Barriers to Oral Medication Adherence for Adolescents with Inflammatory Bowel Disease

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Objective To identify family-reported, adherence-related barriers for adolescents with inflammatory bowel disease (IBD) and examine their relationship to 6-MP/azathioprine and 5-ASA medication adherence. Methods Participants included 74 adolescents, aged 13–17 years, diagnosed with IBD and their caregivers. Adolescents and caregivers jointly completed a measure of barriers to medication adherence. Adherence to medication was measured by family-report, pill-count, and serum assay. Results Families endorsed one to seven total barriers to medication adherence. The most commonly reported barriers included forgetting, being away from home, and interference with an activity. Neither demographic nor disease severity variables were related to the total number of reported barriers. Fewer total reported barriers was related to better adherence by adolescent and maternal report. Conclusion Most families experience at least one barrier to treatment adherence. Effective problem-solving around these barriers and its integration into future treatment protocols may help improve medication adherence in the pediatric IBD population.

Key words adherence; barriers; Crohn’s disease; pediatric; ulcerative colitis.

While still a relatively new area of study, a large body of literature has recently developed documenting rates of adherence to medical regimens across pediatric populations. Reviews suggest adherence rates range from 50% to 55% across various pediatric chronic illness groups (Rapoff, 1999; Rapoff & Barnard, 1991). Interestingly, disease self-management is a particular problem during adolescence, when adherence to treatment regimens often declines (Smith & Shuchman, 2005). Of note, developmental demands during this period (e.g., decline in parental supervision, peer influences, and increase in autonomy) likely contribute to higher rates of adherence-related difficulties (Anderson, Ho, Brackett, Finkelstein, & Laffel, 1997; Butner et al., 2009; Stewart & Dearmun, 2001). Understanding how youth and families follow prescribed regimens during adolescence has significant implications for both treatment effectiveness and long-term health outcomes (Fotheringham & Sawyer, 1995; Higgins, Rubin, Kaulback, Schoenfield, & Kane, 2009; Osterberg & Blaschke, 2005; Smith & Shuchman, 2003).

Adherence is especially important for youth diagnosed with Crohn’s disease and ulcerative colitis (UC), collectively referred to as inflammatory bowel disease (IBD), where even lower rates of adherence have been documented. Affecting approximately 71 of every 100,000 youth (Kappelman et al., 2007), IBD is a chronic disease characterized by intermittent inflammation of the gastrointestinal tract. Previous research describes rates of
nonadherence ranging from 50% to 88% (Hommel, Mackner, Denson, & Crandall, 2008; Mackner & Crandall, 2005; Oliva-Hemker, Abadom, Cuffari, & Thompson, 2007). The unpredictable nature of IBD treatment, disease severity, side-effects and symptoms, and prognosis likely impact youth’s overall behavioral functioning (Mackner, Crandall, & Szigethy, 2006). In addition, while no data are currently available in the pediatric population, research suggests that non-adherent adults diagnosed with IBD are 5.5 times more likely to experience relapse (Kane, Huo, Aikens, & Hanauer, 2003) and have 12.5% higher annual healthcare costs (Higgins et al., 2009) compared to adherent patients. Taken together, the documented rates of nonadherence, unpredictable nature of the disease, and significant health risks and costs associated with nonadherence in IBD suggest that greater understanding of adherence in this population is a critical need.

While a number of models to understand nonadherent behavior have been proposed, the health belief model has gained increasing support in pediatric populations (Bush & Iannotti, 1990). This model posits that an individual’s perceived risk, consequences, benefits, barriers, and cues each impact adherence-related behaviors. Thus, one of the key components in planning effective interventions to improve treatment adherence is appropriately addressing perceived barriers to treatment regimens (Lemanek, Kamps, & Chung, 2001). While previous research suggests that behavioral and multi-component interventions are often effective in improving adherence-related behaviors (Drotar, 2000; Kahana, Drotar, & Frazier, 2008), understanding the key barriers to treatment recommendations is a critical step in planning and implementing such interventions and, perhaps, preventing nonadherence relapse.

Research in other pediatric populations provides preliminary information regarding possible barriers to adherence in pediatric chronic illness. For example, forgetting (Burgess, Sly, Morawska, & Devadason, 2008; Marhefka et al., 2008; Modi et al., 2009; Modi & Quittner, 2006; Zelikovsky, Schast, Palmer, & Meyers, 2008) is a frequently cited barrier across pediatric asthma, cystic fibrosis (CF), human immunodeficiency virus (HIV), sickle cell disease (SCD), and kidney transplant; however, specific barriers often vary depending on the population studied. Multiple barriers are often reported by patients across populations, where the higher number of reported barriers is related to greater difficulty adhering to medical regimens (Marhefka et al., 2008; Modi & Quittner, 2006). Unfortunately, no studies are currently available that document specific barriers within the pediatric IBD population or the relationship between such barriers and treatment adherence. Given its implications for effectively tailoring adherence-related interventions in this population, understanding the specific barriers to treatment adherence in IBD is needed.

The current study documented family-reported barriers to medication adherence and examined their relationship with adolescents’ medication adherence. It was hypothesized that fewer reported barriers would be related to better medication-related adherence as measured by self-report, pill count, and serum assay.

Method
Participants and Procedures
The current study is part of a larger, longitudinal project examining adherence-related behaviors in pediatric IBD. A total of 74 adolescents (ages 13 to 17) diagnosed with either Crohn’s disease or UC (collectively IBD) and their primary caregivers participated in the current study. All adolescents were receiving care at one of two pediatric IBD centers in the Northeast or Midwest regions of the United States. Inclusion criteria required that the adolescent was 13–17 years of age and currently prescribed a 5-aminosalicylic acid (5-ASA) and/or 6-mercaptopurine (6-MP)/azathioprine. Potential participants were excluded if the adolescent (a) was diagnosed with a neurocognitive disorder that would limit their ability to understand or complete measures, (b) was prescribed a current regimen including greater than 1 mg/kg/day of corticosteroids (due to increased risk of behavioral and psychiatric issues [Kayani & Shannon, 2002; Soliday, Grey, & Lande, 1999]), (c) was diagnosed with a comorbid chronic illness, or if the adolescent or caregiver (d) was not fluent in English. Of the 117 patients who were eligible, 88 were able to be contacted for recruitment and 14 declined to participate (due to blood draw requirement, not enough time, and/or not interested in participating in research), resulting in a final sample of 74 adolescents and their parents. Study personnel recruited potential participants in person or by phone to obtain informed consent from caregivers and assent from adolescents. In addition to adolescent- and caregiver-completed questionnaires, adolescents underwent an intravenous blood draw for a 6-thioguanine nucleotide (6-TGN)/6-methylmercaptopurine nucleotide (6-MMPN) assay. Families were compensated $25 for participation. The hospitals’ Institutional Review Boards approved all study procedures.
Measures

Family Demographic Questionnaire
The adolescent’s primary caregiver completed a study-specific, parent-report questionnaire to obtain family demographic data.

Medical Adherence Measure
The Medical Adherence Measure (MAM; Zelikovsky & Schast, 2008) is a semi-structured interview assessing medication knowledge (e.g., regimen), adherence behaviors (e.g., frequency medication is missed or late), organizational systems (e.g., where medication is stored, who supervises medication), and barriers related to illness management. The measure includes 12 commonly identified barriers to medication adherence. Respondents answer yes or no if they perceive each item to be a barrier to medication adherence. For the current study, consensus between parents and adolescents was obtained on all preceding items. The measure also asks respondents to report the number of doses of medication they have missed in the past 7 days and includes a one-item, patient and parent-reported assessment of medication adherence on a 0 (usually miss) to 10 (rarely miss) point Likert scale. Consensus was not required for this item. Research personnel administered the measure jointly to adolescents and caregivers. The MAM has demonstrated adequate reliability and validity in other pediatric populations (Zelikovsky & Schast, 2008; Zelikovsky et al., 2008).

Pill Count
During the clinic visit (or by parent via telephone within 48 hr of the clinic visit if the patient did not bring his/her medications to clinic) study personnel conducted pill counts of 5-ASA and/or 6-MP/azathioprine prescribed to the patient. Previous research supports the validity of pill count via telephone (Pieper, Rapoff, Purviance, & Lindsey, 1989). No significant differences were found between pill count by study personnel compared to pill count by parent via telephone (p > .05). Adherence was calculated as: the number of pills taken/number of pills prescribed ×100, where higher values indicate better adherence. Similar to other studies, the minimum/maximum adherence rate was restricted to 0–100% (Modi & Quittner, 2006) to minimize error resulting from dumping and/or combining of pills for each medication.

Serum Assay
Adolescents currently prescribed 6-MP/azathioprine underwent an intravenous blood draw (5 cc) for a 6-TGN/6-MMPN assay. Preliminary research in this area supports the use of these assays as exploratory biological proxy measures of adherence to 6-MP/azathioprine in individuals diagnosed with IBD (Belaiche, Desager, Horsmans, & Louis, 2001; Hommel, Davis, & Baldassano, 2008). Therapeutic (i.e., adherent) 6-TGN levels range from 230–450 pmol, while 6-MMPN levels above 5,700 pmol indicate greater risk for hepatotoxicity (Mardini & Arnold, 2003).

Pediatric Crohn’s Disease Activity Index
The Pediatric Crohn’s Disease Activity Index (PCDAI; Hyams et al., 1991), is a measure of disease severity for youth diagnosed with Crohn’s disease. The measure includes eight items (history, physical examination) and one laboratory test (albumin) rated on a three-point scale (0, 5, or 10) and two additional laboratory tests [hematocrit (CBC), erythrocyte sedimentation rate (ESR)] rated on a separate three-point scale (0, 2.5, or 5). If not already done for clinical purposes, the CBC, ESR, and albumin were also completed for patients. PCDAI scores range from 0 to 100 with higher scores indicating more active disease. The measure has demonstrated good validity and reliability (Hyams et al., 1991, 2005). Study personnel completed the PCDAI using data obtained from patient chart notes and laboratory values. Reliability for the current sample was adequate (α = .83).

Lichtiger Colitis Activity Index
The Lichtiger Colitis Activity Index (LCAI; Lichtiger et al., 1994) is a measure of disease severity in UC. The measure includes eight items (stools, pain, well-being, etc.). Scores range from 0 to 21 with higher scores indicating more active disease. The measure has demonstrated good validity and reliability in pediatric samples (Fanjiang, Russell, & Katz, 2007; Lichtiger et al., 1994). Study personnel completed the LCAI using data obtained from patient chart notes. Reliability for the current sample was adequate (α = .81).

Statistical Analyses
Descriptive statistics (means, standard deviations, frequencies) were conducted across variables of interest. To examine possible relationships to demographic characteristics, t-tests or correlations were used as appropriate for dichotomous and continuous variables. Bivariate Pearson correlations were used to test for significant relationships between the number of reported barriers and adherence frequency rates (i.e., percent of consumed doses). Given the number of comparisons conducted, a Bonferroni correction was employed, in which significance was adjusted to the p < .01 level to avoid type 1 error. Adherence and
disease-severity measures were treated as continuous variables for analyses. All analyses were conducted in SPSS 15.0 for Windows (SPSS Inc., 2007).

Results

Demographic Characteristics
Adolescents ranged in age from 13 to 17 years (14.97 ± 1.48 years), were 41.9% female, and predominantly of white, non-Hispanic origin (78.4% white, 8.1% African American, 2.8% other, 10.7% missing). The majority of adolescents were diagnosed with Crohn’s disease (81.1% Crohn’s disease, 18.9% UC). Mean disease severity was in the inactive range for youth diagnosed with Crohn’s disease (PCDAI = 11.1 ± 9.8) and for youth diagnosed with UC (LCAI = 2.9 ± 3.9). Caregivers were primarily mothers (68.9% mothers, 6.8% fathers, 1.4% other, 22.9% missing). Most mothers (74.3% married, 10.8% divorced/separated, 4.1% other, 10.8% missing) and fathers (78.4% married, 8.1% divorced/separated, 1.4% other, 12.1% missing) were currently married. Median reported annual family income was $75,001–$100,000.

Medical Regimen Characteristics
In regard to timing of doses, 39.2% of families reported most often missing morning doses of medication, 33.8% reported most often missing bedtime doses, and 32.4% reported most often missing afternoon doses of medication. Most families reported keeping medication on a special shelf or cabinet (91.9%) and almost half of families described using a pill box (44.6%) to organize medications. Medical regimen characteristics are further summarized in Table I.

Medication Adherence
Reported adherence ratings were similar across informant: adolescent (8.5 ± 1.4), mother (8.8 ± 1.2), and father (9.1 ± 0.9). Adherence ratings by family-reported missed doses ranged from 52.4 to 100% (94.7 ± 11.2) for 6-MP/azathioprine and 75.0 to 100% (96.8 ± 4.9) for 5-ASA. Pill count adherence ratings ranged from 0% to 100% (64.4 ± 28.3) for 6-MP/azathioprine and 1.7 to 100% (62.1 ± 27.5) for 5-ASA. Exploratory analyses revealed significantly higher adherence by family-report compared to pill count for both 6-MP/azathioprine (p < .001) and 5-ASA (p < .001). 6-TGN levels ranged from 3.0 to 825.0 (180.0 ± 138.2), and only 13.5% of adolescents fell in the therapeutic range. 6-MMPN levels ranged from 190.00 to 11,865.00 (2,362.8 ± 2,704.5), and 6.8% of adolescents demonstrated elevated levels.

Table I. Medication Regimen Characteristics

<table>
<thead>
<tr>
<th>Time of day families perceive a dose is most often missed</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Morning</td>
<td>39.2</td>
</tr>
<tr>
<td>School/Lunch</td>
<td>9.5</td>
</tr>
<tr>
<td>Afternoon</td>
<td>32.4</td>
</tr>
<tr>
<td>Dinner</td>
<td>12.2</td>
</tr>
<tr>
<td>Bedtime</td>
<td>33.8</td>
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<table>
<thead>
<tr>
<th>Medication organization system</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pill box</td>
<td>44.6</td>
</tr>
<tr>
<td>Special shelf/cabinet</td>
<td>91.9</td>
</tr>
<tr>
<td>Refrigerator</td>
<td>4.1</td>
</tr>
<tr>
<td>Plastic bag</td>
<td>4.1</td>
</tr>
<tr>
<td>In room</td>
<td>5.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary person responsible for ensuring medication is taken</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent</td>
<td>45.9</td>
</tr>
<tr>
<td>Mother</td>
<td>48.6</td>
</tr>
<tr>
<td>Father</td>
<td>5.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Person responsible for having/ordering medication</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescent</td>
<td>27.0</td>
</tr>
<tr>
<td>Mother</td>
<td>89.2</td>
</tr>
<tr>
<td>Father</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*Adds up to >100%; family able to select more than one choice.

Barriers to Medication Adherence
Overall, families endorsed one to seven total barriers to medication adherence (2.9 ± 1.4). The most commonly reported barriers included: forgetting (87.8%), being away from home (47.3%), interference with an activity (44.6%), refusal/defiance (17.6%), ran out/didn’t fill (16.2%), not feeling well (16.2%), and belief that medication is not necessary (14.9%). Family-reported barriers to medication adherence are further summarized in Table II.

Neither demographic (age, gender, minority status) nor disease severity variables were related to the total number of barriers reported. As shown in Table III, significant correlations were found between total number of barriers reported and adolescent (p < .001) and maternal reports of adherence (p < .001), such that fewer total reported barriers was related to better adherence. The relationship between total reported barriers and 6-MP/azathioprine self-reported missed doses on the MAM (p < .05) approached significance and the 5-ASA pill count (p < .01) was significant in the expected direction.

Discussion
The current study is the first to examine disease-specific, family-reported barriers to medication adherence in a sample of adolescents diagnosed with IBD. These findings...
partially supported the primary hypothesis in that a significant relationship was observed between fewer total perceived barriers by family-report and better adolescent and maternal-reported adherence. This is similar to studies examining the relationship between total number of perceived barriers and adherence in other populations (Modi & Quittner, 2006; Zelikovsky et al., 2008) and emphasizes the importance of addressing perceived barriers in future interventions designed to improve adherence in this population. Of note, the current relationship between number of reported barriers and adherence was statistically significant in relation to maternal- and adolescent-reported medication adherence. This is understandable given that family-reported, perceived barriers were used to examine barriers to treatment adherence. It is also likely that total reported barriers do not correlate perfectly with adherence. For example, anecdotal experience suggests that some families may adaptively cope with a number of barriers while other families struggle and exhibit lower adherence rates when coping with only a single barrier. Both active (e.g., refuse to take) and passive (e.g., forgetting) barriers were measured in the current study and collapsed into a single barrier variable. It may be that certain types of barriers differentially impact overall adherence-related behaviors. In addition, shared method variance may also potentially explain statistically significant findings between family-reported total barriers and maternal- and adolescent-reported medication. Salient correlation trends at the $p < .05$ level were also found between total reported barriers and family-reported missed doses of 6-MP/azathioprine on the MAM and objectively measured 5-ASA pill count adherence. Although not related
to barriers, serum assay measures of adherence were modestly correlated with maternal ratings of adherence. While still a relatively novel measure of treatment adherence in this population, these results provide support for the continued exploration of the utility of serum assays as measures of adherence in the pediatric IBD population. Certainly, these findings speak to the continued importance of using multiple methods to assess adherence in order to gain the most comprehensive adherence data (Quittner, Espelage, Levers-Landis, & Drotar, 2000), especially given that no single “gold-standard” of adherence is yet available. Additionally, varying rates of adherence were found using different methodologies in the current study. For example, results suggest that families over-estimate rates of adherence compared to adherence by pill counts and that assays are not significantly correlated with pill counts. While, pharmacokinetics and variation in individual metabolism rates may help to explain some of these differences (Hommel, Davis et al., 2008), research is needed to examine methods of combining data from different adherence assessments to capitalize on strengths of each measure and improve overall accuracy of adherence measurement in this population.

Findings also suggest that all families of adolescents diagnosed with IBD experience at least one barrier to medication adherence. Not surprising, forgetting was the most often endorsed barrier to adherence in this sample. While this finding is similar to studies examining perceived barriers in other pediatric disease groups (Burgess et al., 2008; Marhefka et al., 2008; Modi & Quittner, 2006; Zelikovsky et al., 2008), forgetting may be a difficult barrier to target through intervention. Moreover, it is plausible that forgetting is indicative of another underlying barrier to medication adherence experienced by the individual in question. For example, an adolescent may “forget” to take their morning dose of medication after rushing out the door to catch the school bus. The target of intervention is likely not improving specific memory skills to decrease forgetting, but rather problem-solving with the family to increase the amount of time the teenager has in the morning to provide ample opportunity to take the prescribed medication dose. Introduction of other cues (i.e., electronic monitoring, cell phone reminders) to remind adolescents to take medications at specific times may also prove useful in helping families to address this barrier.

Results also provide additional descriptive information regarding medication management that may be related to subsequent adherence. For example, almost half of families described using a pill box, suggesting that many families are making concerted attempts to organize medications. It may be that the medical team provided education regarding management or recommended strategies (i.e., pill box) to improve adherence; however, as this was not assessed, further discussion regarding the motivation or reasons behind choosing these strategies is not possible. Interestingly, the timing of specific missed doses was relatively similar across the day. While greater difficulty with specific doses seems reasonable, it seems that for this sample, adolescents have difficulty taking their medication regardless of the timing of a particular dose. Future research will help clarify whether specific dose characteristics (e.g., timing of dose, number of doses) are also perceived as possible barriers to medication adherence. In addition, families were divided in regard to who takes primary responsibility for making sure medication is taken, the adolescent or the mother. Similarly, almost one third of adolescents were taking primary responsibility for ordering their medication. These two findings have important implications regarding division of responsibility for disease management tasks. Previous research in other pediatric disease groups suggests that continued parental involvement in disease management is essential to maintaining appropriate adherence and that premature transition of responsibility from parent to adolescent for disease management tasks may result in decreased adherence over time (Ellis et al., 2007; Wysocki et al., 1996). Future research should further examine the contribution of specific organizational strategies and issues concerning transfer of responsibility for disease management tasks as they relate to medication adherence in this population.

Overall, this is the first study to examine the relationship between reported barriers and medication adherence by adolescents with IBD. Strengths of this study include: (a) multi-site data collection, (b) multiple methods of adherence assessment, (c) use of a previously validated measure of barriers to adherence in pediatric chronic illness, and (d) inclusion of both adolescents and their parents. Of course, this study is not without limitations. First, these cross-sectional findings speak to the relationship between total number of perceived barriers and medication adherence, but do not indicate causality. Future longitudinal research will need to examine whether decreasing number of perceived barriers to medication management results in subsequent improvements in adherence-related behavior. Second, the measure used to identify barriers utilized a forced-choice format of commonly endorsed barriers related to adherence. Use of an open-ended interview format for qualitative data analyses may have provided greater breadth of data in regard to specific barriers that individual family’s experience. In addition, consensus regarding responses was obtained. Different responses may have occurred if parents and
adolescents were interviewed separately. Future research will help determine possible differences in perceived barriers by informant. Third, despite multi-site data collection, the sample recruited was mostly white and reported a median family income of $75,001–$100,000. While representative of other recent studies in pediatric IBD (Mackner & Crandall, 2007), the current data may not easily generalize to minority and/or low income families in this population. Certainly, socio-economic issues known to impact adherence in other populations (Bender & Bender, 2005) may also impact number of perceived barriers and/or adherence in adolescent IBD. Similarly, the majority of the sample reported inactive disease; restriction of range may have limited the ability to detect significant relationships between total barriers and disease severity and should be further explored in future research.

Despite the preliminary nature of the current data, these findings provide initial support for a relationship between barriers and adherence behaviors and may be helpful for providers seeking to identify possible barriers to treatment adherence. Interventions that effectively target adherence in pediatric IBD may benefit from tailoring specific intervention components to address the unique barriers faced by individual families. For example, behavioral family systems therapy (BFST; (Harris, Freeman, & Beers, 2009; Robin & Foster, 1989; Wysocki et al., 2006) is one example of a family-based intervention that may help families of adolescents diagnosed with IBD effectively problem-solve around barriers impacting medication adherence. Interventions such as BFST provide for the individualization of treatment to meet a family’s unique needs and address specific barriers that exist for different families. Certainly, current findings suggest important directions for future research in: (a) effective identification and reduction of the most salient barriers for families within future interventions, (b) the continued validation of measures of adherence in pediatric IBD and (c) further examination of specific treatment-related barriers to adherence, especially in this high-risk adolescent age group. Of course, barriers are one of many factors that affect adherence in pediatric disease groups. However, given the current results, disease-specific barriers to treatment regimens should be given appropriate consideration as researchers plan and implement interventions targeting adherence within the IBD population.

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**References**


Bender, B. G., & Bender, S. E. (2005). Patient-identified barriers to asthma treatment adherence: Responses to interviews, focus groups, and questionnaires. *Immunology and Allergy Clinics of North America, 25*(1), 107–130.


