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The Challenge of Compliance and Persistence: Focus on Ulcerative Colitis

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FACULTY

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Kane is active in many professional organizations, including the American College of Physicians, the American Gastroenterological Association, the Crohn's & Colitis Foundation of America, and the American College of Gastroenterology, among others. She is the cofounder of WE CARE in IBD, an organization of women specializing in the field of inflammatory bowel disease (IBD). She has contributed numerous abstracts, journal articles, scientific venues, and book chapters to the medical literature. Kane's recent research has focused on medication adherence rates in patients on maintenance mesalamine therapy.

A reviewer for the *American Journal of Gastroenterology, Gastroenterology,* and *Gut*, Kane is a frequent speaker on issues of medication adherence, management of pregnancy, gender-specific issues in IBD, new therapies for the treatment of Crohn's disease, and the relationship between the menstrual cycle and the gastrointestinal tract.

Diana Brixner, PhD, RPh, is associate professor and chair, Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City. She is also executive director, Pharmacotherapy Outcomes Research Center, which is affiliated with the University of Utah Health Sciences Center and is where she focuses on the design, conduct, training, and communication of pharmacoeconomic and outcomes research studies to demonstrate the value of pharmaceutical therapy.

Brixner has published numerous articles in peer-reviewed journals, including *Cancer Research, Clinical Therapeutics*, and the *Journal of Managed Care Pharmacy.* She has written 3 book chapters; has been issued 1 patent; has been an invited speaker at a variety of professional meetings; and has presented numerous continuing education programs. She served a 2-year term on the executive board of the International Society of Pharmacoeconomics and Outcomes Research and is the current president of this association. Brixner served on the Health Outcomes Committee, Pharmaceutical Research Manufacturers Association. She is a long-standing member of the Academy of Managed Care Pharmacy (AMCP). Brixner served as a member of the Editorial Advisory Board of the *Journal of Managed Care Pharmacy* for several years, and she was a candidate for the 2004 board elections. Currently, she is a diplomat for AMCP to the University of Utah.

David T. Rubin, MD, is associate professor of medicine, Department of Medicine; codirector, Inflammatory Bowel Disease Center; and program director, Fellowship in Gastroenterology, Hepatology, and Nutrition, University of Chicago Medical Center.

Rubin earned his MD with honors from the University of Chicago Pritzker School of Medicine. He completed a residency in internal medicine and fellowships in gastroenterology and clinical medical ethics at the University of Chicago, where he was chief resident and chief fellow. Rubin is board certified in internal medicine and gastroenterology.

Rubin is a member of the American Gastroenterology Association, serving on the Ethics Committee and Subcommittee on Training. He is also a member of the American College of Gastroenterologists, serving on the Professional Issues Committee, and of the Crohn's & Colitis Foundation of America (CCFA), having chaired the Illinois Educational Program from 2005 to 2008. Currently, he serves as the National Chair of Professional Education for CCFA.

Rubin is on the editorial boards for *Clinical Gastroenterology & Hepatology, Inflammatory Bowel Disease*, and *Gastroenterology & Hepatology.* An avid researcher, Rubin's interests include colon cancer screening and prevention, inflammatory bowel disease, teaching of medicine, and clinical medical ethics. He is the principal investigator for several research projects and clinical trials. Rubin has contributed numerous peer-reviewed publications, book chapters, review articles, and abstracts to the medical literature.

Maida J. Sewitch, PhD, is assistant professor of medicine, McGill University, Montreal, Canada, and medical scientist, Divisions of Clinical Epidemiology and Gastroenterology, McGill University Health Centre. Sewitch is focused on training, conducting, and communicating epidemiology and outcomes research studies to enhance delivery and utilization of medication and health services; her main research interest is adherence to guidelines. Sewitch is the 2006 Dorothy J. Lamont Research Scientist, sponsored by the National Cancer Institute of Canada and the Canadian Institutes of Health Research, for her work in colorectal cancer.

Sewitch obtained her PhD from McGill University. Her PhD thesis was on discordant patient-physician perception in inflammatory bowel disease.

Sewitch has published numerous articles in peer-reviewed journals, including *American Journal of Gastroenterology, Canadian Journal of Psychiatry*, and *Rheumatology.* She has been an invited speaker at various professional meetings and is engaged in numerous postgraduate, graduate, and undergraduate teaching programs. She is an associate member of the Department of Epidemiology, Biostatistics and Occupational Health, McGill University, and of the Department of Clinical Epidemiology and Community Studies, St. Mary's Hospital Center, Montreal, Canada, where she is launching a research program in complementary and alternative medicine. Sewitch is a long-standing member of the American Psychosomatic Society and the Canadian Association of Gastroenterology.

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The Challenge of Compliance and Persistence: Focus on Ulcerative Colitis

Target Audience
Physicians and pharmacists treating patients with ulcerative colitis (UC)

Learning Objectives
Upon completion of this activity, participants should be able to
1. describe the many factors that affect compliance and persistence for patients with UC;
2. explain the impact of non-adherence to therapy on patient health;
3. differentiate the strategies that can be applied to improve short-term versus long-term persistence;
4. discuss the psychologic factors that affect persistence; and
5. discuss practical strategies to improve adherence for patients with UC.

This supplement was made possible by an independent educational grant from Procter & Gamble Pharmaceuticals, Inc. This supplement is based on the proceedings of a roundtable meeting, "The Complexity of Compliance and Persistence in Ulcerative Colitis," held May 8, 2007, at the Peninsula Hotel in Chicago, Illinois. The roundtable was supported by an independent educational grant from Procter & Gamble Pharmaceuticals, Inc. Julie Messick, PharmD, wrote this supplement.

*A total of 1 *AMA PRA Category 1 Credit™* and 1.0 contact hour (0.10 CEU) will be awarded for successful completion of this continuing education activity in states that recognize ACPE providers (ACPE Universal Program No. 322-000-07-020-H01-P). For faculty disclosures, please see page S11.

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Description of Activity

The Challenge of Compliance and Persistence: Focus on Ulcerative Colitis is a self-study journal supplement designed for physicians and pharmacists. Participation should take approximately 1 hour. To complete this activity and receive credit, the participant should

1. Read the learning objectives,
2. Read and review the educational supplement, and
3. Complete the posttest and evaluation form and mail or fax them to
   Enduring Materials Coordinator; Continuing Education, G220; PO Box 851; Hershey, PA 17033-0851. Fax: 717.531.5604

Participants must receive a score of 80% or better to receive credit.
Original release date: January 1, 2008. Review/approval date: January 1, 2008. Expiration date: No credit will be given after December 31, 2008.

Be sure to mail the posttest on or before December 31, 2008. After this date, the activity will no longer be designated for credit.

Statements of continuing education (CE) credit will be mailed to participants approximately 6 to 8 weeks after completion of the program. It is recommended that participants keep a copy of their completed materials until they receive their certificate.

For questions regarding CE credit, the posttest, or evaluation, please call Penn State Continuing Education at 717.531.6483 or e-mail ContinuingEd@hmc.psu.edu. Please reference course #G3812-08-R.

Accreditation

***AMA PRA Category 1 Credit™* for Physicians.** This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Penn State College of Medicine and IMED Communications. Penn State College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Penn State College of Medicine designates this educational activity for a maximum of 1 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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The Challenge of Compliance and Persistence: Focus on Ulcerative Colitis

Sunanda V. Kane, MD, MSPH, FACG; Diana Brixner, PhD, RPh; David T. Rubin, MD; and Maida J. Sewitch, PhD

ABSTRACT

BACKGROUND: Non-adherence to therapy is a widespread problem, with typical adherence rates for prescribed medications being approximately 50%. An estimated 20% to 50% of patients with ulcerative colitis (UC) do not take their medications as prescribed, resulting in higher disease-recurrence rates and potentially higher health care costs.

OBJECTIVE: To characterize the problem of non-adherence in UC, to review the many factors affecting compliance and persistence in this population, and to discuss practical strategies to improve adherence in these patients.

SUMMARY: Adherence to and persistence with medication are complex and multifactorial behaviors. Factors shown to affect adherence in UC patients include disease extent and duration, cost of medications, fear of adverse effects, individual psychosocial variables, and the patient-physician relationship. In contrast, recent data do not support an important role for treatment-related factors such as daily dose, regimen, and formulation in influencing adherence in this population, particularly with longer duration of use. Strategies to improve adherence should involve the patient, the provider, and the health care delivery system. For UC patients, knowledge and discussion of the rationale for supporting persistence, such as recent data regarding agents that have a potential chemoprotective benefit, may encourage persistence, even during periods of quiescence. The patient-physician relationship is critical in encouraging adherence, particularly with respect to education, open communication, and agreement regarding the value of the assigned treatment. Health care delivery systems can improve adherence by encouraging the participation of multidisciplinary teams, providing reporting and tracking systems, and eliminating financial barriers where possible.

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Low adherence to prescribed treatments is a ubiquitous problem, with typical adherence rates for prescribed medications being approximately 50% and with a range as broad as 0% to 100%.[1] Aptly termed "America's other drug problem" by the National Council on Patient Information and Education,[2] medication non-adherence can increase disease morbidity and mortality, as well as increase health care costs.[3]

As in other chronic disease states, an estimated 20% to 50% of patients with ulcerative colitis (UC) do not take their medications as prescribed.[4] Despite the demonstrated ability of maintenance therapy to reduce relapse in patients with UC,[5,6] studies in this population suggest adherence rates are as low as 40% in those with quiescent disease.[7] Non-adherence in UC patients creates the potential for significant clinical and economic impact. Because of the complexity and multifactorial nature of medication-taking behavior, however, physicians must work closely with patients to identify reasons for non-adherence and customize interventions targeted to improving adherence.

On May 8, 2007, a group of nationally prominent clinicians and researchers convened to discuss relevant issues regarding the complexity of adherence in UC. Topics addressed by the faculty included general considerations regarding adherence in UC patients, different considerations regarding short-term and long-term adherence, the complexity and multifactorial nature of adherence, and strategies for improving adherence in UC patients. This supplement, which summarizes the discussions from this meeting, is intended to provide relevant information to help gastroenterologists and pharmacists appreciate the importance of, assess, and improve adherence in their UC patients.

Defining Adherence and Persistence

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) defines "medication adherence" or "compliance" as the extent to which a patient acts in accordance with the prescribed interval and dose of a dose regimen.[8] Although the terms adherence and compliance are often used interchangeably,[9] adherence is preferred by many health care providers as it implies a cooperative, 2-way relationship versus the 1-way interaction inferred from the term compliance.[10,11] During the roundtable meeting, David T. Rubin noted, "Compliance implies a paternalistic relationship with the physician, whereas adherence suggests more of a patient/physician accommodation or some negotiated relationship." The term adherence is intended to be a statement of fact, rather than a judgmental term implying blame of the patient, prescriber, or treatment.[1]

"Medication persistence," as defined by ISPOR, refers to the accumulation of time from initiation to discontinuation of therapy and is measured by a time metric.[8] Thus, medication

adherence refers to medication-taking behavior[11] within a specific time interval, whereas medication persistence attempts to capture the amount of time that a patient remains on chronic drug therapy.[12] However, a consistent definition and uniform method of calculation for persistence are currently lacking in the medical literature.[12]

Non-adherent behavior can be broadly classified as involuntary (unintentional) or voluntary (intentional). These 2 types of behavior should be recognized as different phenomena and have been associated with different patient characteristics.[13] Unintentional non-adherence implies a passive process in which the patient is forgetful or careless about adhering to the treatment regimen, whereas intentional adherence is an active decision of the patient to deviate from the treatment regimen.[13,14] Although voluntary non-adherence has been defined as stopping medication in response to feeling better or worse,[14,15] this behavior can also result from economic constraints. Voluntary non-adherence, explained Diana Brixner, could be "simply making a decision that you're not going to pick a prescription up, because it may cost too much, or you're not going to take the medications every day; you're going to take them every other day because you can stretch it out."

Despite the common assumption that the term non-adherence refers to treatment therapy that has been discontinued, it can also refer to patients who continue treatment but fail to follow the treatment regimen correctly.[16] General patterns of non-adherence include under- or overconsuming medication, failing to fill a prescription, taking doses at inappropriate intervals, and administering medication incorrectly.[16,17] By comparing patients' medication bottles and reported use with the outpatient records of 5 cardiologists and 2 internists, Bedell et al. found medication discrepancies in 239 of 312 (76%) patients.[18] While more than half (51%) of the 545 discrepancies resulted from patients taking medications that were not recorded, 29% were due to patients not taking a recorded medication and 20% were due to differences in dosage. Maida J. Sewitch indicated that identifying the general types and patterns of non-adherence is important when designing intervention strategies for altering behavior and increasing adherence. As Brixner noted, a "very different intervention program would be directed for a patient who is forgetful compared to someone who is intentionally or voluntarily non-adherent. There are other issues going on there that should be addressed by a different intervention."

Measuring Adherence

Medication adherence can be measured in a variety of ways. Direct methods for measuring adherence, such as direct observation and measurement of serum drug/metabolite levels or biologic markers, offer the advantage of low bias but may be expensive and inconvenient for patients.[11,19,20] Indirect methods include patient questionnaires or interviews, pill counts, patient diaries, electronic adherence monitors, and prescription refill rates.[11,21] Provided that they are measured at several points in time, prescription refill rates can provide a relatively accurate and inexpensive measure of overall adherence in closed pharmacy systems such as health maintenance organizations or the Department of Veterans Affairs health care system.[20] However, using objective pharmacy data rather than patient-derived information to measure patient adherence has limitations as well. Although some believe it is unlikely that patients will pick up medications they do not intend to take,[7] others doubt the assumption that "a prescription filled is a prescription taken."[20] Refilling a prescription on time does not necessarily ensure that a patient is taking a drug correctly.[19]

Although no gold standard exists,[11] the medication possession ratio (MPR) has become widely adopted as a measure of medication adherence.[12] Because a standard definition for MPR or a consistent method of calculation doesn't exist, it is important to evaluate how MPR was calculated when interpreting literature regarding patient adherence. For example, a frequent definition of MPR is the sum of the days supply of medication divided by the number of days between the first fill and the last refill, plus the days supply of the last refill.[12] With this calculation, lapses in prescription refilling would usually result in an MPR <1.0, whereas early refilling could lead to a ratio >1.0 if the MPR is not truncated at a maximum value of 1.0. Although this measure provides some insight into medication adherence, it does not provide information on the timeliness and consistency of refilling medications.

Prevalence of Non-adherence: The Scope of the Problem

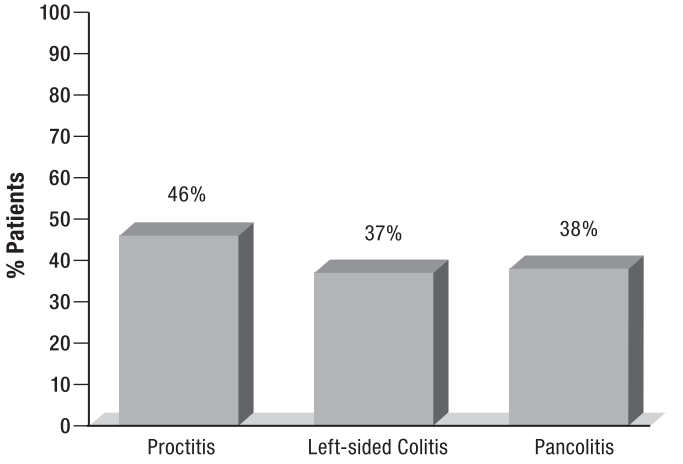
Lack of adherence to therapeutic regimens has been documented for decades[16] and remains a widespread problem. Non-adherence rates with any medication vary widely, with an estimated rate of 20% to 50%.[4,20] Even in clinical trials, where adherence rates can be remarkably high due to patient selection and the attention patients receive from study personnel, average adherence rates range from only 43% to 78% among patients receiving treatment for chronic conditions.[11]

Adherence rates are generally higher among patients with acute conditions than among those with chronic conditions.[11] For example, adherence rates with various antibiotic regimens used to eradicate *Helicobacter pylori* infection typically exceed 90%.[22] Medication persistence among patients with chronic conditions has been found to be extremely low, typically dropping dramatically after the first 6 months of therapy. Poor adherence in such populations has been well documented, with adherence to preventive pharmacologic therapies, such as 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitors (statins) and angiotensin-converting enzyme inhibitors, falling to <50% by the end of 1 year.[16]

Ulcerative Colitis

Patients with UC are at high risk for poor adherence.[23] Not only are patients typically young when diagnosed, but they also must

FIGURE 1 Percentage of Patients Not Using Long-term Mesalamine Therapy, Based on Disease Extent



Rubin G et al. (2002).[25]

cope with a lifelong disease that has an unpredictable course marked by potentially long periods of inactivity.[23] As in other chronic diseases, UC patients are generally required to take their medication throughout their lives, even during periods of symptomatic remission.[9] Maintenance therapy, Rubin said, means "taking something that's effective and safe to reduce the likelihood of a relapse over the next period of time, 12 months, 5 months, 10 years, your life."

Despite the need for lifelong maintenance therapy to reduce relapse, non-adherence is still prevalent among UC patients. As with other chronic conditions, non-adherence rates for short-term therapies in inflammatory bowel disease (IBD) patients tend to be lower (about 20%) than rates for maintenance therapies, which have been found to be as high as 50%.[7,15] In one of the earliest studies on 5-aminosalicylic acid (5-ASA) compliance in UC patients, van Hees and van Tongeren demonstrated that within 6 months of hospital discharge, 21 of 51 (41%) patients had urine sulfapyridine (i.e., acetylated sulfasalazine) levels that were considerably lower than before discharge.[24] Further, 21 of 175 (12%) outpatients taking maintenance sulfasalazine therapy had undetectable urine sulfapyridine levels. These low adherence levels were not improved nearly 20 years later, when a cross-sectional study of 363 UC patients demonstrated that 37% to 46% of patients were not receiving maintenance therapy with aminosalicylates (Figure 1).[25] Regarding these data, Sunanda Kane noted, "Basically, long-term mesalamine has been and continues to be underused by patients."

Involuntary non-adherence is common in IBD patients,[14,15,26] with up to 73% of non-adherent patients with quiescent disease indicating they did not take their medications because they forgot.[27] In a prospective study of 153 IBD patients, patient questionnaire results indicated that nearly 31% of patients were forgetful with their medications, 12% were careless, and nearly 20% stopped taking their medications in response to feeling better or worse (i.e., had intentional non-adherence).[15]

Impact of Non-adherence to Medical Therapy

Medication non-adherence can have significant implications for treatment outcomes, costs, and patient well-being. Non-adherence has been associated with lack of disease control and/or poor outcomes in various chronic conditions, including hypertension,[21,28] heart failure,[29] hypercholesterolemia,[16] diabetes,[30] asthma,[31] organ transplantation,[32] and depression.[33] For example, a longitudinal cohort study of 775 patients with type 2 diabetes found an independent association between increased comorbidity severity and emergency room visits during the year prior to enrollment in a Medicare health maintenance organization with decreased antidiabetic MPRs (i.e., reduced adherence) after enrollment.[30] Similarly, a population-based sample of 137,277 patients with chronic conditions (hypertension, diabetes, hypercholesterolemia, and congestive heart failure) demonstrated that the risk of hospitalization was highest in patients with low levels of adherence.[34] Additionally, in a population-based study of 2,742 patients diagnosed with depression, non-adherence to medication guidelines for depression was associated with fewer prescribing physician visits.[35]

In addition to poor disease outcomes, the association between medication adherence and health care costs has been well established.[20] Low levels of adherence with condition-specific drugs have been associated with higher medical costs for diabetes, hypertension, and hypercholesterolemia.[34] Sewitch et al. demonstrated in a population-based study that taking a recommended first-line antidepressant reduced the risk for hospitalization in patients with diagnosed depression.[35] In fact, it has been estimated that poor medication adherence accounts for 33% to 69% of all medication-related hospital admissions in the United States, resulting in a cost of approximately $100 billion per year.[11] Thus, "We know that it can be expensive to take the medicines, but it might be even *more* expensive to *not* take your medicine," Kane noted.

Ulcerative Colitis

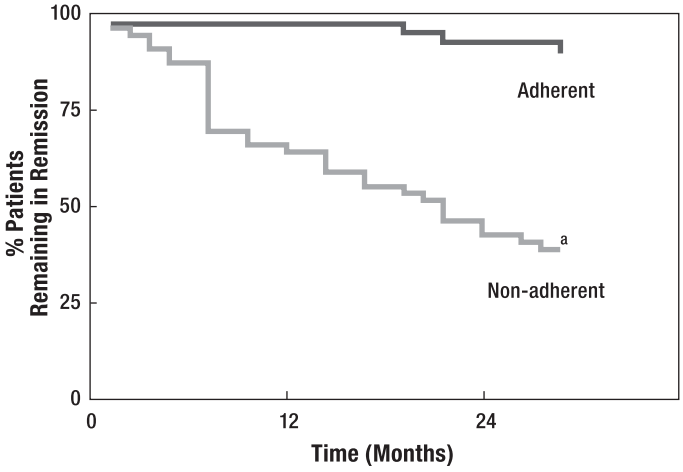
As in other chronic conditions, non-adherence to maintenance therapy has been associated with lack of disease control in UC patients. Kane et al. used pharmacy records to determine non-adherence rates with maintenance mesalamine therapy among 99 UC patients who were in remission for more than 6 months.[26] Patients were followed prospectively and evaluated at 6, 12, and 24 months. Twelve of 12 patients (100%) and 13 of 19 patients (68%) who had clinical recurrence at 6 and 12 months, respectively, were found to be non-adherent with their maintenance medication. The median amount of mesalamine refilled was

significantly lower in those with recurrent disease than in those in remission (50% vs. 80%, $P=0.03$).[26] The risk of maintaining remission was 89% among adherent patients compared with 39% among non-adherent patients ($P=0.001$) (Figure 2).[26]

Given recent data that suggest a protective effect of aminosalicylates on colorectal cancer (CRC) in IBD patients,[36] it has been suggested that adherence with 5-ASA agents may have a positive impact on cancer risk in this population.[9,25] Evolving data support a protective effect of 5-ASAs on CRC, including a meta-analysis of 9 studies involving 1,932 UC patients that found that the use of 5-ASAs was associated with a significantly lower risk of CRC (odds ratio [OR] = 0.51; 95% confidence interval [CI], 0.37-0.69) or a combined endpoint of CRC/dysplasia (OR = 0.51; 95% CI, 0.38-0.69).[36] More specifically, Moody et al. followed the incidence of CRC in 175 UC patients over a 10-year period and found that 5 of 152 patients (3%) who took long-term sulfasalazine developed CRC compared with 5 of 16 patients (31%) who either stopped treatment or were non-adherent ($P<0.001$).[37] The authors concluded that patients who were on long-term sulfasalazine therapy were significantly less likely to develop CRC than were those who were non-adherent or had discontinued therapy.[37] Although the duration and continuity of therapy needed to exert a protective effect are uncertain, these data suggest that adherence with 5-ASA agents may have implications for CRC risk reduction in UC patients.[25]

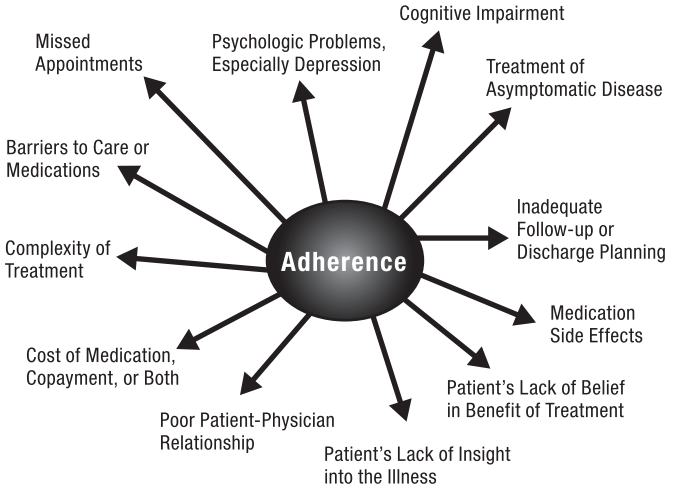
The impact of medication adherence on specific outcomes in UC has not fully been explored.[7] In addition to reducing relapse, "what we'd like to tie into adherence with maintenance therapy is all the things that go along with it, like hospitalization, colectomy, cost of care, resource utilization, and maybe cancer," Rubin said. "These are things that could be tied to longer-term outcomes if patients understand what we really mean by maintenance." However, data suggesting an association between adherence with maintenance therapy and reduction in such outcomes in UC patients are not yet available.

FIGURE 2 Clinical Impact of Non-adherence to Maintenance Mesalamine



[a] $P = 0.001$.
Adapted from Kane SV et al. (2003).[26]

FIGURE 3 The Multifactorial and Complex Nature of Adherence



Osterberg L and Blaschke T. (2005).[11]

Multifactorial Nature of Adherence

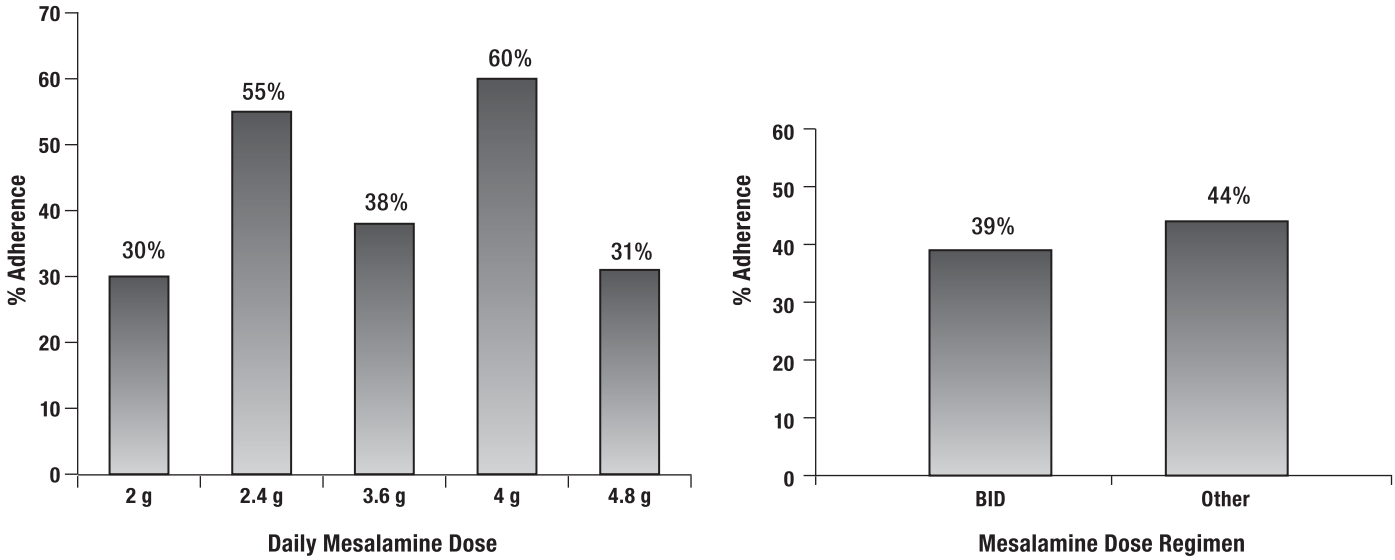
Adherence to medication is complex and multifactorial, with behaviors varying between and within individuals as well as across time.[15] Results of studies in various chronic conditions, including IBD, have demonstrated a variety of reasons that patients fail to adhere to their maintenance medication (Figure 3). Major factors that have been shown to affect adherence can be classified as those related to treatment, those related to the illness, and those related to the patient.

Treatment-Related Factors

Dose Regimen

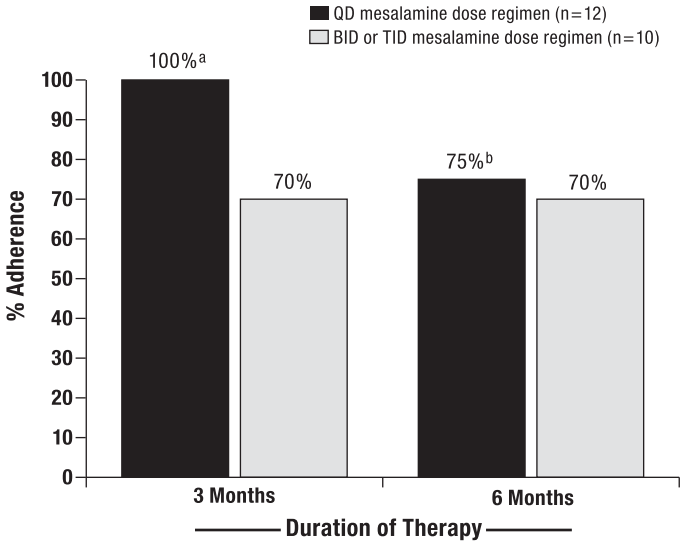
Recent data indicate a poor relationship between daily dose regimen and medication persistence. Brixner et al. examined prescription refill patterns for calcium channel blockers among 19,455 hypertensive patients enrolled in U.S. health plans within the Medstat MarketScan database.[38] The range of persistence at the end of 1 year for the once-daily drugs was found to vary widely, from 17% to 59%. Persistence did not correlate with daily pill load, leading to the conclusion that there are additional

FIGURE 4 Adherence Is Not Related to Daily Dose Regimen[a]



[a] *Data from 94 patients with clinically quiescent UC for >6 months on maintenance mesalamine.*
Adapted from Kane SV et al. (2001)[7] with permission from Blackwell Publishing.
BID=2 times a day; UC=ulcerative colitis.

FIGURE 5 Adherence Is Independent of Dose Regimen



[a] *P=0.04.*
[b] *P=NS at 6 months.*
Kane S et al. (2003).[39]
BID=2 times a day; NS=not significant; QD=1 time a day; TID=3 times a day.

drivers to persistency behavior beyond the indicated dose or actual pill load.

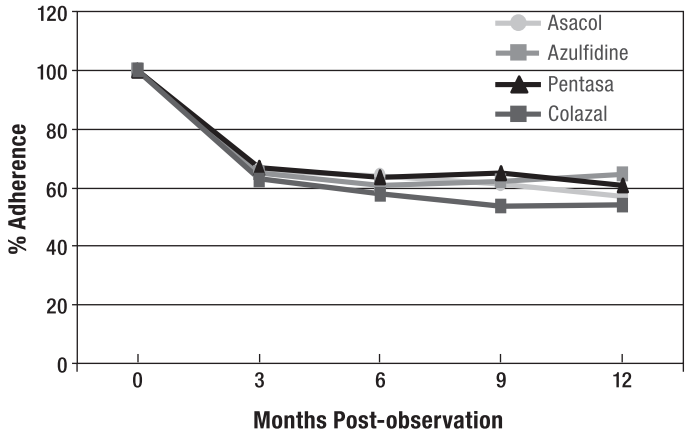
Similarly, studies in UC patients suggest that daily dose, regimen, and formulation do *not* significantly influence adherence in this population.[7,23,39] In a study of 94 patients with quiescent UC, adherence rates were not affected by either dose or dose regimen (Figure 4).[7] Regarding these data, Kane noted, "There was no trend in the dosing and it came down to more patient-related factors than it did treatment-related factors."

A small subsequent study compared adherence among 22 patients with quiescent UC who were receiving once-daily mesalamine with those receiving conventional dosing (i.e., 2 or 3 times daily).[39] Although more patients in the once-daily group were adherent at 3 months compared with the conventional-dosing group ($P=0.04$), there was no substantial difference in adherence between the groups at 6 months (Figure 5).[39] Thus, the impact of the dose regimen diminished over time.

In addition to reinforcing these findings, a recent retrospective cohort study suggests that adherence in UC patients is independent of drug formulation.[40] Magowan et al. used records from multiple U.S. health plans to compare the refill prescription profiles of 1,680 UC patients who had initiated 5-ASA therapy with 1 of 4 formulations: delayed-release mesalamine (Asacol), controlled-release mesalamine (Pentasa), sulfasalazine (Azulfidine), or balsalazide (Colazal). Upon initiation of

treatment, the median daily dose and respective tablet/capsule load were 2.4 g (6 tablets) for delayed-release mesalamine, 4.0 g (16 capsules) for controlled-release mesalamine, 2.0 g (4 tablets) for sulfasalazine, and 6.75 g (9 capsules) for balsalazide. The transition of acute to chronic therapy (at month 3) was found to be the most critical period for determining the degree of prescription loss for 5-ASA use, with the decrease in refills continuing at approximately 1% per month after 3 months. Comparison of the refill profiles over 12 months, however, indicated that adherence in these patients was not affected by formulation type and/or dose regimen (Figure 6).[40]

FIGURE 6 Rapid Decline in Refills at 3 Months, Independent of Formulation



Reprinted from Magowan S et al. (2006)[40] with permission from Blackwell Publishing.

Cost

Cost remains an important obstacle to medication adherence, with lack of coverage, high copayments, and frequent refill requirements all powerful disincentives to adherence.[16] Financial pressures and the cost of medications may force patients to make difficult choices about how and when they will take their medications.[23] Magowan et al. examined the refill rate behavior of 19,194 hypertensive patients receiving nifedipine after treatment initiation for 1 year, stratifying patients into high-copay and low-copay groups (defined as copay above or below $10, respectively).[41] Despite a similar average daily dose and tablet load per day, patients with a low copay were significantly more likely to continue refilling their nifedipine at 1 year than were those with a high copay (45.5% vs. 39.3%, $P<0.001$). A recent study by Brixner et al. demonstrated that in 4 disease states—asthma, hypertension, arthritis, and allergic rhinitis—there was an increase in discontinuation of therapy after changes in health plan benefit designs.[42] The authors concluded that physician prescribing practices should consider the effect of medication cost on patient refill persistence. Kane added that "$10 is costly to someone who may not have it or who feels that this medicine should be free, or $5. So the whole concept of cost is still a bit subjective."

Cost has proven to be a significant barrier to adherence in IBD patients as well. In the largest analysis of predictors of treatment adherence for IBD and the first to use a population-based sample, Ediger et al. reported adherence data from 326 Canadian patients diagnosed with IBD within the previous 7 years.[23] Cost was the most commonly cited obstacle to adherence, with 25% of patients indicating that cost made it difficult for them to take medication regularly.[23] This finding was despite the study being conducted in Canada, where the universal health care program makes it possible for many individuals to have coverage for much of their medication costs.[23] Cost could be an even greater obstacle in circumstances with more limited coverage for medical appointments and medications. With this obstacle in mind, Rubin noted, "When patients go to a pharmacy without first having had a cost discussion with you, they're going to make a decision not to take it if they feel they can't afford it or if they feel it's not worth it." Further complicating this scenario is the possibility that the physician may not be aware that the patient has decided to forego therapy, which can lead to a number of subsequent problems, such as the incorrect assumption of treatment failure, and switch to other therapies.

Adverse Effects

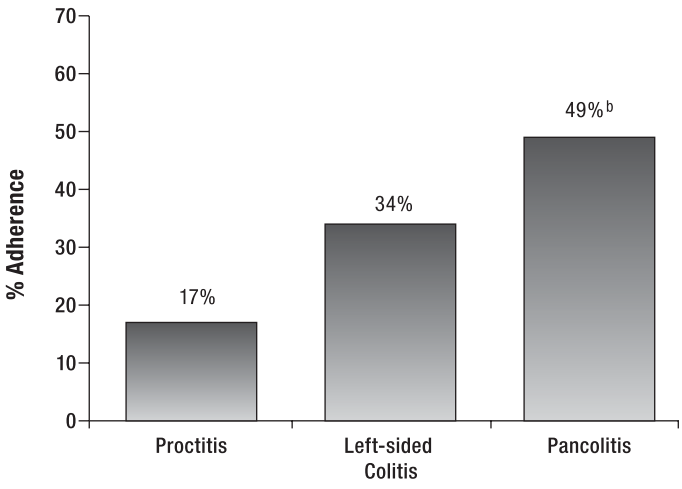
Concern for the safety of treatment has been identified as an important factor in determining adherence. In a large survey of 1,595 UC patients, 74% of patients considered lack of side effects to be very important when choosing treatment for their disease.[43] Moreover, fear of adverse effects of medication has a negative impact on adherence in this population, with 13% of IBD patients citing side effects as an obstacle to adherence.[23] Clinicians may contribute to this problem by failing to explain the side effects and benefits of a medication adequately.[11]

The safety profile of agents used in UC varies widely, ranging from the overall favorable tolerability profile of 5-ASA agents[44] to the more toxic adverse effects observed with corticosteroids, immunomodulators (azathioprine/6-mercaptopurine), and infliximab.[45,46] "We're lucky in terms of UC and aminosalicylate therapy that the vast majority of patients tolerate these drugs extremely well, and their side-effect profile is really very favorable," Kane said.

Illness-Related Factors

Illness-related factors that may affect adherence in UC patients include the severity, extent, and duration of disease; frequency, intensity, and duration of flare-ups; and the type and severity of complications. Rubin et al. found that among 363 UC patients with no history of colorectal surgery, the proportion of patients

FIGURE 7 *Adherence Is Higher in Patients With More Extensive Disease*[a]



[a]*Data from 94 patients with clinically quiescent UC for >6 months on maintenance mesalamine.*

[b]*Trend toward non-adherence in patients with less extensive disease, P=0.04.*

Kane SV et al. (2001).[7]

UC=ulcerative colitis.

currently taking 5-ASA agents was greater in those who had suffered from UC for fewer than 10 years than in those with disease of longer duration.[25] The median duration of disease among patients on 5-ASA therapy was 7 years compared with 12 years in those not receiving 5-ASA agents ($P<0.001$). The likelihood of current 5-ASA use was not related to extent of disease.[25]

In contrast, a potential impact of disease extent on adherence was demonstrated in a study of 94 patients with quiescent UC.[7] When patients were stratified by extent of disease, a significant trend toward non-adherence in those with less extensive disease was observed ($P=0.02$) (Figure 7).[7] Having a diagnosis of left-sided UC was significantly associated with non-adherence on univariate analysis, whereas logistic regression found that having a recent colonoscopy and having a greater extent of disease were positively associated with adherence.[7] Summarizing these data, Kane commented, "The more disease you had, the more likely you were to be adherent. So, if you had pancolitis versus just proctitis, maybe you're more motivated to take your medicine because more of your colon is sick."

A relationship between a more complicated disease course in IBD and better medication-taking behavior has been observed in other studies. Bernal et al. found significantly better adherence among 214 IBD patients with a more complicated disease course as characterized by steroid dependency, steroid refractoriness, need for infliximab, hospitalization, or surgery ($P=0.02$).[47] In a prospective study of 153 IBD patients, Sewitch et al. noted a decreased risk of overall non-adherence in patients with active disease, longer duration of disease, and prescribed steroids.[15] These findings reinforce the observation that a less complicated disease course in IBD tends to be associated with worse medication-taking behavior.[47]

Patient-Related Factors

The patient-physician relationship, as well as individual and psychosocial characteristics, may have a strong influence on adherence.[14] Factors associated with non-adherence in UC patients include age, full-time employment, history of taking more than 4 concomitant medications, male gender, new patient status, psychiatric comorbidity, and single status.[9,15,48] Patient beliefs and perceptions that have been identified as reasons for non-adherence by UC patients include denial of illness and inability to see the need for medication during periods of symptom remission.[9] However, data regarding the relationships of these factors with non-adherence have been inconsistent and remain inconclusive.[15,16]

The Patient-Physician Relationship

The role of psychosocial characteristics and the physician-patient relationship in determining non-adherence was evaluated in a prospective study involving 153 IBD patients.[15] Non-adherence to medication was assessed 2 weeks after an office visit during which patients' psychosocial characteristics and patient-physician discordance were evaluated. Discordance was measured by a questionnaire assessing the physicians' and patients' perceptions of the patients' health status and of the clinic visit. Questionnaires were completed independently by both the physicians and patients immediately after an office encounter.[15]

As in other studies of IBD patients, non-adherence was found to be high (41%), with 33% of patients unintentionally non-adherent to medication and 15% intentionally non-adherent.[15] Overall, patients who were not psychologically distressed were at higher risk for non-adherence than were distressed patients (Figure 8).[15] Moreover, the discordance between the patient and physician regarding their perceptions of the patient's clinical status and of the clinical visit was an important influence on adherence.[15] Poor or ineffectual patient-physician dialogue, as reflected by higher patient-physician discordance, was found to increase the risk of intentional non-adherence in all patients, as well as the risks of overall and unintentional non-adherence in psychologically nondistressed patients.[15] These results support the belief that adherence depends on effective patient-physician dialogue. "When the quality of the relationship is good," Sewitch explained, "the adherence is better. What I tend to think is going on is that patients feel understood and that their problem is understood. Perhaps there's more negotiation that's going on."

The Complexity of Adherence in IBD

Non-adherence is a multifactorial problem, with complex relationships between demographic, psychologic, and medication variables influencing medication-taking behavior. In order to identify factors predictive of 5-ASA non-persistence in UC patients, Kane et al. retrospectively studied 3,574 UC patients in whom 5-ASA therapy had been initiated between October 2002 and September 2004.[49] Consistent with previous estimates of non-adherence in this population,[15] 1,530 (42.8%) patients did not refill their 5-ASA prescription at 3 months. Seven of 15 variables investigated were independently associated with non-persistence, underscoring the multifactorial and complex nature of adherence (Figure 9). The most significant factors predicting non-persistence at 3 months were psychiatric history and copay. Glucocorticoid use and rectal 5-ASA use in the 12 months prior to the index date were significantly associated with a decreased risk of not refilling, whereas age and endoscopy within 12 months of the index date were not significant predictors.[49]

In their cross-sectional study of 326 IBD patients involved in the Manitoba IBD Cohort Study, Ediger et al. found a number of potential obstacles to adherence in this population.[23] As mentioned previously, the most frequently cited self-reported obstacle to adherence was cost (25%), followed by side effects (13%), unpleasant associations with medication (13%), uncertainties about the effectiveness of the medication (12%), and forgetfulness (10%).[23] Adherence decreased as the number of obstacles to medication use increased, a relationship observed in both men and women. Another finding consistent across genders was the likelihood of patients with high interpersonal agreeableness to report higher levels of adherence than of those with low agreeableness. This finding, consistent with that of Sewitch et al.,[15] highlights the importance of the patient-physician relationship and agreement for adherent behavior.[15,23]

An additional finding of interest from these data was that several specific predictors of adherence differed significantly among men and women. For example, full-time employment predicted low adherence only in men, whereas younger age predicted low adherence only in women.[23] The importance of such gender interactions in determining adherence requires further study.

Strategies for Increasing Adherence in UC Patients

Although a variety of interventions to improve adherence have been proposed, there are no accepted, fully effective strategies in widespread clinical use.[3] Many strategies that have been used are primarily unidimensional in nature[20] and offer only limited long-term improvements in "real-world" settings.[9] Given that the factors that determine adherence are interrelated and potentially influence each other, interventions that target only 1 factor may not be optimal.[20]

Interventions to improve adherence have ranged from simple adjustments in the medication regimen to complex multidisciplinary interventions aimed at improving communication between patients and physicians.[4] Common strategies used to improve dose regimens have been effective in some patients and include using pill boxes to organize daily doses, simplifying the regimen to once-daily dosing, and using cues to remind patients to take their medications.[4,11] Educational interventional strategies such as individual and/or group counseling sessions, with or

FIGURE 8 Psychological Stress Reduces Non-adherence

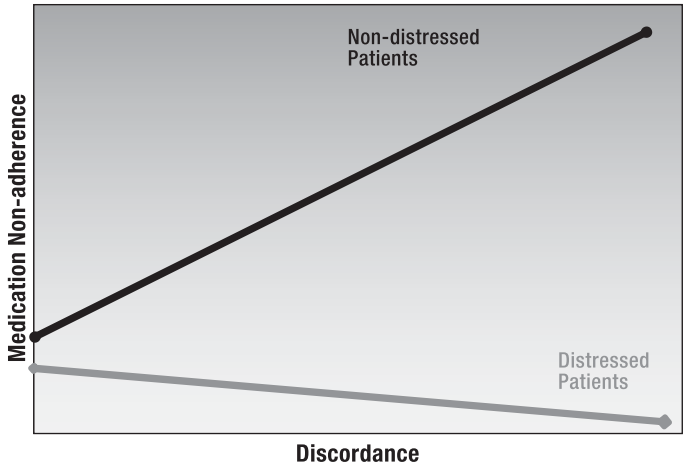


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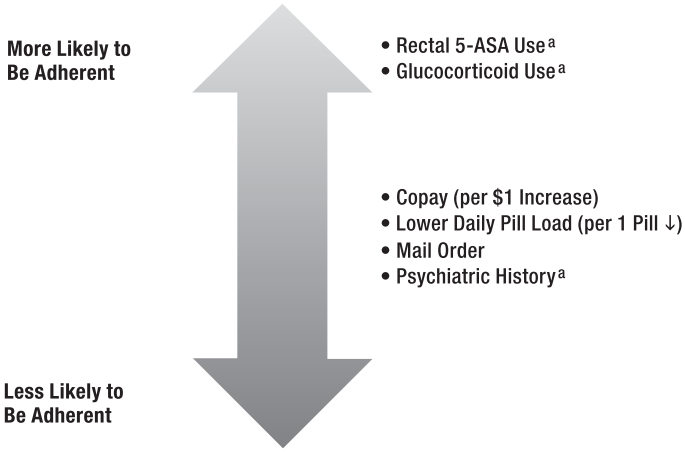
FIGURE 9 Significant Factors Associated With Risk of Not Refilling 5-ASA at 3 Months



[a] *≤12 months prior to index date. Data from 3,574 UC patients with 5-ASA Rx's; 1,530 (42.8%) patients did not refill at 3 months.*
Kane S et al. (2007).[49]
5-ASA=5-aminosalicylic acid.

without written materials, have improved adherence in patients with various chronic diseases.[4] While some behavioral interventions such as repeated assessment of medication use with feedback appear to be effective, other methods (e.g., directly observed therapy, specialized packaging, and cognitive behavioral therapy) have not been shown to enhance adherence significantly.[4]

Although commonly seen as a patient problem, non-adherence must be addressed on several levels, including the patient, the provider, and the health care system.[16] Patients need the knowledge, attitude, and skills to follow a prescribed regimen appropriately. To that end, multidisciplinary efforts to explain the use of medications, provide continuing education, monitor the treatment regimen, minimize side effects, and remind and motivate patients to adhere are important patient interventions.[20]

The provider also plays a critical role in adherence to therapy, with the physician-patient relationship known to have a significant effect on adherence.[10,15,16] The patient should believe in the physician, as well as in the value of the treatment assigned for his or her problem.[10] "I think implied in the relationship," Rubin said, "is that there's going to be some mutually agreed-upon goals and that you're both going to do your part to reach them. What is missing often in the dialogue is a statement of what those goals are, which often falls by the wayside in a busy practice."

Adherence can be encouraged by open communication between patient and physician, with patients allowed ample time to discuss concerns and ask questions.[9] On the simplest level, physicians should always ask about adherence to medication.[16] To establish a good therapeutic relationship, physicians should use open-ended questions and an appropriate tone and not underestimate or overestimate the patient's level of understanding.[9] "I think we need to make it our responsibility to ask our patients: 'What do you think about this? Is this going to be possible for you? Is this reasonable?'" Rubin said. The patient should be encouraged to express his or her beliefs, fears, and expectations regarding adherence, and, when possible, the physician could customize the medication regimen in accordance with the patient's wishes.[10,11] According to Kane, "You have to be able to simplify it for the patient and work within their lifestyle, their education level, their understanding, and their comfort zone."

Lastly, health care delivery systems and policy organizations can provide the kind of supportive environment that facilitates effective interventions to promote adherence.[3,16] For example, providing support to build a multidisciplinary team and allow the collective effort of other health care professionals (e.g., pharmacists, nurses) can offer the social support and patient satisfaction with care that can improve adherence. Comprehensive pharmacy care programs have been shown to improve medication adherence in several chronically ill populations, including depressed patients[50] and elderly patients with hypertension and/or hypercholesterolemia.[3] Health care systems can also provide reporting and tracking systems that will better enable providers to monitor patient adherence.[16] Interactive computer-based disease management programs can provide online support to the patient,[51,52] encouraging them to continue taking medications, while at the same time collecting patient information on a large scale to track patient outcomes based on side effects, adherence, cost, and effectiveness. Additionally, and whenever possible, coverage plans, generic formulations, and refill requirements should be leveraged to remove financial barriers to adherence.[3,16] A health plan needs to consider the impact of higher copay levels or other benefit designs on patient access to medications. Some health plans have begun to consider alternative approaches to formulary management, such as eliminating copayments altogether for chronic disease states such as diabetes.[53]

Conclusions

Non-adherence is a prevalent problem in chronic disease states, with typical adherence rates of approximately 50%. In keeping with these estimates, 40% of patients with quiescent UC have been found to be adherent with maintenance therapies. Non-adherence can significantly affect disease outcomes and cost in a number of chronic conditions. The risk of maintaining remission was 89% among adherent patients compared with 39% among non-adherent patients. Moreover, it is possible that non-adherence with maintenance 5-ASA therapy leads to a greater risk of CRC and higher overall costs of care for UC.

Adherence to medication is complex and multifactorial. Patient- and disease-related characteristics that have been shown to affect adherence in UC patients include disease extent and duration, full-time employment, male gender, new patient status, patient-physician discord, and single status. Patient beliefs and perceptions (e.g., denial of illness, inability to recognize the need for medication during disease remission) can also affect adherence. In contrast, recent data indicate that treatment-related factors such as daily dose, regimen, and formulation do not significantly influence adherence in this population. Moreover, studies in UC patients demonstrate that the impact of dose regimen diminishes over time. Other potential barriers to adherence include the cost of medications and patients' fears of adverse effects.

Efforts to improve adherence should involve not only the patient, but also the provider and health care delivery systems. Patient-education efforts should address the rationale for the use of medications, as well as a discussion of potential side effects. For UC patients, knowledge and discussion of rationale supporting persistence, such as recent data regarding agents that have a potential chemoprotective benefit, may encourage persistence, even during periods of quiescence. The patient-physician relationship is critical in encouraging adherence, particularly with respect to education, open communication, and agreement regarding the value of the assigned treatment. Finally, health care delivery systems may support improved adherence by encouraging the participation of multidisciplinary teams, providing reporting and tracking systems, and eliminating financial barriers where possible.

DISCLOSURES

Sunanda V. Kane has received grant/research support from AstraZeneca and Procter & Gamble Pharmaceuticals, Inc.; is a consultant/scientific advisor for Abbott Laboratories, Centocor, Inc., Elan, Procter & Gamble Pharmaceuticals, Inc., Shire Pharmaceuticals Group, and UCB Pharma; and is a member of the speakers' bureaus for Abbott Laboratories, Centocor, Inc., Novartis, Procter & Gamble Pharmaceuticals, Inc., Prometheus, Shire Pharmaceuticals Group, and TAP. **Diana Brixner** is a consultant/scientific advisor for Procter & Gamble Pharmaceuticals, Inc. **David T. Rubin** is a consultant and speaker for Procter & Gamble Pharmaceuticals, Inc., Salix Pharmaceuticals, Inc., and Shire Pharmaceuticals Group, and is a consultant for Axcan Pharma. He has received grant support from Procter & Gamble Pharmaceuticals, Inc. and Salix Pharmaceuticals. **Maida J. Sewitch** reports no bias or conflict of interest relating to this article.

The supplement was written by **Julie Messick,** PharmD, a professional medical writer who had the recommendations, review, and approval of the authors. Messick discloses that her spouse is an employee of GlaxoSmithKline.

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Continuing Education for this program is processed through the AMCP.org Online Learning Center site at www.amcp.org (CE/CME Center). You can also take the test by mailing this posttest and evaluation form to the Enduring Materials Coordinator, Penn State Continuing Education, G220; PO Box 851; Hershey, PA 17033-0851 or faxing it to 717.531.5604. It is recommended that participants keep a copy of their completed materials until they receive their certificate. For questions, please call Penn State Continuing Education at 717.531.6483 or e-mail ContinuingEd@hmc.psu.edu. Please reference activity code **G3812-08-R**. Be sure to mail the posttest and evaluation form on or before December 31, 2008. After this date, the activity will no longer be designated for credit. A CME certificate will be mailed within 6 to 8 weeks.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission.

In order to receive CE credit for this program immediately, you must complete the following forms online:

1. Posttest form for this program, "The Challenge of Compliance and Persistence: Focus on Ulcerative Colitis," on the AMCP.org Online Learning Center site. To receive CE credit, you must receive a score of at least 80%. You will have 2 opportunities to pass the posttest.
2. Program Evaluation form

Upon successful completion of this activity online, you will automatically receive your CE statement. Your CE credits will be automatically archived and tracked for you on the AMCP.org Online Learning Center site. All information is kept confidential.

Note: *There is a $10 processing fee for nonmembers. (See payment instructions on site.).*

To complete this activity, go to www.amcp.org (CE/CME Center), where you will access the posttest and evaluation form.

Posttest Worksheet: The Challenge of Compliance and Persistence: Focus on Ulcerative Colitis
(If you're not completing this activity online, record your posttest answers on the posttest answers/evaluation form.)

1. Which of the following accurately describes medication persistence?
   a. Measured by a time metric
   b. Implies a paternalistic relationship with the physician
   c. Is used interchangeably with the term "adherence"
   d. All of the above

2. Examples of unintentional, or involuntary, non-adherence include
   a. deciding not to take a medication due to cost constraints.
   b. discontinuing medication in response to feeling better.
   c. not taking medication due to forgetfulness.
   d. all of the above.

3. Indirect methods of measuring medication adherence include
   a. serum drug/metabolite levels.
   b. prescription refill rates.
   c. biologic markers.
   d. all of the above.

4. General patterns of non-adherence include
   a. discontinuing medication completely.
   b. taking doses at inappropriate intervals.
   c. overconsuming medication.
   d. all of the above.

5. Which of the following statements regarding non-adherence is/are true?
   a. Average non-adherence rates are estimated to range from 20% to 50%.
   b. Non-adherence rates tend to be higher for short-term therapies than for long-term therapies.
   c. Medication persistence among patients with chronic conditions tends to be stable over the first 2 years of disease.
   d. All of the above.

6. Clinical trials in ulcerative colitis (UC) patients have demonstrated an association of medication non-adherence with the following outcomes:
   a. Increased rate of disease recurrence
   b. Increased colectomy
   c. Increased hospitalization rate
   d. All of the above

7. Which of the following statements regarding medication persistence in UC patients is/are true?
   a. Mesalamine dose is not a critical determinant of persistence.
   b. The transition from acute to chronic therapy that occurs around 3 months is a critical period for determining degree of prescription loss.
   c. Patients with extensive disease may be more adherent than those with proctitis.
   d. All of the above.

8. Patient characteristics that have been linked to non-adherence in UC include
   a. single status.
   b. psychiatric comorbidity.
   c. history of more than 4 concomitant medications.
   d. all of the above.

9. A recent study examining the patient-physician relationship in inflammatory bowel disease (IBD) patients demonstrated that
   a. psychologically distressed patients are at higher risk of non-adherence than are nondistressed patients.
   b. patient-physician discordance does not influence adherence.
   c. effective patient-physician dialogue is an important determinant of adherence.
   d. all of the above.

10. Which of the following factors have been cited by IBD patients to be obstacles to medication adherence?
    a. Cost
    b. Fear of medication adverse effects
    c. Uncertainties about the effectiveness of their medication
    d. All of the above

11. A recent study demonstrated that the most significant factors determining non-persistence with 5-ASA therapy in UC patients at 3 months were
    a. dose, dosage formulation, and dose regimen.
    b. endoscopy within 12 months and age.
    c. psychiatric history and copay.
    d. married status, glucocorticoid use, and rectal 5-ASA use.

12. The largest analysis of predictors of treatment adherence for IBD recently demonstrated that
    a. the likelihood of adherence decreased as the number of patient-reported obstacles to medication use increased.
    b. specific predictors of adherence differed between men and women.
    c. patients with high interpersonal agreeableness have higher levels of adherence than do those with low agreeableness.
    d. all of the above.

13. Interventions to improve adherence should involve
    a. patients.
    b. providers.
    c. health care delivery systems.
    d. all of the above.

14. Which of the following is/are an important strategy for improving adherence in UC patients?
    a. Specialized packaging
    b. Encouraging open communication between patients and physicians
    c. Directly observed therapy
    d. All of the above

15. Health care delivery systems may promote adherence by
    a. providing reporting and tracking systems.
    b. encouraging multidisciplinary team involvement.
    c. leveraging coverage plans to eliminate financial barriers.
    d. all of the above.

ACTIVITY CODE G3812-08-R

The Challenge of Compliance and Persistence: Focus on Ulcerative Colitis

POSTTEST ANSWERS

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15

CREDIT APPLICATION

Name (please print) _____ Degree _____

Specialty _____

Address _____

City _____ State _____ ZIP _____

E-mail _____ Phone _____ Fax _____

I verify that I have completed this CE/CME activity (signature) _____

Actual time spent on the activity (up to 1 hour) _____

EVALUATION

Evaluation of this activity is integral to the continuing medical education (CME) process. CME certificate requests cannot be processed without completion of the evaluation form. Please evaluate this educational activity by completely filling in the circles using a dark pen or pencil.

Overall Evaluation	Very High	High	Moderate	Low	Very Low
1. Extent to which overall objectives were achieved	O	O	O	O	O
2. Extent to which you are satisfied with the overall quality of the supplement	O	O	O	O	O
3. To what extent did the supplement present scientifically rigorous, unbiased, and balanced information?	O	O	O	O	O
4. To what extent was the supplement free of commercial bias?	O	O	O	O	O
5. To what extent did this supplement change your knowledge/attitudes?	O	O	O	O	O
6. To what extent did this educational activity change your skills?	O	O	O	O	O
7. To what extent will you make a change in your practice as a result of your participation in this educational activity?	O	O	O	O	O

8. Which of the following best describes the effect of this activity on your performance? (choose one)

- O This activity will not change my behavior because my current practice is consistent with what was taught.
- O This activity will not change my behavior because I do not agree with the information presented.
- O I need more information before I can change my practice behavior.
- O I will immediately implement the information in my practice.

9. I will use the information obtained O immediately O within the coming year O never

The Posttest Answers/Evaluation Form may be faxed or mailed to:
Enduring Materials Coordinator, Penn State Continuing Education, G220;
PO Box 851; Hershey, PA 17033-0851; Fax: 717.531.5604.

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