

Attitudes to Mesalamine Questionnaire: A Novel Tool to Predict Mesalamine Nonadherence in Patients with IBD

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- OBJECTIVES:** Poor adherence to mesalamine is common and driven by a combination of lifestyle and behavioral factors, as well as health beliefs. We sought to develop a valid tool to identify barriers to patient adherence and predict those at risk for future nonadherence.
- METHODS:** A 10-item survey was developed from patient-reported barriers to adherence. The survey was administered to 106 patients with ulcerative colitis who were prescribed mesalamine, and correlated with prospectively collected 12-month pharmacy refills (medication possession ratio (MPR)), urine levels of salicylates, and self-reported adherence (Morisky Medication Adherence Scale (MMAS)-8).
- RESULTS:** From the initial 10-item survey, 8 items correlated highly with the MMAS-8 score at enrollment. Computer-generated randomization produced a derivation cohort of 60 subjects and a validation cohort of 46 subjects to assess the survey items in their ability to predict future adherence. Two items from the patient survey correlated with objective measures of long-term adherence: their belief in the importance of maintenance mesalamine even when in remission and their concerns about side effects. The additive score based on these two items correlated with 12-month MPR in both the derivation and validation cohorts ($P < 0.05$). Scores on these two items were associated with a higher risk of being nonadherent over the subsequent 12 months (relative risk (RR) = 2.2, 95% confidence interval = 1.5–3.5, $P = 0.04$). The area under the curve for the performance of this 2-item tool was greater than that of the 10-item MMAS-8 score for predicting MPR scores over 12 months (area under the curve 0.7 vs. 0.5).
- CONCLUSIONS:** Patients' beliefs about the need for maintenance mesalamine and their concerns about side effects influence their adherence to mesalamine over time. These concerns could easily be raised in practice to identify patients at risk of nonadherence (Clinical Trial number NCT01349504).

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at <http://www.nature.com/ajg>

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Despite its proven efficacy in reducing disease relapse, adherence to mesalamine therapy by patients is variable, with regard to both prescribed interval and dose regimen (1,2). Prevalence of nonadherence in patients with ulcerative colitis (UC) has been reported to be as high as 50%, particularly in those with quiescent UC (3). Mesalamine nonadherence

not only increases a patient's risk for relapse but has also been associated with higher health-care costs and risk for complications (4–6).

Mesalamine adherence can be improved only if the correlated factors of this behavior are more fully understood, and can be measured in order to screen for, and predict, nonadherence as well

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as to target adherence-improvement interventions. Epidemiological studies of nonadherence in patients with UC have identified numerous correlates, including male gender, lack of health insurance, lower education levels, and frequent dose schedules (7–10). However, few of these factors can be altered in practice, and simple universal interventions have not produced significant improvements in nonadherers (11–13). We previously reported that reminding patients to take their medications through phone calls did not significantly impact overall medication adherence (13).

Behavioral studies have provided descriptions of patient beliefs that may influence adherence behaviors (14–16). Nonadherence may be based on a patient's decision not to take medicine, and this "intentional nonadherence" stems from personal beliefs of potential risks from the treatment and perceived need of the treatment. Whether these beliefs are contributory to nonadherence in patients with inflammatory bowel disease (IBD) remains unknown.

From the literature on IBD and other chronic diseases, a number of questionnaires have been developed for clinical use to ascertain which patients are at highest risk of "poor adherence" on the basis of self-reports of adherence behaviors (17–19). The primary limitation of this approach is the reliance on self-reports on nonadherence, as patients have been found to overestimate their adherence to medication when asked in a clinical setting (20,21). We previously also concluded that patient self-reports of mesalamine adherence were not reliable, as they did not correlate with urine salicylate levels measured in the clinic; many patients self-reporting "high adherence" had similar urine salicylate levels to controls not taking mesalamine (22). In addition, currently available questionnaires may measure nonadherence but do not provide insights into the types of health beliefs potentially behind adherence behaviors.

The objectives of our study were the following: (i) develop a simple questionnaire that assesses the patient-reported barriers to mesalamine adherence; and (ii) examine relationships between responses on this assessment with quantitative measures of adherence over time (pharmacy refills) resulting in a refined screening tool.

Methods

Development of patient-reported item questionnaire. We previously published the results of a study of patient-reported barriers to adherence from focus groups and individual interviews (16). Briefly, 27 patients with IBD completed interviews/focus groups to elicit their perceived barriers to adherence, and analyses of these responses were grouped under common themes (16). The themes were used by an expert panel (JG, DL and AM) to devise a test questionnaire that encompassed these patient-reported themes; each item was presented on a 5-point Likert scale, as previously described (23).

Prospective patient population. To test this 10-item questionnaire, a prospective observational study was performed in a single tertiary referral center over 18 months ($N=106$). The study was approved by the local institutional review board (2011P000067). All patients currently attending the Center for Inflammatory Bowel Disease who were prescribed stable doses of mesalamine

for UC were invited to participate during a routine clinic visit. Seventy-five percent of invited patients agreed to participate in the study.

Enrollment measures. After each individual was enrolled, a urine sample was obtained during the enrollment visit, and each patient completed the 10-item survey, a simple self-report of medication-taking behavior (Morisky Medication Adherence Scale (MMAS-8)), a disease activity score (Simple Clinical Colitis Activity Index), and a quality-of-life score (short Inflammatory Bowel Disease Questionnaire). These measures were explained and recorded by the research assistant. The MMAS-8 has been reported to correlate well with patients' adherence as measured by pharmacy refills in some disease states, although conflicting data exist on its performance in patients with IBD (18,19,24). A score of <6 is considered "low adherence" using this scale. The Simple Clinical Colitis Activity Index is a validated measure of disease activity in patients with UC (25). The short Inflammatory Bowel Disease Questionnaire is a validated measure of quality-of-life in patients with IBD (26). The medication history, current mesalamine dosing schedule, daily mesalamine dose, and time of last dose before enrollment were also recorded. Urine samples were frozen at -80°C for subsequent analysis in batches. Urinary salicylate levels were measured by ferric nitrate colorimetric assay ("Trinder reaction") using serum salicylate assay reagents and instrumentation from Roche Diagnostics (Indianapolis, IN) as previously described (FDA approved for use in serum, not urine) (22,27). After enrollment, no further clinical interactions beyond standard care took place.

Pharmacy refills. As all physicians use an electronic prescribing program, all mesalamine refills were tracked by tracking each enrollee's electronic medical record prospectively at 3-month intervals, over 12 months. For completeness, patients' pharmacies (local and mail order) were contacted to collect information on refill history from other sources (e.g., primary care physicians or nonelectronic refills). Six subjects moved their care to a different (external) provider during the study, but their refill data were still collected from their pharmacies when in-state. Free samples are not permitted at our institution, and only 5% of the cohort was hospitalized over the study period, and hence other sources of medication are limited.

Adherence to mesalamine was determined by calculating a standard measure of medication refill pattern over time: the medication possession ratio (MPR) (28). By tracking this over a 12-month period after enrollment, it allows the distribution of a patient's refill activity to be averaged, and accounts for "pill hoarding" or premature refills. This method is considered a suitable "gold standard" indirect measure of patient adherence and a suitable surrogate for directly observing therapy or pill counts (28,29). Patients with "low" MPR typically are taking fewer pills per day over an extended period than prescribed. Other refill calculation measures were also recorded as secondary end points: continuous single-interval medication availability and continuous multiple-interval medication gap (28).

Survey testing and validation. Individual items from the 10-item survey of patient-reported adherence factors were assessed for relationships with 12-month MPR scores in all 106 patients using Spearman correlations. A computer-generated random sample of 60 participants was used to identify which items correlated with 12-month nonadherence. These items (Attitudes to Mesalamine questionnaire) were then validated in the remaining 46 individuals. To confirm the validity of these items, receiver operating characteristics were calculated and compared with 12-month refill patterns and MMAS-8 scores.

Statistics. Dichotomous variables were compared between groups by means of the χ^2 test or Fisher's exact test where appropriate. Continuous variables were compared using *t*-tests if normally distributed, or with the Wilcoxon test if non-normal. To determine whether individual items could distinguish adherers from nonadherers over 12 months, a receiver operating characteristic curve was plotted and area under the curve was determined. Pharmacy refill scores were dichotomized and used to classify adherence as "low adherence" (MPR < 0.6) based on previously validated criteria (19,29). The primary longitudinal adherence outcome was MPR over 12 months. Multivariate logistic regression was used to determine whether individual variables were independently associated with outcomes. All data were analyzed using JMP (SAS Institute, Cary, NC). All authors had access to the study data and have reviewed and approved the final manuscript.

Results

A 10-item survey was developed by the expert group to reflect the common barriers to adherence reported by patients (**Supplementary Table S1** online). One hundred and six patients met the inclusion criteria and were enrolled in a prospective quantitative study; **Table 1** outlines the demographics of the study population, which are typical for our center's UC population. Two-thirds of this cohort has a graduate degree. This cohort was in remission at enrollment (mean Simple Clinical Colitis Activity Index score was 1, mean short Inflammatory Bowel Disease Questionnaire score 56) and representative of our clinical population. The majority of participants reported adherence with health maintenance behaviors at enrollment, including mesalamine adherence (**Supplementary Table S2** online).

Enrollment characteristics. The 10-item survey was applied to all 106 participants at enrollment; the distributions of responses on a 5-point Likert scale are illustrated in **Supplementary Figure S1** online; scores at the higher end of the scale reflected positive attitudes toward adherence. The Cronbach alpha for the entire survey in the cohort was 0.82, suggesting good internal consistency. Of the original 10 items, 8 individual items correlated significantly with MMAS-8 scores at enrollment (**Supplementary Table S3** online), and the cumulative score from the 10-item survey also correlated with MMAS-8 scores ($r^2 = 0.6, P < 0.01$; **Figure 1**). However, only three items (Q1, Q7, Q8) correlated with spot urine salicylate levels (Spearman's $\rho = 0.2$ for each), and these questions all

Table 1. Baseline characteristics of enrolled cohort

Demographics	N=106
Female	56%
Mean age (STD), years	42 (19)
Private insurance	86%
<i>Disease characteristics</i>	
Mean disease duration (STD)	15 (17)
Mean SCCAI score (STD)	1.1 (2)
Mean sIBDQ score (STD)	56 (11)
<i>Medication regimen</i>	
Mesalamine formulation	
Pentasa	5%
Asacol	48%
Asacol HD	10%
Lialda	34%
Apriso	3%
Mean mesalamine dose (STD)	3.8g (1.4)
<i>Dosing schedule</i>	
Once-day	38%
Twice-a-day	38%
Three-times-a-day	24%

HD, high-dose; SCCAI, Simple Clinical Colitis Activity Index; sIBDQ, short Inflammatory Bowel Disease Questionnaire; STD, standard deviation.

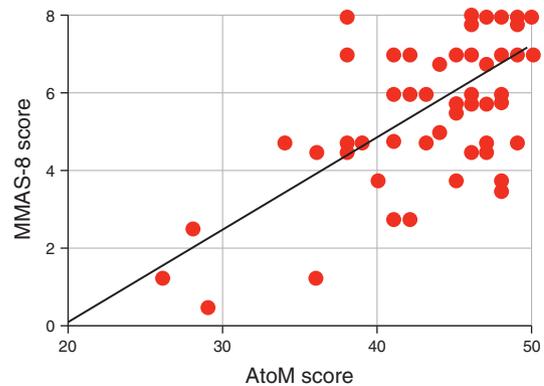


Figure 1. Attitudes to Mesalamine (AtoM) score (x axis) plotted against Morisky Medication Adherence Scale (MMAS)-8 scores (y axis) in 106 patients enrolled.

related to skipping pills or doses in general (see **Supplementary Table S1** online). These measures all reflect recent adherence, but not long-term adherence.

Follow-up adherence. All participants then had their pharmacy refills tracked for 12 months after enrollment, using MPR calculations.

Table 2. Correlation (Spearman, ρ) between MMAS-8 total score, and individual items in the initial 10-item survey

Survey question	Spearman ρ	P
Q1. Have you forgotten to take your mesalamine during the last 4 weeks?	0.8	<0.01
Q2. Does your busy lifestyle lead you to forget to take your mesalamine?	0.6	<0.01
Q3. Social embarrassment about taking pills causes me to skip taking my mesalamine sometimes	0.2	0.1
Q4. Co-pays or insurance issues can make me delay getting mesalamine refills when I need them	-0.1	0.5
Q5. I sometimes do not take my mesalamine because I am not sure if it is helping my colitis	0.4	<0.01
Q6. It is important to continue to take mesalamine, even when I feel well	0.4	<0.01
Q7. I only need to take my mesalamine when I have symptoms from my colitis	0.4	<0.01
Q8. I sometimes skip mesalamine pills because there are too many pills to take each time	0.4	<0.01
Q9. If I have to take mesalamine at different times during the day, I skip the mid-day doses	0.4	<0.01
Q10. Concerns about possible side effects is a reason I sometimes do not take my mesalamine pills	0.4	<0.01

MMAS, Morisky Medication Adherence Scal.

The 10-item survey was correlated with subsequent 12-month adherence patterns in a computer-generated list of 60 subjects randomly identified from the total 106 participants. As can be seen from **Table 2**, only Q6 and Q10 correlated significantly with 12-month refill patterns. Q6 relates to patients' belief in the importance of maintenance mesalamine even when in remission, and Q10 asks about patients' concerns about side effects (see **Supplementary Table S1** online). **Figure 2** illustrates the relationship between 12-month pharmacy refill patterns and scores of 1–5 on the Likert scale of Q10.

These two items (Q6 and Q10) were then tested in the remaining 46 participants, and remained significantly associated with 12-month refill patterns (Spearman $\rho=0.3, 0.2$, respectively). Rankings of Q6 and Q10 on the Likert scale were significantly associated with all measures of mesalamine adherence over 12 months (**Table 3**). A receiver operating characteristic curve was generated for a cumulative score on Q6 and Q10 to identify patients who were “low adherers” (MPR <0.6) over 12 months (**Figure 3**); these two items had an area under the curve of 0.7, in comparison with the MMAS-8, which had an area under the curve of 0.5 for the same outcome. As a dichotomous questionnaire would be easier to administer in practice, we determined the relative risk of nonadherence in patients who did not “strongly” agree with the adherence beliefs in both Q6 and Q10 (**Table 4**). Low adherence over 12 months occurred in 44% of this group, compared with 21%

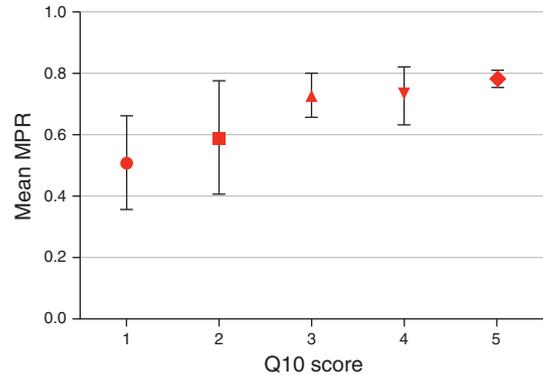


Figure 2. Mean medication possession ratio (MPR; y axis) grouped by patient responses to Q10 of the Attitudes to Mesalamine (AtoM) survey. Higher MPR levels indicate higher adherence. Responses on the Q10 Likert scale range from “strongly agree” with nonadherence behavior (1) to “strongly disagree” (5) with nonadherence behavior.

of those who “strongly” agreed with the adherence statements in these questions (RR=2.2, 95% confidence interval=1.5–3.5). In a nominal logistic regression model, containing each individual question's score, Q6 and Q10 remained independently associated with the outcome of MPR <0.6 ($P<0.05$).

Discussion

This study provides novel insights into our understanding of mesalamine nonadherence in clinical practice in patients with UC. First, although patients reported many themes and items in the focus groups as “barriers to adherence”, only two identified barriers actually correlated with their long-term adherence behavior over time: their belief in the importance of maintenance therapy when asymptomatic, and their concerns about side effects. Other patient-reported factors, such as medication costs and social embarrassment, were not associated with longitudinal nonadherence. Surprisingly, items specific to recent adherence (MMAS-8) did not correlate with long-term adherence (MPR), although the reasons for persistent nonadherence may differ from those for occasional nonadherence. Second, a simple two-item questionnaire could identify patients who were twice as likely as others to be nonadherent over 12 months; this not only flags this group for clinicians but also provides a basis for tailored educational interventions.

Patient-reported beliefs about medications have a more important role in determining their adherence behavior compared with clinical or sociodemographic factors (30). Other groups have reported that patients' doubts about the necessity for long-term maintenance therapy are common in IBD and other conditions and may inform their decision-making toward their medications (9,14,31). These studies did not attempt, however, to correlate these attitudes to objective measures of adherence *per se*. In this study, we provide the first data to confirm that these doubts are associated with objective evidence of longitudinal nonadherence

Table 3. Correlation (Spearman ρ) between 12-month refill patterns (MPR), and individual items in the initial 10-item survey

Survey question	Spearman ρ	P
Q1. Have you forgotten to take your mesalamine during the last 4 weeks?	0.1	NS
Q2. Does your busy lifestyle lead you to forget to take your mesalamine?	0.01	NS
Q3. Social embarrassment about taking pills causes me to skip taking my mesalamine sometimes	-0.1	NS
Q4. Co-pays or insurance issues can make me delay getting mesalamine refills when I need them	-0.1	NS
Q5. I sometimes do not take my mesalamine because I am not sure if it is helping my colitis	0.1	NS
Q6. It is important to continue to take mesalamine, even when I feel well	0.3	0.006
Q7. I only need to take my mesalamine when I have symptoms from my colitis	0.1	NS
Q8. I sometimes skip mesalamine pills because there are too many pills to take each time	0.1	NS
Q9. If I have to take mesalamine at different times during the day, I skip the mid-day doses	0.01	NS
Q10. Concerns about possible side effects is a reason I sometimes don't take my mesalamine pills	0.2	0.04

MPR, medication possession ratio; NS, not significant.

Table 4. Association between a score of 5/5 on Q6 and Q10 of the 10-item survey, and 12-month refill patterns

Objective adherence measure	P value
CSA (absolute)	0.003
MPR (absolute)	0.04
CMG (absolute)	0.01

CMG, continuous multiple-interval medication gap; CSA, continuous single-interval medication availability; MPR, medication possession ratio.
P values generated from Wilcoxon test of mean CSA/MRP/CMG according to Q6 and Q10 score of 10 (yes/no).

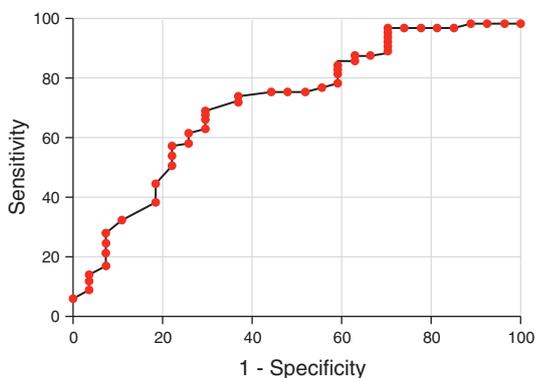


Figure 3. Receiver operating characteristic curve for a cumulative score on Q6 and Q10 of the Attitudes to Mesalamine survey to identify those with a medication possession ratio <0.6 (low adherers) over 12 months.

over time, based on pharmacy refills. Although the importance of maintenance therapy is usually emphasized in practice, it may be that the message is somehow lost or not believed; IBD patients could reproduce only half of the information provided in prescribing consultations in one study (32). Patients' prior experiences also have a key role in future adherence, and hence promoting the benefits of maintenance therapy may be less effective in those who have flared while on maintenance agents (33).

Similarly, patients' concerns about side effects have also been reported as a reason for them not taking their medications in IBD

(9,32,34). This is surprising, as the safety profile of mesalamine is considered relatively benign by clinicians. In this study, patients who "strongly agreed" that concerns about side effects sometimes prevent them from taking their mesalamine had a lower 12-month refill pattern compared with those with more ambivalent attitudes to this topic. Education and reassurance would be obvious solutions to this issue, although, as noted above, prior side effects may influence their doubts about adherence to any medications. Adherence behaviors are certainly not static, and the central role of patients' beliefs may only affect adherence at certain phases of their therapy (35). An understanding of these factors may allow adherence interventions tailored to the individual nonadherer, rather than generic solutions with mixed results (13,36,37).

Limitations of this study include the fact that the interviews were conducted with patients who attended a tertiary referral practice and hence may not represent patients in the community. All patients were in remission at enrollment, and therefore current severity of disease activity may not have influenced their attitudes, although prior experiences may have. Reassuringly, many of the themes that emerged from the focus groups included items that have been reported from other qualitative studies of adherence (14,30,31,34). In addition, we used pharmacy refill patterns to measure adherence, rather than directly observed therapy, which would be impractical. This measure is considered a "gold standard" for indirect measurements of adherence, but may overestimate or underestimate adherence in some cases (28). Finally, 25% of eligible patients who were invited to enroll in this study declined. These patients may have self-selected themselves because of different adherence behaviors to the enrolled group, which we may not have captured. We also do not currently have data on whether refill patterns changed during periods of relapse in the 12 months of follow-up.

In conclusion, this study identifies key patient beliefs that influence their persistence with mesalamine maintenance regimens. The brief Attitudes to Mesalamine survey could be used to screen for these attitudes in practice, and target patient education interventions accordingly. Further studies will be required to gauge the applicability of this survey in different populations in the community.

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CONFLICT OF INTEREST

Guarantor of the article: Alan C. Moss, MD, FACC.

Contributions: Y.L., J.G., N.C., A.C., A.B., G.H., D.L.: study design, acquisition of data and analysis, critical review of the manuscript. A.C.M.: study design, analysis and interpretation of data, statistical analysis, drafting of the manuscript, study supervision.

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