11	.14	2.42
		6-MP MAM Adherence	−.01	−.04		
		5-ASA MAM Adherence	−.31	−1.70		
Equation 7 (DV = PedsQL 4.0 Psychological Health Summary Score)						
	1	Age	.10	.88	.69	25.20**
		CDI Total Score	−.84	−7.09**		
	2	6-TGN Adherence	.11	1.08	.13	4.77*
		6-MP MAM Adherence	.07	.60		
		5-ASA MAM Adherence	−.37	−2.97**		

*$p < .05$; **$p < .01$.

variance in the Physical Health Summary Score ($t = 2.27$, $p < .05$), and 5-ASA MAM adherence predicted significant variance in the Psychological Health Summary Score ($t = -2.97$, $p < .01$). Moreover, within the Psychological Health Summary Score, only the Social Functioning subscale ($t = -3.22$, $p < .01$) was significantly predicted by 5-ASA MAM adherence. Finally, 6-MP MAM adherence was a nonsignificant predictor (Table II).

Discussion

Although adherence and parent-reported QOL were not correlated, results partially supported the primary hypothesis in that 6-MP/azathioprine nonadherence as measured by sub-therapeutic 6-TGN levels was significantly related to poorer patient-reported physical health QOL. This is plausible given that one might expect that nonadherence to result in poorer disease functioning and, consequently, poorer physical health perceptions. Disease severity in this sample was primarily mild to moderate or better, and disease severity was not related to the PedsQL 4.0 Total score. However, compared with other subscales on the PedsQL 4.0 the Physical Health Summary Score might be particularly sensitive to significant nonadherence in this population, which would explain why the measure resulting in the highest estimates of nonadherence in this study (i.e., 6-TGN assays) was the only measure related to physical health QOL. Nevertheless, this issue warrants further investigation.

Interestingly, greater self-reported adherence to 5-ASA medication was related to poorer overall psychological health QOL, and particularly social functioning QOL; however, this measure of adherence was not related to emotional or school functioning QOL. Moreover, while self-report adherence to 5-ASA medications was related to poorer QOL, self-report 6-MP/azathioprine adherence was not. Importantly, self-report assessments can result in inflated adherence estimates (Rapoff, 1999). However, a considerable attribute of self-report adherence assessments is that they provide information about a patient's *perception* of his/her adherence. Thus, given the mean differences in daily dose of 6-MP ($M = 1.49$) and 5-ASA ($M = 9.11$), the current findings suggest that the perception of taking multiple pills is related to poorer QOL in this population, or that adherence to more complex (i.e., greater number of pills and/or doses per day) medication regimens might be associated with poorer QOL than less complex regimens. Further, better perceived adherence may not lead to any discernable improvement in disease functioning, resulting in poorer perceived QOL. These findings also highlight the saliency and sensitivity of social functioning in IBD (Mackner & Crandall, 2006) and the potential relationship between treatment regimen factors (e.g., regimen complexity) and social functioning. Indeed, complex regimens could require patients to engage in treatments in the presence of peers at times, which might result in negative self-evaluations of social competence and acceptance. This, however, requires further investigation.

The inverse relationship between self-report adherence and QOL is supported by a recent study in children with sickle cell disease (Barakat, Lutz, Smith-Whitley, & Ohene-Frempong, 2005), which examined provider and parent estimates of adherence and found that greater adherence was significantly related to poorer overall QOL. The authors speculated that socioeconomic status (SES), volitional nonadherence, and interference in activities due to treatment adherence might have accounted for the inverse relationship. Given the middle to upper middle class SES of our sample, it is unlikely that SES played a role in the current findings. Volitional nonadherence might have influenced these results; however, this was not specifically assessed. Yet, similar to the sickle cell sample, our patients might have experienced disruption in desired activities resulting from dosing schedules involving multiple pills and doses per day. Although speculative, it is plausible that patients perceive adherence to medical regimens as burdensome to some extent, resulting in poorer patient QOL. This is consistent with an inverse relationship between routine burden and QOL reported in asthma patients (Fiese, Wamboldt, & Anbar, 2004).

Another important observation of this study concerns the use of a multimethod adherence assessment approach. Use of this methodology is exploratory at this stage in adherence research, but such an approach has merit. For example, use of this method in the present study highlights the potential variation in adherence measures and might reveal subtle yet salient relationships between adherence and disease outcomes such as QOL that could go unnoticed with unimodal adherence assessment. Clearly, this methodology warrants further utilization to determine which measures and combinations of measures best represents patient adherence and concomitant disease outcomes.

This preliminary study is limited by the modest sample size, which precludes broad generalization. In addition, although the SES of this sample is similar to other recent research in pediatric IBD (Mackner & Crandall, 2005), it might not represent the IBD population in general. However, it is possible that SES of the IBD

population is negatively skewed compared with other disease populations, as IBD primarily afflicts Caucasians (CCFA, 2008). Nevertheless, this must be considered when interpreting these findings. Also, the current study did not include electronic monitoring of adherence, which can provide considerable details about adherence behavior (e.g., timing and frequency of presumed consumption) that other measures cannot (Rapoff, 1999). However, this study utilized a multimethod assessment approach comprised of measures that are more likely to be used in actual clinical settings. Finally, 6-TGN levels are limited as adherence indicators as they are subject to pharmacokinetic variation and drug metabolism in patients. Further, TPMT activity and liver functioning tests were not conducted simultaneously with 6-TGN assays to examine potential pharmacokinetic interference. These factors might help explain the high percentage of participants who exhibited subtherapeutic 6-TGN values, though this is speculative given that the extent to which TMPT activity interferes with 6-TGN metabolite measurement has not been empirically examined. Results of 6-TGN values as adherence markers must be taken with considerable caution given that this measure quantifies concentration of only one 6-MP/azathioprine metabolite in blood, and does not quantify actual pill consumption.

Although clinical implications from this preliminary data would be premature, providers and patients might benefit from discussing the potential impact of patients' treatment regimens on overall functioning. Future replication is needed in larger samples utilizing longitudinal designs to determine directionality and stability of the findings in this study. In addition, multimethod adherence assessment should be examined in future studies to examine the efficacy of particular measures or combination of measures in assessing adherence in this population. Issues pertaining to adherence burden should also be examined in relation to various medications and dosing schedules. Finally, the impact of adherence/nonadherence on disease outcomes should continue to be a focus of research in order to better understand the impact of this disease management behavior on patient well being.

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