Pediatric inflammatory bowel disease: Diagnostics, treatment and psychosocial consequences
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Adherence to oral maintenance treatment in adolescents with inflammatory bowel disease

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Submitted
ABSTRACT

Objectives: To systematically review the rates of non-adherence to oral maintenance treatment in adolescents with inflammatory bowel disease (IBD), and to describe perceived barriers to adherence and psychosocial factors involved.

Design: Systematic review

Data sources: Studies published in Medline, Embase and Psychinfo up to December 2012.

Inclusion criteria: Studies that had collected data on adherence to thiopurines or aminosalicylates in a cohort of adolescents with IBD. Case reports and case series were excluded.

Results: 19 studies were included. Lack of uniformity of outcome measures made pooling of data impossible. Rates of medication non-adherence ranged from 3 to 73%. The most frequently reported barriers were 'just forgot', 'wasn’t home' and 'interferes with activity'. Family dysfunction, peer victimization, poor health related quality of life, poor child coping strategies, anxiety and depressive symptoms were associated with medication non-adherence.

Conclusions: Non-adherence to oral maintenance therapy in adolescents with IBD is a significant health care problem. Difficulties in family and social interactions, as well as psychosocial dysfunction can jeopardize IBD treatment outcome and should receive attention early in the course of disease.

Impact on clinical practice: Insufficient response to oral maintenance treatment that is actually due to non-adherence can lead to unnecessary escalation in therapy.
INTRODUCTION

Inflammatory bowel disease (IBD) is a lifelong disease, characterized by chronic relapsing inflammation of the gastrointestinal tract, comprising two major disorders: Crohn’s disease (CD) and ulcerative colitis (CU). IBD is characterized by intermittent and unpredictable symptoms like abdominal pain, diarrhea and fatigue. IBD disease management involves multiple medications with varying regimes, dietary modifications (nutritional therapy in CD) and in some cases surgical interventions. International guidelines advocate a so-called step-up approach, with the least toxic drugs prescribed in the first instance. If these drugs fail to sustain remission (or significant side effects occur) than more expensive and toxic agents may be prescribed. If this is done without first reviewing adherence to first line medication, the arsenal of effective drugs quickly becomes exhausted.

Adolescents are known to be the least adherent group of patients in pediatrics (1). There is, however, no gold standard for the measurement of non-adherence and each method of adherence assessment has its limitations and strengths (2). Subjective methods are the self-reported or parent-reported adherence surveys. They provide an abundance of data regarding timing, frequency and patterns of non-adherence. However, they are limited by potential response bias and recall bias. Objective methods are pill count, pharmacy refill records and biological assays. Pill counts are fairly accurate and easy to use in a clinical setting, but they can easy be manipulated, both negatively and positively and it doesn’t guarantee consumption. The strength of using refill data is that one can obtain information about medication use during a time period when the patients and their families were not aware that adherence was being evaluated. However, pharmacy records do not guarantee the adolescents actually consumed the prescribed medications and non-adherence can be underestimated by recent/ large refills. A medication monitoring system which records the date and time of each pill bottle opening can increase objectivity of medication adherence. However, they can malfunction and only confirm opening of the device rather than medication ingestion. Biological assay, concerning 6-thioguanine (6-TG) levels, can be done in adolescents who are currently prescribed thiopurines (6-mercaptopurine/azathioprine). Serum assays are feasible, but expensive, are limited in quantifying adherence and can be manipulated by patient-initiated dosing changes. Furthermore, bioassays are subject to pharmacokinetic and pharmacodynamic variations. Therefore, sub-therapeutic 6-TG levels are not always the result of non-adherence. Cases in which both 6-TG and 6-MMP levels are sub-therapeutic/ unquantifiable likely indicate non-adherence.

There is a growing interest in medication adherence in patients with chronic disease. The purpose of this article is to provide a systematic review of the literature concerning medication adherence in adolescents with IBD. We focussed on rates of non-adherence.
for oral maintenance therapy (thiopurines or aminosalicylates) in adolescents with IBD, perceived barriers to treatment adherence and the psychosocial factors involved.

**METHODS**

**Identification of studies**
We searched for studies published in Medline, Embase and Psychinfo up to December 2012. The search strategy was [adherence or compliance] AND [adolescent* or teen* or child* or pediatric*or paediatric*] AND [Crohn* or ulcerative colitis or inflammatory bowel disease]. We restricted our search to studies published in English only. For further relevant studies we checked the reference lists of identified studies. All potentially relevant studies were retrieved as full papers.

**Study selection**
Two reviewers (LMS, TZH) independently screened all abstracts of identified published articles for eligibility using the following inclusion criteria.

1. Study examined data from original research. Case reports and case series were excluded.
2. The study population consisted of adolescents aged 12-18 years.
3. Participants had a medically confirmed diagnosis of CD, UC, or indeterminate IBD.
4. Outcome measures included medication adherence rates, as part of a study or as an outcome of intervention in a treatment study.
5. The medication regimen included oral thiopurines (6-mercaptopurine/azathioprine) and/or aminosalicylates (5-aminosalicylic acid).

Any disagreements regarding the inclusion of articles were resolved by discussion.

**Quality assessment and data extraction**
Study quality was assessed by using a previously published checklist for the evaluation of observational studies (3). Each item was scored as “yes,” “no,” or “unclear.” We did not calculate summary scores because their interpretation is problematic and potentially misleading. From the checklist we chose six of the best differentiating items (table 1).

- **Study participants:**
  
  *Criteria for inclusion:* Were the criteria for inclusion of subjects described?
  
  *Generizability:* Have the demographic characteristics of the study sample clearly been described and do they represent the IBD population?
• **Validity and reliability testing:** Have the laboratory tests, instruments and/or questionnaires to measure medication adherence rates and factors affecting medication adherence undergone validity and reliability testing?

• **Design-specific sources of bias:** If bias was decreased by using a multi-method medication adherence assessment we scored this item as ‘no’. Studies scored ‘yes’ if only one method of adherence assessment was used. Selection bias was not taken into account because this was present in most studies as adolescent who are non-adherent will participate less often.

• **Control of confounding:** Studies scored ‘yes’ if in the statistics paragraph or in the results section assessment of control of confounders was mentioned. If only univariate or bivariate analysis were mentioned we scored this item as ‘no’, also when no significant bivariate correlation was found.

• **Statistical method:** Where the statistical tests used to analyze the data clearly described? Disagreement between the two reviewers was resolved by discussion. Following quality rating, methodological, demographic and clinical information were systematically extracted from each article.

**RESULTS**

**Study selection**
The study includes results of electronic searches up to December 2012. A total of 507 papers were identified, of which 19 met our inclusion criteria (4-21). After reading the full text, 1 study was additionally excluded, because this study comprised secondary data from another included study (22). Table 2 lists the characteristics of the 18 remaining studies, including 2 randomized controlled trials (pilot studies), 1 prospective cohort study, 2 retrospective observational studies and 13 cross-sectional observational studies. Clinical diversity between the studies was large with regards to medication type, assessment methods, reporter of adherence and outcome measures. Lack of uniformity of outcome measures made pooling of data impossible.
Table 1. Summary of methodological quality of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Criteria for Inclusion</th>
<th>Generizability</th>
<th>Validity &amp; reliability testing</th>
<th>Design specific bias</th>
<th>Control of confounding</th>
<th>Statistical methods</th>
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<tbody>
<tr>
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<td>Study</td>
<td>Participants (N)</td>
<td>Age range</td>
<td>Study design</td>
<td>Outcomes assessed</td>
<td>Assessments</td>
<td>Significant results</td>
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<tr>
<td>Gray et al (2011)</td>
<td>IBD n=79 (UC 20%, CD 80%) no control group</td>
<td>13-17 y mean age 15.5 y</td>
<td>Cross-sectional</td>
<td>Medication adherence, barriers to adherence, relationship with anxiety/depressive symptoms</td>
<td>MAM, CBCL-YSR</td>
<td>Reported adherence: adolescent 8.6/10 (adolescent and parent together). Barriers: just forget 84.8%, was not home 43%, interferes with activity 34.2%. Other: The presence of anxiety/depressive symptoms intensified the negative impact of barriers to adherence on adolescent’s adherence. A significant correlation was found between disease severity and patient rated adherence and adherence barriers.</td>
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<tr>
<td>Greenley et al (2010)</td>
<td>IBD n=64 (UC 18%, CD 82%) no control group</td>
<td>11-18 y mean age 15.13 y</td>
<td>Cross-sectional</td>
<td>Medication adherence, barriers to adherence</td>
<td>Medication Adherence Questionnaire</td>
<td>Reported adherence: 65% of adolescents, 66% of mothers reported perfect adherence (5-point scale 0= never, 4= always adherent). Barriers: lack of time 33%, feeling well 16%, side effects 14%, misbelief 14%. Other: Adolescents with &gt;1 daily medication administration and multiple medications reported more adherence barriers, individuals with imperfect adherence on maternal report had significantly more barriers.</td>
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<tr>
<td>Greenley et al (2012)</td>
<td>IBD n=51 (CD 86%) no control group</td>
<td>11-18 y mean age 14.7 y</td>
<td>Prospective cohort assessment</td>
<td>Medication adherence, role of youth and maternal involvement</td>
<td>MAM, IBD-FRQ Medication Events Monitoring System</td>
<td>Reported adherence: adherence rate of 96%. Pill count adherence: adherence rate of 93%, 28% of the sample adherence below 80%. Other: High levels of adolescent involvement in their medication regime is associated with better adherence.</td>
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<tr>
<td>Hommel et al (2008)</td>
<td>IBD n=36 (UC 14%, CD 86%) no control group</td>
<td>13-17 y mean age 15.69 y</td>
<td>Cross-sectional</td>
<td>Medication adherence, Quality of Life (QOL)</td>
<td>MAM, Pill count, serum assay, PedsQL, CDI</td>
<td>Reported adherence: 93.2% for 6-MP and 97% for 5-ASA (scores 0-100%, &lt;80% nonadherent). Pill count adherence: 62.6% for 6-MP/AZA, 51.5% for 5-ASA. Assay adherence: 19.4% in therapeutic range Other: 6-MP/AZA non-adherence was related to poorer patient-reported physical health QOL. Greater self-reported 5-ASA adherence was related to poorer patient reported psychological health QOL.</td>
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</table>
### Significant results

**Reported adherence:** non-adherence frequency (doses missed) of 6% and 3% and prevalence (not taking 80% of medication) of 10% and 2% for resp. 6-MP/AZA and for 5-ASA.

**Pill count adherence:** non-adherence frequency of 38% and 49% and prevalence of 64% and 88% for resp. 6-MP/AZA and for 5-ASA.

**Assay adherence:** 14% in therapeutic range

**Non-adherence prevalence of 36%.**

**Reported adherence:** non-adherence frequency of 8% for 6-MP/AZA, 5% for 5-ASA, prevalence was 13% for both.

**Pill count adherence:** non-adherence frequency of 42% and 50% and prevalence of 81.3% and 93.3% for resp. 6-MP/AZA and for 5-ASA.

**Barriers:** MAM: Just forget 87.5%, wasn't home 75%, interferes with activity 68.7%.

**Interview:** forgetting 93.7%, other activities 93.7%, regimen complexity 62.5%, difficulty swallowing pills 56.2%.

**Other:** Number of reported barriers was positively correlated with objective non-adherence for 6-MP/AZA.

**Adolescent 8.5/10, parents 8.9/10.**

**Barriers:** just forget 85.5%, was not home 43.5%, interferes with activity 38.7%.

**Other:** Parental ratings of medication adherence and perceived barriers to adherence predicted disease severity, after controlling for behavioural and disease parameters.

**Individually tailored treatment resulted in a 4% gain (not significant) in 6-MP/AZA adherence (52% baseline; 56% post treatment) and a 25% gain (not significant) in 5-ASA adherence (43% baseline; 68% post treatment).**

<table>
<thead>
<tr>
<th>Participants (N)</th>
<th>Age range</th>
<th>Study design</th>
<th>Outcomes assessed</th>
<th>Assessments</th>
<th>Significant results</th>
</tr>
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<tbody>
<tr>
<td>Hommel et al (2009)</td>
<td>IBD n=42 (UC 14%, CD 86%) no control group</td>
<td>13-17 y mean age 15,62 y</td>
<td>Cross-sectional</td>
<td>Medication adherence, objective vs subjective</td>
<td>MAM, pill count, serum assay</td>
</tr>
<tr>
<td>Hommel et al (2010)</td>
<td>IBD n=16 (UC 6%, CD 94%) no control group</td>
<td>13-17 y mean age 15,75 y</td>
<td>Cross-sectional</td>
<td>Medication adherence, barriers to adherence</td>
<td>MAM, pill count, Treatment adherence interview</td>
</tr>
<tr>
<td>Hommel et al (2011)</td>
<td>IBD n=62 (UC 21% or CD 79%) no control group</td>
<td>13-17 y mean age 15,47 y</td>
<td>Cross-sectional</td>
<td>Medication adherence, barriers to adherence, disease severity</td>
<td>MAM, PCDAI, LCAl, CBCL, YSR, CDI</td>
</tr>
<tr>
<td>Hommel et al (2011)</td>
<td>IBD n=14 (UC 21%, CD 79%) waitlist controls</td>
<td>11-18 y mean age 14.89 y</td>
<td>Randomized controlled trial (pilot study)</td>
<td>Medication adherence, to evaluate the efficacy of an individually tailored...</td>
<td>Pill count</td>
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<tr>
<td>Study</td>
<td>IBD n</td>
<td>Mean Age (y)</td>
<td>Study Design</td>
<td>Compliance Method</td>
<td>Adherence Description</td>
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<tr>
<td>Hommel et al (2012)²²</td>
<td>40</td>
<td>15.4</td>
<td>Randomized controlled trial (pilot study)</td>
<td>Pill count, Treatment Regimen Adherence Questionnaire, Medication Event Monitoring System</td>
<td>Reported adherence: adolescent 87% for 6-MP/AZA and 93% for 5-ASA, parents 83% for 6-MP/AZA and 89%. Pill count adherence: 66% for 6-MP/AZA, 51% for 5-ASA. With monitoring system 89%. Other: group based treatment resulted in a 6% gain (not significant) in 6-MP/AZA adherence and a 25% gain (p&lt;0.01) in 5-ASA adherence (both adolescent report).</td>
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<tr>
<td>Ingerski et al (2010)²³</td>
<td>74</td>
<td>14.97</td>
<td>Cross-sectional</td>
<td>MAM, pill count, serum assay</td>
<td>Reported adherence: adolescent 8.5/10, mother 8.8/10, father 9.1/10, adherence ratings by family reported missed doses 94.7% for 6-MP/AZA and 96.8% for 5-ASA. Pill count adherence: 64.4% for 6-MP/AZA, 62.1% for 5-ASA. Assay adherence: 13.5% in therapeutic range. Barriers: Just forgot 87.8%, was not home 47.3%, interferes with activity 44.6%. Other: Fewer total reported barriers was related to better adherence by adolescent and maternal report.</td>
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<tr>
<td>Janicke et al (2009)²⁴</td>
<td>38</td>
<td>14.5</td>
<td>Cross-sectional</td>
<td>Child, parent and clinician estimate of adherence, SEQ</td>
<td>Reported adherence: child= 2.4, parent= 2.5, clinician= 2.5 (4 point scale: 0= rarely, 4= always adherent). Other: Peer victimization was negatively associated with child report of adherence. Child reported positive social interactions moderated the relationship between child reported peer victimization and parent/self-reported medication adherence.</td>
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</tbody>
</table>
### Significant results

**Serum adherence:** 18% in the therapeutic range, 12% of patients were non-adherent, adolescents 29% > adults 8%.

**Other:** Patients living in more socially deprived areas were more likely to be non-adherent.

**Reported adherence:** Adherence rate (80% cutoff) was 79.8%.

**Barriers:** too busy (55.6%), difficult to swallow (17.8%).

**Other:** Non-adherence was associated with older age and longer disease duration.

**Pill count adherence:** 50% for 6-MP/AZA and 34% for 5-ASA (80% cutoff).

**Pharmacy refill scores** ranged from 0% to 194%.

**Prescription refill scores** was significantly greater for patients adherent to 5-ASA.

**Assay adherence:** 27.6% of measurements in the therapeutic range, non-adherence prevalence of 16%.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants (N)</th>
<th>Age range</th>
<th>Study Design</th>
<th>Outcomes assessed</th>
<th>Assessments</th>
<th>Significant results</th>
</tr>
</thead>
</table>
| Kamperdis et al (2012) | Retrospective observational study | IBD n=238, 49 adolescents, 189 adults (UC 43%, CD 53%, IBDU 4%) no control group | mean age 18.7 and 38 y | Medication adherence | Serum assay | **Serum adherence:** 18% in the therapeutic range, 12% of patients were non-adherent, adolescents 29% > adults 8%.

**Other:** Patients living in more socially deprived areas were more likely to be non-adherent. |
| Kitney et al (2009) | Cross-sectional | IBD n=119 (UC 40%, CD 56%, IBDU 4%) no control group | No info mean age 13.2 y | Medication adherence, barriers to adherence, factors associated with non-adherence | Medication Adherence Questionnaire | **Reported adherence:** Adherence rate (80% cutoff) was 79.8%.

**Barriers:** too busy (55.6%), difficult to swallow (17.8%).

**Other:** Non-adherence was associated with older age and longer disease duration. |
| Mackner et al (2005) | Cross-sectional | IBD n=50 (UC 8%, CD 76%, IBDU 16%) no control group | 11-17 y mean age 14.69 y | Medication adherence, factors associated with non-adherence | Medication adherence interview, CBCL, CDI, Piers Harris Self-Concept Scale, FAD, CSI | **Reported adherence:** always adherent adolescents 48%, parents 38%, (5-point scale 0= never 4= always adherent).

**Other:** Family dysfunction and poor child coping strategies were associated with worse adherence. |
| Oliva-hemker et al (2007) | Cross-sectional | CD n=51, no control group | 1-17 y mean age 14.2 y | Medication adherence, factors associated with non-adherence | Pharmacy refill records | **Pill count adherence:** 50% for 6-MP/AZA and 34% for 5-ASA (80% cutoff).

Prescription refill scores ranged from 0% to 194%.

**Other:** The mean number of total health care visits and emergency department visits was significantly greater for patients adherent to 5-ASA. |
<p>| Ooi et al (2007) | Retrospective chart review | IBD n=56 (UC 7%, CD 75%, IBDU 18%) no control group | No info mean age 12.4 y | Medication adherence | Serum assay | <strong>Assay adherence:</strong> 27.6% of measurements in the therapeutic range, non-adherence prevalence of 16%. |</p>
<table>
<thead>
<tr>
<th>Author(s)</th>
<th>IBD n=</th>
<th>Mean age</th>
<th>Study Design</th>
<th>Tools</th>
<th>Adherence</th>
<th>Other Factors</th>
</tr>
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<tbody>
<tr>
<td>Reed-Knight et al (2011)</td>
<td>90 (UC 26%, CD 74%)</td>
<td>11-18 y</td>
<td>Cross-sectional</td>
<td>MAM, TSRQ, IBD-FRQ, issues checklist</td>
<td>Reported adherence: adherence rate of 89.5% based on adolescent report and 92.8% based on parent report. Longer time since diagnosis, greater perceived disease severity and a lack of motivation to adhere predicted lower adherence.</td>
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<tr>
<td>Schurman et al (2011)</td>
<td>78 (UC 25%, CD 75%)</td>
<td>1-17 y</td>
<td>Cross-sectional</td>
<td>IBD-Care Behaviors, PedsQL</td>
<td>Reported adherence: accidental non-adherence: adolescents 73.1%, parents 70.1%, volitional adherence: adolescents 35%, parents 30%. Greater frequency of volitional non-adherence was significantly associated with greater disease activity and with poorer parent reported psychosocial QOL.</td>
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**Note:**
- IBD = inflammatory bowel disease, UC = ulcerative colitis, CD = Crohn's disease, MAM = medical adherence measure, PCDAI = pediatric Crohn's disease activity index, LCAI = Lichtiger colitis activity index, 6-MP/AZA = 6-mercaptopurine/azathioprine, 5-ASA = 5-aminosalicylic acid, CBCL = child behaviour checklist, YSR = youth self report, PedsQL = pediatric quality of life inventory, CDI = children's depression inventory, SEQ = social experience questionnaire, FAD = family assessment device, CSI = coping strategies inventory, TRSQ = treatment self-regulation questionnaire, IBD-FRQ = IBD family responsibility questionnaire.
Rates of non-adherence pediatric IBD

The documented rates of medication non-adherence in adolescents with IBD ranged from 3 to 73%, and are listed in table 2 (4-21). Self-report questionnaires were the most commonly used methods to measure adherence (4,5,7-10,12-14,16,17,20,21). The most used standardized questionnaire was the MAM, a semi-structured interview which can be filled in separately by the adolescent and parents or together. The MAM has demonstrated adequate validity ($r=0.40$, $p<0.05$) and reliability ($r=0.89$, $p<0.05$) (23). The MAM asks respondents to report the number of doses of medication they have missed in the past 7 days and includes a one-item assessment of medication adherence on a 0 (usually miss) to 10 (rarely miss) point likert scale. Mackner et al. interviewed adolescents and parents separately and found no significant differences in reported medication adherence rates (17). Also in the study of Schurman et al. parents and adolescents agreed reasonably well on the frequency of non-adherence (21). Reed-Knight et al. found a significant difference between parent and adolescent report of adherence, with adolescents reporting less adherence (20).

Several studies used objective methods of assessment, alone or in combination with self-report questionnaires, including pill count (7-9,12,13), pharmacy refill records (18) and biological assay (7,8,13,15,19). Some studies measured medication adherence using self-report, pill count and serum assay analyses at the same time (7,8,13). These studies showed that self-reported medication adherence rates were much higher than the rates measured with objective methods. Greenley et al. compared adherence rate measured with a medication events monitoring system with patient self-report and showed that adolescents who were non-adherent based on the electronic monitoring overestimated their adherence by 23%, whereas adherent adolescents overestimated their adherence by only 2% (6). Pill count and pharmacy refill data showed that adherence to aminosalicylates is worse compared to thiopurines (7-19,12,13,18). However, with self-reported questionnaires adolescents reported slightly better adherence to aminosalicylates compared to thiopurines.

6-TG levels below 100 pmol (15), 230 pmol (7,8,13) and 235 pmol (19), whether or not in combination with unquantifiable range for 6-MMP (8,19), were considered as indicative for non-adherence. Studies using serum levels showed that only 13.5-19.4% of adolescents fell in the therapeutic range (7,8,13,15), and 16-36% of adolescents were considered non-adherent based on their 6-TG and 6-MMP levels (8,15,19).

Only two randomized controlled pilot studies have been performed which evaluated the efficacy of an individually tailored and a family-based group behavioral treatment for non-adherence in adolescents with IBD (11,12). Patients in both studies attended a 4 weekly multicomponent treatment protocol targeting educational, organizational, behavioral and family factors. Comparison of medication adherence of the individually tailored treatment
group with a wait list control group demonstrated that individually tailored treatment resulted in a 4% gain in adherence to thiopurines and a 25% gain in adherence to aminosalicylates (both not significant), measured by pill count (11). Comparison of medication adherence of the group-based behavioral treatment group with a usual care control group demonstrated that group based treatment resulted in a 6% gain in adherence to thiopurines (not significant) and a 25% gain in adherence to aminosalicylates (p<0.01), based on adolescent report. Non-significant differences were found between the conditions with pill count, electronic monitoring and based on parent-reported adherence (12).

**Barriers to medication adherence**

Perceived barriers to medication adherence have been evaluated in six studies (4,5,9,10,13,16). Barriers were mostly assessed with the earlier mentioned MAM, which includes 12 forced choice questions and 1 open-ended question. Mean number of reported barriers ranged from 2.33 to 3.44, with ‘just forget taking the medication’ being the most common reason for non-adherence. ‘Wasn’t home’ and ‘interferes with activity’ were also frequently reported medication adherence barriers (4,9,10,13). Barriers reported in studies using other forced choice measures were ‘side effects’, ‘feeling well’, ‘no belief in medication regime’ and ‘difficulty swallowing pills’ (5,16). Hommel et al. (9) used an open ended interview to survey barriers to medication adherence. Most frequently reported barriers were ‘forget taking the medication’, ‘interferes with activity’, ‘regimen complexity’ and ‘difficulty swallowing pills’. Schurman et al. assessed reasons for volitional non-adherence which were ‘got better’, ‘wanted better control’ and ‘make routine easier to follow’ (21).

Medication regime characteristics play a central role in experiencing different and multiple medication adherence barriers. Adolescents whose regime involved more than 1 daily medication administration reported more adherence barriers than did those whose regimen involved 1 or less than 1 daily medication administration. The same association was found regarding number of daily medications, adolescents on monotherapy reported significantly fewer barriers than adolescents on multiple medications (5). Multiple studies have shown that fewer total reported barriers are related to better medication adherence (5,9,13).

**Associations between family and social interactions and medication adherence**

Ingerski et al. showed that that the mother has a prime position in managing the IBD medication regime during adolescence. In 89% of the cohort the mother appeared to be the primary responsible person for re-ordering IBD medication, and in 49% the primary person responsible for ensuring that medication is taken (13). Increased maternal involvement in IBD care and less perceived parent-child conflict has been identified as a protective factor for better adherence of over-the-counter medications (20), but not for better adherence of prescribed medication (6,20). Adolescents who were more involved in remembering to
take their own medications were nearly eight times more likely to be adherent (6).
Mackner et al. revealed a significant relationship between medication non-adherence and family dysfunction. Specifically, families with appropriate rules and consequences for behavior had children who were more adherent (17).
Janicke et al. examined the relationship between peer victimization (the experience among children of being the target of emotional, verbal or physical attacks by peers), prosocial support and medication adherence. Peer victimization was negatively associated with reported adherence. Positive social interactions moderated this negative relationship between peer victimization and medication adherence (14).

**Associations between psychosocial factors and medication adherence**
The relationship between medication adherence and health-related quality of life (HRQoL) has been assessed in two studies (7,21). In both studies the Pediatric Quality of Life Inventory (PedsQL) was used to assess HRQoL. In the study of Hommel et al. non-adherence to 6-MP/AZA, as measured by subtherapeutic 6-TG levels, was significantly related to poorer patient reported physical functioning QoL. In contrast, greater self-reported 5-ASA adherence was related to poorer patient-reported overall psychosocial health QoL, and particularly social functioning QoL (7). In the study of Schurman et al. greater frequency of volitional non-adherence was significantly associated with poorer parent reported psychosocial health QoL (21).
Also poor child coping strategies are associated with worse adherence (17). Three studies used the Children Depression Inventory to assess depressive symptoms. In 15-18.5% of adolescents with IBD clinically elevated depressive symptoms were recorded (7,11). There was no significant correlation found between depressive symptoms and medication adherence (7,17).
Gray et al. found a significant correlation between anxiety/depressive symptoms and medication adherence, and showed that the presence of anxiety/depressive symptoms intensifies the negative impact of perceived barriers on adolescent’s medication adherence (4).

**DISCUSSION AND FUTURE DIRECTIONS**
In our systematic review we included 18 studies in adolescents with IBD, which were selected for their focus on adherence to thiopurines or aminosalicylates. Pooling of data was not possible, due to lack of methodological robustness and heterogeneity in outcome measures. Nevertheless several important lessons can be drawn from our study.
Non-adherence rates of oral maintenance treatment in adolescents with IBD are elevated, and range from 3% to 73% (4-21). Adolescents with IBD encounter different challenges...
which can interfere with good medication management. The most frequent barriers to medication adherence reported by adolescents and their parents were ‘just forgot’, ‘wasn’t home’ and ‘interferes with activity’. The underlying cause of the reported barriers may vary between adolescents and their families, thereby intervention programs should not consist of an one-size-fits-all approach, but should cover multiple interventions taking into account the needs of the adolescent and their families (9).

Previous research in other pediatric disease groups suggests that continued parental involvement in disease management is essential to maintain appropriate adherence and that premature transition of responsibility from parent to adolescent for disease management tasks may result in decreased adherence over time (26,27). The study of Ingerski et al. clearly showed that the mother has a prime position in managing the IBD medication regime during adolescence (13), however increased maternal involvement in IBD care has not been identified as a protective factor for better adherence of prescribed medication (6,20). Ideally, the disease management should be a shared decision between the adolescent and their parents to minimize the potential for declines in adherence due to parent-teen conflict (4).

Adolescents with IBD appear to be at a higher risk of reduced HRQoL and of developing psychiatric conditions such as anxiety or depression compared with their healthy peers (28). Psychosocial dysfunction of adolescents with IBD can lead to medication non-adherence and therefore jeopardize IBD treatment outcome. Therefore, healthcare physicians working with adolescents with IBD should screen for psychosocial problems in adolescents with IBD, such as anxiety, depressive symptoms and impaired HRQoL and support should be offered when necessary.

Implications for clinical practice:
Pediatric IBD patients are treated according to a step-up strategy, indicating that when oral maintenance therapy has failed, due to intolerance or insufficient response, anti-TNF therapy is initiated. Insufficient response to oral maintenance therapy that is actually due to non-adherence can lead to unjustified and too early escalation in therapy, and as a consequence may lead to increase in health costs. The effect of non-adherence on patient clinical outcomes and health care costs has not been established in adolescents with IBD. Research from the adult literature suggests that consequences of medication non-adherence can be severe. Adults who are non-adherent are up to 5.5 times more likely to experience a relapse in symptoms (24) and generate 12.5% greater annual health costs than adherent patients (25). Kamperidis et al. showed that adolescents were more frequent non-adherent than adults (15). This suggests that consequences of medication non-adherence in adolescents with IBD might even be greater.
Comparison with other reviews:
Two narrative reviews have been published in recent years on the rates of medication non-adherence in adolescents with IBD, perceived barriers to treatment adherence and the impact of psychosocial factors on medication adherence (2, 29). Because several studies have been published in the intervening years our systematic review is an important addition to this field of research.

Methodological limitations of the reviewed studies:
The lack of socioeconomic and ethnic diversity in most studies limits generalization to economically disadvantaged or minority populations. Future studies should include more ethnically and socioeconomic diverse groups of adolescents. Furthermore, the limited factors found in the reviewed studies that were significant correlated to medication adherence can be the result of a limited statistical power due to small samples. The majority of studies included patients from a wide age range, with varying disease severity and disease durations, which also may have influenced medication adherence. Control for these confounding factors was not always executed adequate. Moreover, the cross-sectional design of most included studies precludes the ability to make conclusions concerning the causal relations between variables. Future research that is longitudinal in nature would provide valuable insight in the direction and mechanism of the associations found. At last, several studies used only one, subjective method to measure medication adherence. The difference in subjective and objective medication adherence outcome emphasizes the relevance of using a multi-method medication adherence assessment. We advise to use at least two different measures of adherence, including at least one objective measure.

Conclusions:
Non-adherence to oral maintenance treatment in adolescents with IBD is a significant health care problem and can lead to unnecessary escalation in therapy. During routine follow up appointments standard evaluation of medication adherence, experienced barriers to adherence, and psychosocial problems are of major importance and should be an integral component of the comprehensive care of children and adolescents with IBD. Early interventions to enhance oral medication adherence, with special attention for individual underlying reasons of non-adherence, should be offered.
REFERENCES


