

Ask the Experts: UPDATES IN ULCERATIVE COLITIS

PRACTICAL STRATEGIES FOR IMPROVING TREATMENT ADHERENCE



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Target Audience

Nurse practitioners (NPs) and physician assistants (PAs) in primary care practice.

Activity Goal

To familiarize NPs and PAs in primary care practices with practical strategies for improving adherence to treatment by their patients with ulcerative colitis (UC).

Learning Objectives

After completing this activity, participants should be better able to:

1. Recognize the patient-, treatment-, and disease-related factors that may increase the risk of treatment nonadherence for their patients with UC.
2. Incorporate information about the consequences of treatment nonadherence into discussions geared toward educating patients about their disease.
3. Integrate strategies for increasing treatment adherence into individualized management plans for each of their patients with UC.

Accreditation Information

The University of Nebraska Medical Center College of Nursing Continuing Nursing Education is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is provided for 1.5 contact hours under ANCC criteria.

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This program has been reviewed and is approved for a maximum of 1.5 hours of AAPA Category I CME credit by the Physician Assistant Review Panel. Approval is valid for one year from the issue date of December 23, 2009. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

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The estimated time to complete this activity is 1.5 hour.

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Ulcerative colitis (UC) is a chronic inflammatory disease of the colon characterized by periods of relapse and remission.¹

Treatment of UC is a 2-stage process involving induction of remission and prevention of relapse.^{2,3} Treatment of UC is life-long and is associated with high nonadherence rates, particularly during the asymptomatic remission phase.^{1,4}

Treatment nonadherence in UC is associated with increased morbidity, including a greater risk of symptomatic relapse,⁵ increased risk of colorectal cancer (CRC),⁶⁻⁸ and possibly reduced health-related quality of life (HRQOL)⁹⁻¹¹ and increased health-care costs.¹² Thus, measures to improve treatment adherence are an important aspect of a successful treatment regimen for UC.

This issue of *Ask the Experts: Updates in Ulcerative Colitis* discusses strategies for improving treatment adherence in UC. It is the final issue of 3 continuing education newsletters on UC. The first issue focused on key strategies for early diagnosis. The second issue highlighted current approaches to medical therapy.

UC Treatment Overview

Because the exact cause of UC is unknown, disease-modifying therapies are not available. Medical therapy is focused on relieving the signs and symptoms of UC and inducing and maintaining remission.^{2,13} Therapy is guided by the clinical severity of an acute attack and the anatomic extent of disease.^{2,13} There are 2 classes of agents used for the treatment of UC: anti-inflammatory and immunomodulatory (Table 1).^{2,3,14}

TABLE 1. Agents Used in the Treatment of Patients With Ulcerative Colitis

Anti-inflammatory	Immunomodulatory
5-ASA compounds	6-MP
<ul style="list-style-type: none"> • Sulfasalazine • Olsalazine • Balsalazide • Mesalamine 	<ul style="list-style-type: none"> Azathioprine Cyclosporine Infliximab
Corticosteroids	

5-ASA = 5-aminosalicylic acid; 6-MP = 6-mercaptopurine. Kornbluth A, et al²; Langan RC, et al³; Kefalides PT, et al.¹⁴

5-Aminosalicylic (5-ASA) compounds are the mainstay of UC therapy. Current treatment guidelines recommend 5-ASA compounds (oral and/or topical) as first-line treatment for the induction and maintenance of remission of mild-to-moderate UC (Figure 1).^{3,13} Although corticosteroids, cyclosporine, and infliximab also are effective for the induction of remission of mild-to-moderate UC, these agents normally are not used as first-line agents. Oral corticosteroids generally are recommended only for patients with mild-to-moderate UC who are refractory to 5-ASA compounds or patients who have moderate-to-severe disease. In patients with severe disease requiring hospitalization, parenteral corticosteroids, parenteral cyclosporine, and infliximab are the therapeutic choices. However, because the safety of parenteral cyclosporine is controversial, many practices do not use it. Infliximab also is considered an alternative treatment in patients with moderate-to-severe disease refractory to other therapies (Figure 1).^{3,13} The immunomodulators, azathioprine (AZA) and 6-mercaptopurine (6-MP) have no utility in inducing remission as they have a slow onset of activity, taking about 3 months to reach full activity.¹⁵

Corticosteroids are not recommended for maintenance therapy because of the associated serious adverse effects, including infections, glucose intolerance, osteoporosis, psychiatric disturbances, and dependence.^{15,16} In patients who respond to the infliximab induction regimen of 3 doses infused at 0, 2, and 6 weeks, infliximab may be continued as maintenance therapy with infusions every 8 weeks.¹⁵ AZA and 6-MP have a limited role as maintenance therapy and only are used for lowering or weaning off corticosteroid use in patients with chronic, active corticosteroid-dependent UC.¹⁵

Nonadherence in UC

Despite the efficacy of UC therapies in inducing and maintaining remission, nonadherence rates are high among patients with UC, especially in those with quiescent disease.¹⁷ In an interview-based study of patients with UC, the nonadherence at any timepoint during treatment (for flares, chronically active disease, or maintaining remission) was found to be 42% in patients receiving 5-ASA, 45% in those on topical steroids, 40% in patients on systemic steroids, and 29% in those on immunosuppressants.¹⁸ However, in patients with quiescent UC who are receiving 5-ASA maintenance therapy, nonadherence rates can be as high as 60%.¹⁷

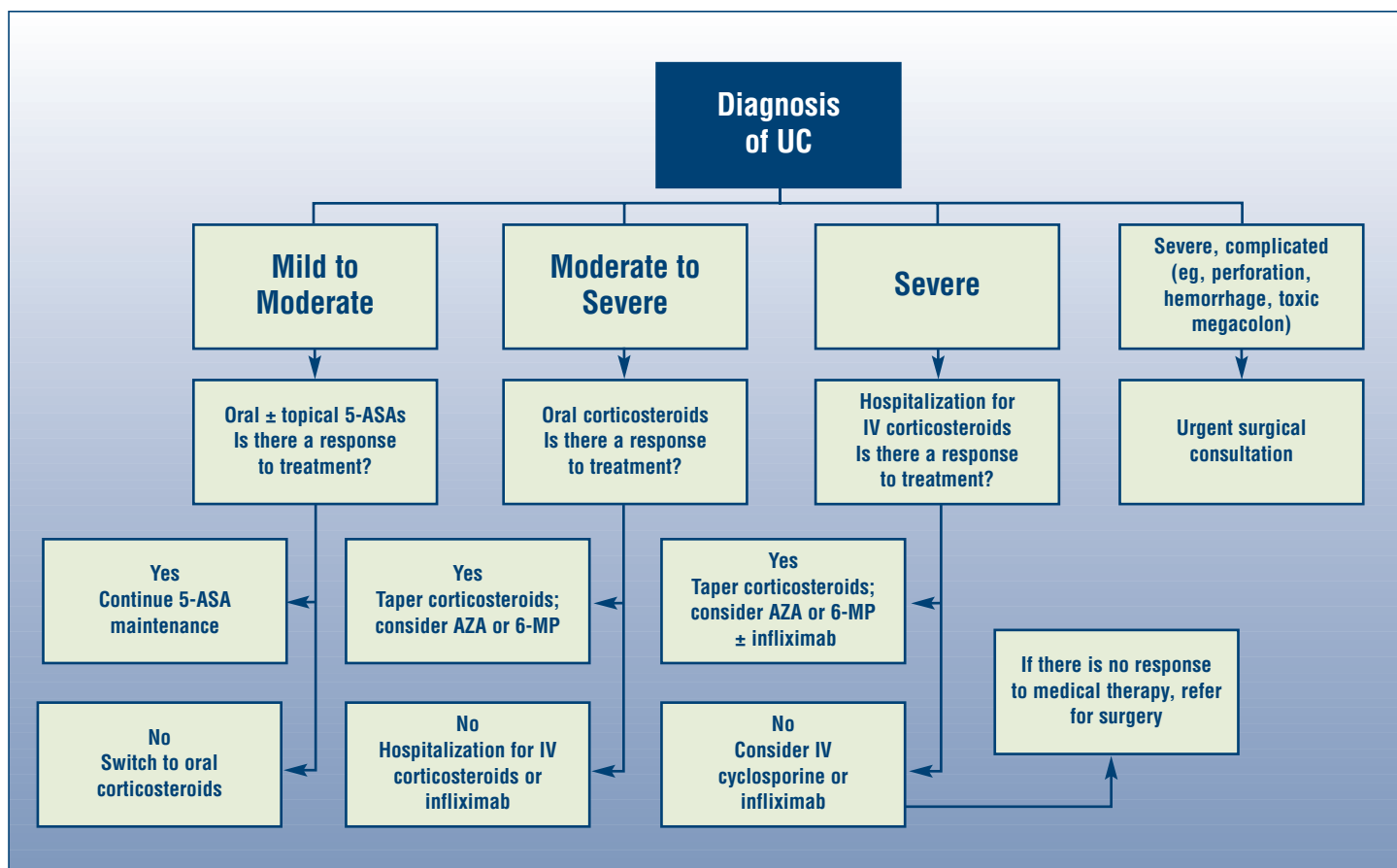


Figure 1. Treatment algorithm for UC. 5-ASA = 5-aminosalicylic acid; AZA = azathioprine; IV = intravenous; 6-MP = 6-mercaptopurine; UC = ulcerative colitis. Adapted from Langan RC, et al³; Panaccione R, et al.¹³

Reasons for nonadherence are multifactorial with complex relationships among demographic, psychological, and medication variables that influence medication-taking behavior. The reasons for nonadherence may change over time within patients and between patients, which adds to the complexity.¹⁹ Nonetheless, some major identifiable factors that affect medication adherence have been broadly categorized into patient-related, treatment-related, and disease-related factors.²⁰

Patient-Related Factors

Patients may be unintentionally (involuntarily) or intentionally (voluntarily) nonadherent to therapy. Unintentional nonadherence is a passive process in which the patient is forgetful or careless about adhering to the treatment regimen.²¹ Some general patterns of unintentional nonadherence include under- or overconsuming medication, failing to fill a prescription, taking doses at inappropriate intervals, and administering medication incorrectly.²² Intentional adherence is an active decision to deviate from the treatment regimen.²¹ In the latter case, the patient

intentionally stops taking medications because of feeling better/worse with treatment or because of cost issues. Alternatively, in an attempt to reduce cost, the patient might take the medication less frequently than prescribed so as not to have to refill as often.²⁰

In patients with inflammatory bowel disease (IBD), unintentional nonadherent rates usually are higher than intentional nonadherence rates: 67% versus 35%²³; 33% versus 15%.²⁴

A number of patient characteristics, including age, single status, male gender, new patient status, and full-time employment, as well as patient clinical history—taking >4 concomitant medications and psychiatric comorbidity—have been associated with nonadherence in UC (Table 2).²⁴⁻²⁷ A firm relationship between some of these factors and nonadherence, however, has not been demonstrated.^{20,24} Other factors, such as the perceptions or beliefs of patients and patient-clinician dialogue, are also important contributors to nonadherence. Disbelief in the need for so much medicine, disease denial, and lack of perceived treatment benefits during symptom-free periods are some of the self-reported

TABLE 2. Patient-Related Barriers to Adherence

Patient-clinician relationship (eg, unsupportive or uncommunicative)

Patient characteristics

- Younger age
- Male gender
- Single status
- New patient
- Full-time employment

Patient clinical history

- Taking >4 concomitant medications
- Psychiatric comorbidity

Patient beliefs and perceptions

- Disbelief in the need for so much medication
- Denial of illness
- Lack of perceived benefit of treatment, especially in symptom remission

Sewitch MJ, et al²⁴; Kane SV²⁵; Sewitch MJ, et al²⁶; Nigro G, et al.²⁷

TABLE 3. Treatment-Related Barriers to Adherence

Pill burden/regimen/formulation

Mode of delivery

Cost

Adverse effects

Ockene IS, et al²²; Kane SV, et al²⁹; Loftus EV Jr.³⁰

TABLE 4. Disease-Related Barriers to Adherence

Severity, extent, duration of disease

Frequency, intensity, duration of flares

Type/severity of complications

Kane SV, et al.²⁰

perceptions/beliefs of patients with UC that hinder adherence to treatment.²⁵ Poor or ineffectual patient-clinician dialogue, as reflected by higher patient-clinician discordance regarding perceptions of the patient’s clinical status and clinic visit, was found to increase the risk of nonadherence in IBD patients.²⁴

Treatment-Related Factors

Although treatment-related factors such as pill burden, dosing frequency, formulation type (immediate or controlled release) usually are considered determinants of nonadherence, this might not be true in patients with UC. A retrospective cohort study showed that daily dose, regimen, and formulation do *not* significantly influence adherence (prescription refill rates during a 12-month period) in patients with UC (Figure 2).²⁸

Other treatment-related factors that may contribute to nonadherence in UC include cost of therapy and adverse effects (Table 3). In addition, an inconvenient and intrusive drug delivery mode, such as rectal formulations, can lead to reduced adherence compared with oral formulations.²⁹ Cost is an important obstacle to medication adherence—lack of coverage, high copayments, and frequent refill requirements—are powerful disincentives to adherence.²² Side effects and fear of side effects of medications also are contributors to adherence in patients with UC.³⁰

Disease-Related Factors

Disease-related factors also may affect adherence in patients with UC (Table 4).²⁰ Adherence is higher in patients with extensive disease (Figure 3),¹⁷ shorter disease duration,³¹ and more complicated disease course (steroid dependency; steroid refractoriness; need for infliximab, hospitalization, or surgery).³²

Consequences of Nonadherence

Clinical Relapse

Nonadherence to maintenance therapy can increase the risk of UC relapse. A cohort study of patients with UC (N = 99) in remission for >6 months showed that patients who were nonadherent to their prescribed 5-ASA maintenance therapy had an almost 6-fold increased risk of clinical relapse compared with those who were adherent (61% vs 11%, $P = .001$). Moreover, nonadherent patients had a 39% chance of remaining in remission during a 2-year period while adherent patients had an 89% chance of maintaining remission (Figure 4).⁵

Increased Risk of CRC

In UC, the risk of developing CRC increases with disease extent and duration. The lifetime risk of CRC in UC is ~20%.³³

Epidemiologic studies have shown that regular use of 5-ASA therapy in patients with UC significantly reduces the risk of developing CRC by up to 75%.^{7,8} In a 10-year cohort study, 31% of patients with UC who stopped sulfasalazine therapy on physician-advice or were nonadherent to treatment developed CRC compared with 3% who continued long-term treatment.⁶ These data suggest a protective effect of 5-ASA against CRC in patients with UC. A systematic review and meta-analysis of 9 studies involving 1932 patients with UC confirmed that use of 5-ASA compounds was associated with a significantly lower risk of CRC (odds ratio [OR] = 0.51; 95% confidence interval [CI], 0.37-0.69).³⁴

Reduced Quality of Life

Several studies have shown that symptomatic UC impacts quality of life (QOL) and disease activity is a significant predictor of reduced health-related life satisfaction.⁹⁻¹¹ Consistent use of oral 5-ASA, in contrast, can improve HRQOL, as shown in a randomized, placebo-controlled, double-blind trial of patients with UC (N = 374) using mesalamine capsules at 1 g, 2 g, and 4 g daily.³⁵ In this study, function-related QOL parameters assessed included 5 pertinent clinical symptoms (daily trips to the toilet, stool consistency, rectal bleeding, abdominal/rectal pain, and rectal urgency) and 7 general life capabilities (ability to sleep, sexual relations, routine outdoor activities, social activities, indoor activities, work/occupation, hobbies/recreation). Significant improvements in

each of these 12 QOL parameters were seen in patients taking mesalamine at 2 g and 4 g daily compared with placebo ($P < .05$).³⁵

Increased Healthcare Costs

Nonadherence has an economic impact on the individual and the healthcare provider due to hospitalizations, surgical intervention, additional treatment and diagnostics, and loss of earnings.^{12,36} Costs associated with the medical care of patients with UC are considerable, particularly patients who require hospitalization. A UK study estimated that the mean cost of care during 6 months for patients with UC was \$2228; 50% of which was due to hospitalization cost (inpatient costs and surgery).¹² The high percentage of nonadherent patients at increased risk of relapse is likely to contribute to the overall high costs associated with the treatment of UC. This was shown to be the case in the UK study where disease relapse was associated with a 2- to 3-fold increase in costs for nonhospitalized cases and a 20-fold increase in costs for hospitalized cases compared with quiescent cases.¹² Likewise, a recent US study found a 2-fold increase in gastroenterology-related inpatient cost in nonadherent versus adherent patients (22.8% vs 11.7%, $P < .01$).¹⁹ Improving adherence should have a positive impact on the economic burden associated with relapsing UC. In the US study, patients who were persistent with medications incurred 12.5% lower medical costs ($P = .03$) than those who were nonadherent. Moreover, a small case-control

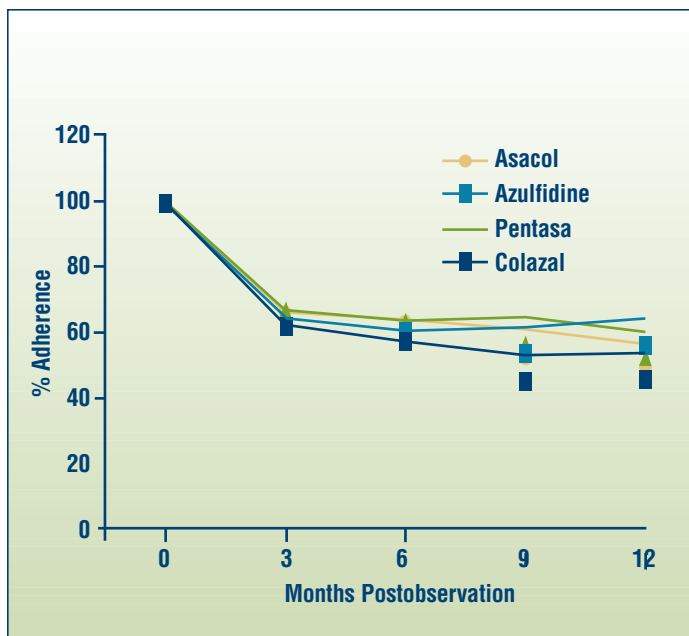


Figure 2. Adherence in UC independent of formulation type and/or dose regimen. Reprinted with permission from MacMillan Publishers Ltd: *Am J Gastroenterol*. Magowan S, et al,²⁸ © 2006.

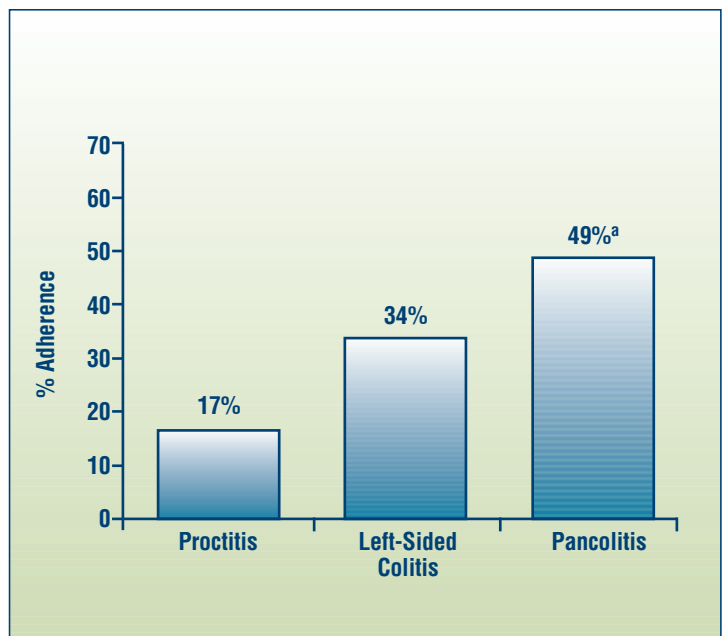


Figure 3. Adherence is higher in more extensive disease. ^a Trend toward nonadherence in patients with less extensive disease ($P = .04$). Reprinted with permission from Kane SV, et al.²⁰

TABLE 5. Strategies to Improve Adherence

Patient education

- Rationale for use of medications
- Discuss chemoprotection for CRC
- Discuss adverse effects of medications and how to deal with them
- Procedure for prescription refills

Clinician-patient communication

- Open communication
- Ability to call about prescription concerns

Individualization of therapy

- Best time to take medications
- Decreasing pill burden
- Ensure new medication will not interact with current medications
- Frequent, convenient office visits to maintain adherence
- Adherence aids: pill boxes, dosing reminder, pharmacy refill reminder programs

Adapted from Hawthorne AB, et al⁴; Kane SV, et al.²⁰

study showed that regular long-term use of rectal and oral 5-ASA compounds reduced the overall cost of managing symptomatic relapses 48%.³⁷

Strategies for Increasing Adherence

Strategies to improve adherence should focus on the factors that increase nonadherence as well as patient concerns and beliefs (Table 5).^{4,20}

Patient Education

Educating patients on why medications are recommended, how medications should be taken to produce optimal benefit, and potential side effects of medications is one of the most important strategies to increase medication adherence in patients with chronic conditions.³⁸ However, patient education is more than just giving patients some information. It needs to be tailored to the needs of the individual patient. Patients' concerns and misunderstandings about therapy need to be identified and resolved; patient's expectations of therapy needs to be identified, reinforced, and amplified; potential benefits of treatment need to be emphasized;

patient instructions should be concise and reinforced with written materials or Web-based information; and adherence to therapy should be an ongoing topic of discussion at each office visit. The benefit of patient education in improving adherence was shown in a study of patients with IBD (N = 69). In this study patients who had undertaken an IBD education program, consisting of pamphlets and ad hoc education by a physician, demonstrated improved knowledge, patient satisfaction, and a positive trend towards greater adherence compared with patients who received standard care.³⁹

Educating partners, caregivers, family, and friends may also be beneficial as they have an important role in supporting patients and encouraging adherence.⁴

Good Clinician-Patient Communication

Building a good clinician-patient relationship via open communication is another strategy that may improve medication adherence. Attributes of a good clinician-patient relationship include a longitudinal relationship between patient and clinician (continuity of care); concordance, or agreement, between the patient and clinician on the problem or need and its management; patient trust in the clinician to act in their best interest; ability of the clinician to enable the patient toward effective self-care (patient enablement); and patient involvement in the treatment decision-making process.^{4,20,40}

The benefits of a guided self-management program in UC were revealed in a randomized controlled trial where patients

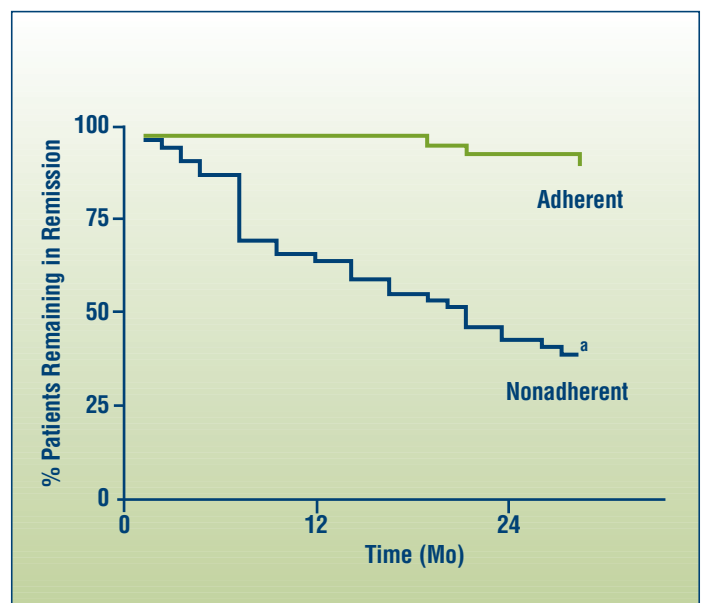


Figure 4. Maintenance of remission in patients adherent to 5-ASA therapy. ^aP = .001. Adapted from Kane SV, et al, © 2003, with permission from Elsevier.⁵

assigned to this program were found to have an accelerated treatment provision, a reduction in hospital visits without an increase in morbidity, and a greater confidence in their ability to cope with the disease compared with patients receiving normal treatment and follow-up. In addition, the self-management program has the potential to reduce costs due to reduced use of healthcare services.⁴¹ However, whether self-management programs do increase adherence to therapy in UC remains to be shown.

Individualization of Therapy

Choosing an appropriate medication regimen that is convenient for the patient and takes into consideration medication costs and adverse effects may contribute toward improving medication adherence. When possible, simplifying the dosing regimen to once daily rather than 3 to 4 times a day also may enhance adherence.³⁸

However, daily dose, regimen, and formulation do *not* appear to significantly influence adherence in UC.²⁸

Other intervention strategies that rely on psychological and behavioral techniques such as prompting pill taking by activities of daily living, adherence aids (eg, charts, pill containers), and pharmacy refill reminder programs also may increase adherence to therapy for chronic conditions. A review of the literature showed that the introduction of adherence, aids and refill or follow-up reminders increased adherence, with increases ranging from 6% to 25%.⁴² To what extent these behavioral intervention measures are useful in improving adherence in patients with UC remains to be seen.

Because there is no single cause of nonadherence, there is not likely to be just 1 intervention that will improve adherence in all persons—a combination of strategies needs to be used to maximize medication adherence.

CASE 1: 25-YEAR-OLD MAN WITH UC FLARE

History and Presentation

A 25-year-old man presents complaining of bloody stools (5-6 daily), urgency, and cramping for the past 3 weeks. He finally decided to contact your office and request an urgent visit after experiencing nocturnal defecation for the last 2 nights. He also complains of fatigue and weight loss and states, “I’m just too busy to be sick.”

He had been diagnosed with UC to the hepatic flexure during colonoscopy at age 22, after presenting with 8 to 10 bloody stools, cramping, urgency, and fatigue. His UC initially was treated with a prednisone 40-mg taper and 4.8 g/d 5-ASA. He did well for nearly 2 years. He canceled an appointment 8 months ago and never called to reschedule. He obtains his medication through a mail order pharmacy that allows him to buy a 3-month supply with 3 refills (a 1-year supply of medication).

Asked whether he has stayed on his medication, he replied that with starting a new job requiring frequent travel, moving away from his family, and feeling well, he has not remembered to take it. Further questioning revealed that he has been off 5-ASA therapy for 10 months. He also mentions that his mother had been heavily involved in his care after he initially was diagnosed. He is unsure of why he really needs to take “so many pills all the time when I feel fine.” He recently resumed his 5-ASA therapy, but his symptoms have not been curtailed.

Discussion

Beth-Ann Norton, MS, RN, CS, ANP, and Sunanda V. Kane, MD, MSPH, discuss strategies for improving treatment adherence in patients with UC.

What is the best way to broach the issue of treatment nonadherence with patients?

Beth-Ann Norton: One of the first things I do when patients present with a UC flare is to determine whether they are taking their medications. For this patient, I would gently ask, “If you’re too busy to be sick, have you been too busy to remember to take your medication?” Often, patients will admit at that point that they have not taken their medication.

Sunanda V. Kane: You’re right. It has to be a gentle discussion—nonconfrontational and nonjudgmental. Many patients want to please their healthcare provider and they’re not necessarily going to own up to nonadherence.

What are the contributing factors to treatment non-adherence for this patient?

BN: One of the red flags for this patient is that he canceled an appointment 8 months ago and never rescheduled. Another problem is that his clinician has no control over his refills because he walked out of the office after his last appointment with a 1-year prescription for medication, which he can choose to fill or not. This patient falls into the category of passive or involuntary nonadherence. He forgets to take his medication because he was feeling well and he was busy.

SK: I think he probably started by just forgetting because he was well, but then, when he realized that his behavior wasn't leading to any negative consequences, he was purposely nonadherent. This is an unfortunate situation because it often leads to an educational stumbling block for us. We try to explain that flares come and go, patients will flare if they don't stay on medication all the time, and we can't predict when the flare is going to occur.

BN: These unpredictable episodes of relapse could mean that this patient will have to be on medication for the rest of his life, and that's a hard thing for a 25-year-old to think about. Also, because this patient is young, he probably has fewer self-management skills than older patients. Self-management skills and coping skills are important for someone with chronic illness. When this patient's UC initially was diagnosed, his mother was heavily involved with his care because he was in college. Now, he's on his own, and he says he's unsure of why he needs to take so many pills all the time when he feels so well.

SK: And he's male and single and does not have a support group, which puts him at greater risk for nonadherence and flare. Some data suggest that sometimes females are more likely to be nonadherent to treatment. In patients with Crohn's disease, women may be less adherent than men to infliximab therapy.⁴³ Infliximab is given intravenously, and patients have to take time out of their daily schedule to receive it. Women tend to have caregiver issues and put off their own healthcare to take care of others in the family.

BN: Infliximab also is used to treat UC, so these nonadherence issues also may be relevant here. Another thing we need to discuss about this young man is that he didn't keep his scheduled appointment 8 months ago. Was this because he was well or because he didn't have a good connection with his healthcare provider?

How can clinicians help improve treatment adherence?

SK: I explain to patients that when they're sick, they need to take their medicine. When they're well, they need to take their vitamin. People are eager to have control over their health and prevent illness. I tell them this medicine does both of those things. It can prevent illness if they continue to take it.

BN: When we reconnect with this patient in the office, we need to make him understand that we're there to get him better, but we also need to re-educate him about his disease and what medication can do for him.

SK: Exactly. And what it can't do for him—which is cure him. It is unfortunate that he can feel entirely well despite the underlying inflammation. Also, if we make the next appointment before our patients walk out the door, we have a better rate of their returning for the next visit. I'll say, "I want to see you back in 6 months, let's

set that up now" rather than "I want to see you in 6 months, give us a call." This way patients feel that we really care about them and are committed to them. There will still be a no-show rate, and some patients may call and want to change the appointment because they don't know what they'll be doing in 6 months, but we've made the connection.

BN: And patients will be more likely to call to reschedule.

SK: Or they may call and say, "I have this appointment, but I'm feeling well and don't want to come." At least their decision can be documented.

BN: I'll tell patients, "Even if you're well, we want to see you at least once each year. If we don't see you, we cannot prescribe your medication. And if we cannot prescribe your medication, you will get sick again."

SK: Regardless of which therapy is prescribed, there's a honeymoon of 3 months. After 3 months, there's a big drop-off in refills. So, I always ask for the follow-up visit at 3 months. The purpose is 2-fold: to make sure patients are well—and they probably are feeling well—then provide another opportunity for education. When their UC is diagnosed, patients may experience overload if we give them too much information at that first visit. At the 3-month follow-up, when they're feeling well, we can spend more time talking about how adhering to the maintenance regimen can avoid some of the complications of UC.

BN: When they begin to feel well after the initial treatment, that's when denial of the illness process may begin—particularly when patients are young. Young patients don't want to appear different—they don't want to be seen taking medication when having dinner with friends or during a lunch break at work—so they don't. It's important to bring them back into the office to reconnect and re-educate.

SK: And by the time of the follow-up, they have surfed the Internet, talked to their friends, and heard about all of these wonderful things that are going to cure their disease. They may tell you that they don't need their prescription medications anymore. This is when I dangle the carrot in front of them, "We obviously have to make things as easy as we can for you, both during treatment of the active disease and during maintenance therapy. If you stay well, we can decrease the dose."

How can simplifying the treatment regimen help adherence to therapy?

SK: With the advent of so many different formulations of 5-ASA compounds, clinicians now have more choices regarding the number and size of pills. Obviously, the more medicine that is put in a capsule, the bigger it has to be.

BN: With some formulations, the patient can open the capsule and sprinkle the medication into applesauce or pudding, for example, and take it that way. This is helpful for people who have an aversion to swallowing big pills. We do have some simple treatment options to offer patients now, for example, once-daily dosing, twice-daily dosing. Patients can take the medication in the morning before they leave for work and when they return home or at bedtime. They don't have to worry anymore about that midday dose.

SK: Historically, immunomodulator therapy has been given twice daily, but for patients who need this treatment, I give it once a day.

BN: I do as well. This helps patients remember to take the drug. Often, especially in the case of patients who are younger than 30 years, I encourage them to take it at bedtime when bone marrow production turnover is a little bit greater. Maybe they'll incorporate it that much sooner.

SK: Bedtime dosing also helps avoid any drug-related nausea because the patient will sleep through it.

BN: For this patient, keeping the medication regimen simple will help give him the confidence to go forward and deal with his illness. Prescribing fewer pills that need to be taken fewer times during the day will help him stick with his treatment plan.

CASE 1: 25-YEAR-OLD MAN WITH UC FLARE *(continued)*

Current Findings

- Nonadherence to prescribed treatment
- Physical examination: ulcerative lesion on left leg (possible pyoderma gangrenosum)
- Colonoscopy: pancolitis

Discussion *(continued)*

What should be the next step in the management of this patient?

BN: This patient has not undergone a colonoscopy since his UC initially was diagnosed; thus, a repeat examination is warranted. The colonoscopy reveals pancolitis. Because the extent of his disease has increased, he is complaining of joint aches and weight loss; and he has the beginnings of some skin ulcerations, which may signal pyoderma gangrenosum, and because his flare has not been curtailed fully with the resumption of his 5-ASA therapy, prednisone should be added to his drug regimen. Remembering how much he disliked prednisone therapy will encourage the patient to stay on his 5-ASA treatment.

SK: Right. Time tends to make patients forget how sick they were or how bad the flare was. All it takes for them to remember is a few days of prednisone.

BN: Weight gain, moon facies, and acne are big problems for young patients. This patient also has the worry about taking time off from a new job. The realization that he should have stayed on his 5-ASA treatment will hit hard.

SK: Another point to reinforce with patients is that staying on their prescribed regimen can be more cost-effective than treating the flare. If prednisone doesn't control this patient's flare, he may need hospitalization for intravenous therapy. Hospitalization is more expensive than copayments for maintenance therapy.

BN: Even if hospitalization for the flare is not required, there are the costs for traveling some distance to their clinician's office, parking, and losing time from work.

SK: Patients who come to the Mayo Clinic often need to take 2 days off from work.

BN: For this patient the consequences of nonadherence include the side effects of prednisone, increased healthcare costs, lost time from work, and extraintestinal manifestations of UC, which he never had before. In addition to joint aches, he has skin ulceration, which could result in permanent scarring.

SK: Another potential complication is CRC. This is an important reason for patients to stay on their medication.

What additional support for treatment adherence is available to patients with UC?

BN: An important thing to stress to patients when they leave your office is that they have a team of people caring for them. I give them a packet of information about UC because they may leave the office feeling overwhelmed and a little afraid. They need to feel they have a connection so they don't sit at home and dwell on the information. They can call before their next appointment and ask questions or share concerns.

SK: We also refer patients to the Crohn's & Colitis Foundation of America—the CCFA. Its Information Resource Center is available almost 24 hours at 1-888.MY.GUT.PAIN (888.694.8872).

BN: In New England, we have a very strong chapter of the CCFA, including the support program, the Power of Two. This program connects patients with UC or Crohn's disease with someone in their age group who has the same disease. They can talk one-on-one and get to the nitty gritty about life with IBD.

SK: If patients feel that someone cares and that there's somebody else out there, they're more connected to the community of IBD. They can therefore feel more comfortable about their treatment.

CASE 1: 25-YEAR-OLD MAN WITH UC FLARE *(continued)*

Follow-up

The patient returns to your office toward the end of his prednisone taper and reports that he is sticking with the full-dose 5-ASA. He wants to know what will happen if he flares again. You inform him that if he has a flare requiring prednisone again within the next 12 months, he will need to switch to an immunomodulating medication to avoid corticosteroids.

Commentary

BN: Avoidance of steroids is important when treating young people who face a lifetime of disease. The cumulative effects of prednisone can be debilitating. The use of 5-ASA compounds in mild-to-moderate UC has been the mainstay of therapy for more than 60 years and has been proven to be safe and effective over time. Immunomodulating medications and biologics are, overall, better and safer alternatives for repeat flares than steroids.

SK: It is clear from this discussion that treatment nonadherence is multifactorial and making time to discuss and resolve these issues with patients is important. Some healthcare providers do not think they have the time to have these discussions; however, it actually saves time in the long run to educate patients early, as worse outcomes and more complicated disease are even more time consuming.

CASE 2: 55-YEAR-OLD MAN WITH UC FLARE

A 55-year-old man with long-standing stable UC presents with a flare. His primary care clinician has prescribed an expensive cardiac medication, and the patient can no longer afford his 5-ASA medication and had to cut back.

Discussion

What strategies can be used to address treatment nonadherence in this patient?

SK: The first step is to go through the differential of why this patient has a flare. The most likely scenario is that he's not taking his medicine. The question is why. He may be too embarrassed to say that he couldn't afford it, or he may be up-front about it and angry.

BN: We have this voluntary, yet involuntary, form of nonadherence.

SK: Exactly. And when you talk with him he says, "I've been prescribed a dual therapy pill for my hypercholesterolemia and hypertension that's supposed to be more convenient, but it's really expensive. So I have to choose between this pill and my UC medication because my insurance plan has a deductible. I can't take as much as I want, and on some days I don't take any."

BN: Because he felt well, he may have thought he could get away with not taking his UC medication. His other 2 problems could lead to serious heart disease, and most people in this country die of heart disease, not UC.

SK: His cardiac medications took precedence. One way to approach the issue is to say, "You don't have any symptoms from hypercholesterolemia and hypertension, but you do have symptoms from the UC flare—having to rush to the bathroom and coping with incontinence. So, in that sense, your UC medicine may be more important for certain times. It's not that heart disease is less important; it's that your UC is more at the forefront in terms of your everyday quality of life."

BN: At this point, it's become an inconvenience for him.

SK: What I do in this situation is review his insurance policy with him to determine what medications are covered and how much he has to pay. For policies that don't cover any medicine at all, a solution is difficult to find. However, sometimes there's just a copay issue, or his insurance company prefers a different formulation than the one you prescribed. In that case, you can change the prescription so the copay becomes minimal or disappears.

BN: Alternatively, I may not feel that I can make a move on the patient's medication because he's on an older drug, such as sulfasalazine, and there is no less expensive option. One approach to the problem might be to contact the primary care clinician or the cardiologist and ask if there's another treatment they could consider because our patient's UC is flaring and the last thing I want to do with someone with high blood pressure is put them on prednisone.

SK: You bring up 2 excellent points. One is that sometimes a switch to sulfasalazine is a good choice for the patient. Perhaps the reason it wasn't prescribed initially was only patient convenience or mild side effects. The other point is about communicating with the other healthcare providers. If you can do it while the patients are sitting in your office, they feel they are part of a team working to make them better.

BN: Many drug manufacturers have patient assistance programs that are worthwhile exploring. The CCFA's Web site has links to the different manufacturers of drugs for UC.

SK: Switching patients to another therapy may give them the opportunity to get insurance coverage. Another strategy is to treat them aggressively to get the flare under control and then lower the

dose of 5-ASA to 1.6 g/d instead of 2.5 or 3 g/d—trying to use the lowest dose possible to maintain control. Remember, we need to consider multiple factors, not just the cost of the drug. This patient is 55 years old; we need to consider not only his hypertension and hypercholesterolemia, but also the osteoporosis, cataracts, and diabetes that may result from the use of corticosteroids.

BN: We also need to control his inflammation because he's getting older, he's had his disease for a long time, and his chance of developing colon cancer is rising.

SK: There's also interesting data in the rheumatoid arthritis literature that suggests that patients with chronic immune disorders have a higher risk for coronary artery disease, perhaps because of the systemic inflammation, and worse outcomes. We definitely want to work with this patient's primary care clinician and cardiologist to maximize therapy for all of his conditions.

BN: This patient clearly understood the importance of adhering to his UC treatment. He was upset because he had to disrupt his regimen. The duration of his disease actually made him more adherent and more likely to keep his follow-up appointments because he understood what it was like to get sick.

Are new strategies emerging to help foster treatment adherence?

SK: Pharmacies are taking a more active role in encouraging patients to stick with their medication regimens. Many offer automated refill calls. If patients haven't refilled their prescription, the pharmacy will make a courtesy call to let them know their refill is overdue. There's still the issue of what to do if the patient doesn't pick it up. Another concept that's emerging is that of interval empathy. When patients come back for follow-up, it's not so much to remind them that they have a disease as it is to remind them that we care about them. It gives us the opportunity to empathize with them about UC and to tell them they're doing a great job taking care of themselves.

BN: That's terrific. I had not heard that expression used before.

SK: Some interesting trends are developing. A recent article looked at time trends in the care of patients with IBD.⁴⁴ One of the findings was that fewer patients are going to the gastroenterologist and more are going to primary care clinicians for their care.

BN: Then it's extremely important for primary care clinicians to know about the importance of follow-up colonoscopies and laboratory monitoring for patients receiving immunomodulating therapies.

CASE 2: 55-YEAR-OLD MAN WITH UC FLARE (continued)

Follow-up

This patient contacted the pharmaceutical company regarding a patient assistance program. Because he was able to document that he could not afford his therapy, he was given his medication on a "compassionate" basis. He continues to do well on his daily regimen.

Commentary

SK: Cost of treatment can be a big deterrent for some patients and must be addressed. There are multiple avenues for help, usually from the pharmaceutical industry. It does require some work on

PCE TAKEAWAYS

- Treatment of UC is associated with high nonadherence rates; up to 60% during the asymptomatic remission phase.
- Nonadherence in UC is associated with an increased risk of symptomatic relapse, an increased risk of CRC, possibly reduced HRQOL, and increased healthcare costs.
- Factors shown to affect adherence in patients with UC include disease extent and duration, cost of medications, fear of adverse effects, individual psychosocial variables, and the patient-clinician relationship.
- Treatment-related factors such as daily dose, regimen, and formulation are not important in influencing adherence in patients with UC. This is in contrast to other chronic conditions.
- Strategies to improve adherence should include education on the rationale for treatment and the benefits of continued treatment.
- The patient-clinician relationship is critical in encouraging adherence, particularly with respect to open communication, education, and agreement regarding the value of the assigned treatment.

the patient's part, but it is worth it in the long run. Local charities and organizations can also be of tremendous value.

BN: Open communication with this patient and his other clinicians was a key element in his treatment. In this tough economy, many people face decisions about whether to pay for medications or their bills and food. Looking into copay assistance or patient assistance programs offered through most pharmaceutical companies can make a real difference in patients' lives.

References

1. Kane SV, Accortt NA, Magowan S, Brixner D. Predictors of persistence with 5-aminosalicylic acid therapy for ulcerative colitis. *Aliment Pharmacol Ther.* 2009;29:855-862.
2. Kornbluth A, Sachar DB; Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 2004;99:1371-1385.
3. Langan RC, Gotsch PB, Krafczyk MA, Skillinge DD. Ulcerative colitis: diagnosis and treatment. *Am Fam Physician.* 2007;76:1323-1330.
4. Hawthorne AB, Rubin G, Ghosh S. Review article: medication non-adherence in ulcerative colitis—strategies to improve adherence with mesalazine and other maintenance therapies. *Aliment Pharmacol Ther.* 2008;27:1157-1166.
5. Kane SV, Huo D, Aikens J, Hanauer S. Medication nonadherence and the outcomes of patients with quiescent ulcerative colitis. *Am J Med.* 2003;114:39-43.
6. Moody GA, Jayanthi V, Probert CSJ, Mac Kay H, Mayberry JF. Long-term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. *Eur J Gastroenterol Hepatol.* 1996;8:1179-1183.
7. Eaden J, Abrams K, Ekbom A, et al. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther.* 2000;14:145-153.
8. Van Staa TP, Card T, Logan RF, et al. Aminosalicilate use and colorectal cancer risk in inflammatory bowel disease: a large epidemiological study. *Gut.* 2005;54:1573-1578.
9. Han SW, McColl E, Barton JR, et al. Predictors of quality of life in ulcerative colitis: the importance of symptoms and illness representations. *Inflamm Bowel Dis.* 2005;11:24-34.
10. Janke KH, Klump B, Gregor M, Meisner C, Haeuser W. Determinants of life satisfaction in inflammatory bowel disease. *Inflamm Bowel Dis.* 2005;11:272-286.
11. Saibeni S, Cortinovis I, Beretta L, et al. Gender and disease activity influence health-related quality of life in inflammatory bowel diseases. *HepatoGastroenterology.* 2005;52:509-515.
12. Bassi A, Dodd S, Williamson P, et al. Cost of illness of inflammatory bowel disease in the UK: a single centre retrospective study. *Gut.* 2004;53:1471-1478.
13. Panaccione R, Rutgeerts P, Sandborn WJ, Feagan B, Schreiber S, Ghosh S. Review article: treatment algorithms to maximize remission and minimize corticosteroid dependence in patients with inflammatory bowel disease. *Aliment Pharmacol Ther.* 2008;28:674-688.
14. Kefalides PT, Hanauer SB. Ulcerative colitis: diagnosis and management. *Hospital Physician.* 2002;53-63. http://www.turnerwhite.com/pdf/hp_jun02_colitis.pdf. Accessed September 16, 2009.
15. Lichtenstein GR, Abreu MT, Cohen R, Tremaine W; American Gastroenterological Association. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology.* 2006;130:935-939.
16. Carter MJ, Lobo AJ, Travis SP; IBD Section, British Society of Gastroenterology. Guidelines for the management of inflammatory bowel disease in adults. *Gut.* 2004;53(suppl 5):V1-V16.
17. Kane SV, Cohen RD, Aikens JE, Hanauer SB. Prevalence of nonadherence with maintenance mesalazine in quiescent ulcerative colitis. *Am J Gastroenterol.* 2001;96:2929-2933.
18. Cervený P, Bortlík M, Kubena A, et al. Nonadherence in inflammatory bowel disease: results of factor analysis. *Inflamm Bowel Dis.* 2007;13:1244-1249.
19. Kane S, Shaya F. Medication non-adherence is associated with increased medical health care costs. *Dig Dis Sci.* 2008;53:1020-1024.
20. Kane SV, Brixner D, Rubin DT, Sewitch MJ. The challenge of compliance and persistence: focus on ulcerative colitis. *J Manag Care Pharm.* 2008;14(1 suppl A):S2-S12.
21. Lowry KP, Dudley TK, Oddone EZ, Bosworth HB. Intentional and unintentional nonadherence to antihypertensive medication. *Ann Pharmacother.* 2005;39:1198-1203.
22. Ockene IS, Hayman LL, Pasternak RC, Schron E, Dunbar-Jacob J. Task force #4—adherence issues and behavior changes: achieving a long-term solution. 33rd Bethesda Conference. *J Am Coll Cardiol.* 2002;40:630-640.
23. López-San Román, Bermejo F, Carrera E, et al. Adherence to treatment in inflammatory bowel disease. *Rev Esp Enferm Dig.* 2005;97:249-257.
24. Sewitch MJ, Abrahamowicz M, Barkun A, et al. Patient nonadherence to medication in inflammatory bowel disease. *Am J Gastroenterol.* 2003;98:1535-1544.
25. Kane SV. Systematic review: adherence issues in the treatment of ulcerative colitis. *Aliment Pharmacol Ther.* 2006;23:577-585.
26. Sewitch MJ, Leffondre K, Dobkin PL. Clustering patients according to health perceptions: relationships to psychosocial characteristics and medication nonadherence. *J Psychosom Res.* 2004;56:323-332.
27. Nigro G, Angelini G, Grosso SB, Caula G, Sategna-Guidetti C. Psychiatric predictors of noncompliance in inflammatory bowel disease: psychiatry and compliance. *J Clin Gastroenterol.* 2001;32:66-68.
28. Magowan S, Kane S, Lange JL. 5-ASA prescription refill rates for ulcerative colitis are independent of formulation and dosing regimens. *Am J Gastroenterol.* 2006;101:S447. Abstract 1144.
29. Kane SV, Hanauer SB. National adherence rates with IBD therapy: PO vs PR. *Am J Gastroenterol.* 2001;96:S296.
30. Loftus EV Jr. A practical perspective on ulcerative colitis: patients' needs from aminosalicilate therapies. *Inflamm Bowel Dis.* 2006;12:1107-1113.
31. Rubin G, Hungin AP, Chinn D, Dwarakanath AD, Green L, Bates J. Long-term aminosalicilate therapy is under-used in patients with

- ulcerative colitis: a cross-sectional survey. *Aliment Pharmacol Ther.* 2002;16:1889-1893.
32. Bernal I, Domenech E, Garcia-Planella E, et al. Medication-taking behavior in a cohort of patients with inflammatory bowel disease. *Dig Dis Sci.* 2006;51:2165-2169.
 33. Brentnall TA. Molecular underpinnings of cancer in ulcerative colitis. *Curr Opin Gastroenterol.* 2003;19:64-68.
 34. Velayos FS, Terdiman JP, Walsh JM. Effect of 5-aminosalicylate use on colorectal cancer and dysplasia risk: a systematic review and meta-analysis of observational studies. *Am J Gastroenterol.* 2005;100:1345-1353.
 35. Robinson M, Hanauer S, Hoop R, et al. Mesalamine capsules enhance the quality of life for patients with ulcerative colitis. *Aliment Pharmacol Ther.* 1994;8:27-34.
 36. Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of followup evaluation. *Gastroenterology.* 2006;131:719-728.
 37. Piodi LP, Ulivieri FM, Cermesoni L, et al. Long-term intermittent treatment with low-dose 5-aminosalicylic enemas is efficacious for remission maintenance in ulcerative colitis. *Scand J Gastroenterol.* 2004;39:154-157.
 38. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. *Arch Intern Med.* 2007;167:540-550.
 39. Waters BM, Jensen L, Fedorak R. Effects of formal education for patients with inflammatory bowel disease: a randomized controlled trial. *Can J Gastroenterol.* 2005;19:235-244.
 40. Kerse N, Buetow S, Mainous AG 3rd, et al. Physician-patient relationship and medication compliance: a primary care investigation. *Ann Fam Med.* 2004;2:455-461.
 41. Robinson A, Thompson DG, Wilkin D, et al. Guided self-management and patient-directed follow-up of ulcerative colitis: a randomised trial. *Lancet.* 2001;358:976-981.
 42. Krueger KP, Felkey BG, Berger BA. Improving adherence and persistence: a review and assessment of interventions and description of steps toward a national adherence initiative. *J Am Pharm Assoc.* 2003;43:668-678.
 43. Kane SV, Dixon L. Adherence rates with infliximab therapy in Crohn's disease. *Aliment Pharmacol Ther.* 2006;24:1099-1103.
 44. Herrinton LJ, Liu L, Fireman B, et al. Time trends in therapies and outcomes for adult inflammatory bowel disease, Northern California, 1998-2005. *Gastroenterology.* 2009;137:502-511. [Epub 2009 May 13].