

Review article: how to control and improve adherence to therapy in inflammatory bowel disease

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SUMMARY

Any chronic disease is a risk situation for non-adherence to treatment. This results in suboptimal medication, and poor disease control. Adherence and compliance are directly related to therapeutic success, which is further complicated in inflammatory bowel disease patients.

There is a wide array of circumstances that increase the likelihood of non-compliance in a given patient: difficult-to-follow treatment schedules (multiple doses and multiple drugs), insufficient patient information, longer evolution of the disease and inactive disease. Depression, male gender, active employment and living alone are also associated with poorer adherence to therapy.

Monitoring drug intake is possible in many circumstances, directly or indirectly (urinary salicylate levels; erythrocyte metabolites and increased mean corpuscular volume and bilirubin in patients under azathioprine; blood levels of ciclosporin or tacrolimus). However, such measures are probably better utilized for dose adjustment and not for the identification of non-compliant patients. High-risk patients are a target group in which pre-emptive intervention could ensure better compliance.

If the question of non-adherence arises, for instance, as a possible cause of therapy failure, the patient should be carefully approached. This should take into consideration factors that may be corrected and, most importantly, should aim at building a better patient-doctor relationship.

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INTRODUCTION

Any discussion on medical therapy must take into account the very significant difference between two related terms: efficacy and effectiveness. The first term describes the effect of a drug under ideal conditions; a perfect situation, in which the prescribed dose is exactly the dose that patients take and tolerate. Conversely, effectiveness is used to indicate the effect of the same drug under real conditions, taking into account treatment losses and suboptimal drug exposure due to a vast array of causes: patients who do not take the drug, altered metabolism or interactions resulting in lower drug exposure, etc. These two words represent, respectively, the conditions of clinical trials and real daily medical practice.

The thing is that efficacy and effectiveness are not similar. Clinical observations in very diverse areas of medicine corroborate this assertion. For example, it has been repeatedly shown that in the real world, about half of coronary patients stop taking part or all of their drugs during 1 year of follow-up.¹ Thus, one has to remember C. Everett Koop, a former Surgeon General of the USA, who put into words something that is evident, but very frequently forgotten: drugs do not work in patients who do not take them.

This is where one should consider a very important concept: adherence. This is best defined as the extent to which an individual's behaviour coincides with medical advice. We are not talking here about the blind and ignorant adherence to a prescription, because adherence does not only include taking a dose, but also taking it properly. It also accounts for other issues, such as keeping appointments and adopting lifestyle modifications, such as diet and smoking. Many of us use a more restricted term, compliance. This is appropriate, but only if one remembers that compliance is just a numerical term that describes the proportion of the intended drug dose that actually reaches the patient.

The shift from compliance to adherence, accompanies the change of paradigm that western medicine has witnessed. The old therapeutic setting, in which an omniscient doctor indoctrinated a submissive patient, has evolved into a much more complex and interesting situation. Nowadays, patient and doctor interact on the same level, and also experience the influence of external agents (society, economy, patient's relatives and friends) on their therapeutical relationship. An optimal adherence implies that patient and health pro-

vider collaborate to achieve a common goal, and that medical decisions take into account who the patient is and what the patient wants or needs.

ADHERENCE AND INFLAMMATORY BOWEL DISEASE

Adherence is generally optimal in diseases of short course, which are characterized by one or more symptoms whose appearance is predictable and continuous, that annoy the patient and that are easily and quickly controlled by the prescribed drug. An example would be an isolated headache. The opposite situation is represented by diseases that run an unpredictable course, with long periods of low activity, during which the advantages of taking a drug are difficult to appreciate. These are situations in which adherence, and thus compliance, has to be ensured by an optimal patient-doctor relationship.

Inflammatory bowel disease (IBD) is a typical high-risk situation for non-optimal adherence and compliance. First, it is a chronic condition, whose intensity waxes and wanes in an unpredictable fashion. The patient may feel that a perfect follow-up of a treatment does not guarantee a 100% protective effect. Also, if he or she decides to stop medication during a period that would naturally consist of long-term remission, the resulting lack of symptoms may reinforce this action. Patients with IBD are often young, and the disease usually strikes during a period of the patient's life where major personal and social goals are being confronted for the first time: independence from the family, finishing school, starting work, finding a companion and perhaps forming a family. Hence, being diagnosed with a chronic disease for which sophisticated modern medicine can give no effective cure is logically followed by some degree of rebellion. The impact on lifestyle can be significant: diet limitations, reduced activity, distortion of body image, altered bowel habits, etc. All this makes IBD a socially stigmatizing condition. Furthermore, the goals of IBD therapy are difficult to understand. For instance, a remote possibility of a low-grade colonic dysplasia is easily accepted by the doctor as a good reason for yearly endoscopic surveillance in long-standing ulcerative colitis (UC), but probably not so much by the patient. Finally, a very important part of IBD therapy is maintenance treatment. This could be defined, from a patient's viewpoint, as taking lots of pills for a very long time, to fight something

(a flare-up) that is not guaranteed to appear, with a weapon (lots of pills, again, and maybe some enemas) that is not completely effective. Let us remember that medical trials are not real life, and that sometimes medical recommendations emerge that are possible to follow during a limited time span, but not so easily during longer periods.

What are our data? Is adherence optimal in IBD patients? Self-rated adherence in IBD patients varies widely, from 0% to 90%; but in reality, when objective measures of adherence were used, it was found that nearly 50% of patients do not take medications as prescribed, with slightly more than 12% having no detectable levels of the drug, indicating an absolute non-compliance.² Other authors, measuring metabolites in the blood, discovered that they were conspicuously absent again in about 10% of patients, who were full non-compliers, and that levels decreased with follow-up, leading to under dosage in about half of the cases.^{3, 4} In our own investigations⁵, voluntary non-compliance was detected in 35% of IBD patients, whilst 13% had no detectable urine salicylate levels. Other authors^{6, 7} found that adherence rates to mesalazine and azathioprine averaged 41–55% and 75%, respectively, of the total prescribed doses.

But perhaps this adherence rate is adequate, and does not result in poorer disease control. Or does it? In other areas of medicine, like coronary heart disease, it is well known that poor adherence is associated with increased mortality.⁸ A protean work in this field, whose results should be kept in mind by any person working with IBD patients,⁹ showed that UC patients who were compliant had a 90% chance of remission maintenance, compared with 40% of non-compliant patients. The difference was so striking that it could be predicted that patients who adhered properly to the therapeutic scheme had an almost complete chance of staying in remission. The superior results achieved by certain kinds of therapy compared with others can be explained by their higher practicality and compliance.¹⁰

Another reason to aim for optimal compliance in IBD patients, is not the short- to medium-term prevention of flare-ups, but the long-term prevention of late complications like colorectal cancer in UC patients.¹¹

A key question, then, is how to detect non-adherence. Compliance¹² can be assessed by direct methods, such as direct observation of the actual drug intake, determination of blood levels and the study of biological markers that indicate drug exposure. Indirect

methods have also been implemented and used, like questionnaires, pill counts, clinical response, diaries and electronic monitors, although many of them are only practical during clinical trials.

We know that self-reporting is inaccurate: studies have shown that 100% self-reported adherence contrasts with more than 10% complete absence of mesalazine metabolites in the urine, or 12% in the blood.^{2, 5} One should also be ready to detect not only underdosing, but also overdosing, and pills being taken without following advice. It is sometimes adequate to double check by asking accompanying persons, or by asking the patients about side effects.

Measurement of drugs, metabolites or both is a more straightforward way to detect adherence. In IBD patients treated with mesalazine, there is a good correlation between urinary mesalazine and urinary salicylate assay, which is widely available.¹³ In those who are taking azathioprine or mercaptopurine (mercaptopurine, and MP to 6-MP), measurement of 6-thioguanine nucleotides is a possibility, although its use is not widespread. Other biological tools to detect drug impregnation have been used, like increases in mean corpuscular volume or indirect bilirubin and decreases in the leucocyte count; all have been postulated as surrogate markers of thiopurine therapy adherence.¹⁴ For some drugs, like ciclosporin or tacrolimus, blood levels are routinely assayed. Finally, in other drugs, such as infliximab, compliance is assured by intravenous administration.

A realistic option for detecting non-adherence is to target patients at risk. Adherence can be affected by four factors: illness, treatment, patient characteristics, and the therapeutic relationship between patient and doctor. Different variables related to each of these factors have been associated with poor adherence (Table 1).

Thus, there are four main possibilities for the detection of non-adherence: self-reporting, systematic investigation, targeting at-risk patients, and targeting non-responders. Self-reporting is frequently inaccurate, and systematic investigation can be both cumbersome and inconvenient from a patient–doctor relationship point of view. So the most realistic approach is to keep in mind that non-adherence is possible and probable. Patients with clinical predictors of non-adherence probably warrant special pre-emptive attention: make clear what the treatment is for, what one should expect from it and that good compliance is essential for therapeutic effect. In general, if a patient is responding, it is not necessary to check

Table 1. Variables associated with poorer adherence in inflammatory bowel disease patients^{2, 5-7, 9}

Illness-related factors
Less severe disease
Longer duration of disease
Few previous complications
Little extension of disease
Patient factors
Single, as opposed to married or in a stable relationship
Male gender
Full-time employment
High depression scores
Diminished quality of life
Treatment-related factors
Three times as opposed to two times per day dosing
Patients taking more than four drugs
Patient-doctor relationship
Patient-doctor discordance
Patients who do not completely trust their doctors
Patients who do not feel adequately informed about their disease or their therapy

adherence. If a patient does not respond, or loses response, one should always consider non-adherence as a possible cause.

But the key question is: how can we improve adherence? Indeed, is any attempt to improve adherence a waste of time? Well, it is probably not. We know that non-adherence rates in IBD patients range from 10% to 40%. It is also clear that adherent patients fare much better than non-adherent patients.⁹ Thus, to detect and improve adherence would significantly empower any of the current therapeutic options. Let us recall that efficacy is defined as the effect a treatment achieves under ideal conditions, and effectiveness refers to the effect under real conditions. So, if we want to know the true cost-effectiveness of a therapy, we have to take into account treatment losses, and trying to correct them is the first step in making therapies work better.

If we want to improve adherence, without becoming paranoid, we should keep an eye on patients at risk, and on non-responders. Once the possibility of non-adherence arises, one should try to help. But how? All the recommendations are general, and few have been substantiated by systematic investigations.¹⁵⁻¹⁷ Nevertheless, they all make sense, and most are easily implemented, even in a busy practice.

The common step to all such measures is probably to consider patients individually. Some important actions include:

1 ask patients about their doubts and concerns, especially relating to medication, but also about the way and intensity that the disease and the therapy impact on their lifestyle; inform on disease and therapy;^{16, 17}

2 detect patients with depression, and offer assistance; depression is a major determinant of non-adherence;¹⁷

3 discuss with the patient proper doses and best dosing times; some simpler schedules can be marginally less efficacious, but this can be compensated by a higher compliance;¹⁵

4 emphasize the value of the treatment¹⁶ and

5 provide simple instructions.

Inflammatory bowel disease patients have many concerns,¹⁸ like low self-esteem, altered body image, loneliness, uncertainty about the disease and about ostomy, and not being able to take care of themselves.¹⁷ Those concerns are rarely shared with their doctor, less so in younger female patients.^{19, 20} A directed doctor interview can identify such problems, check their possible influence on adherence, and may result in better adherence rates.²¹ These, in turn, are associated with less clinical relapses.⁹

In some instances, treatment modifications can help us to rescue a non-compliant patient. It has been shown¹⁵ that once daily mesalazine results in a significantly higher adherence at 3 months, but not in a higher relapse rate. Also,²² patients prefer 1 g mesalazine doses to 0.5 g mesalazine doses.

Patient associations can provide a very important frame for personal support and good quality information. The Internet gives patients access to an overwhelming amount of medical opinions, not all of which are sound or substantiated. We have to assume that our patients, or someone who cares for them, will sooner or later perform an Internet search on their condition, and that they might do this more frequently than patients with other diseases.^{23, 24} The much-feared consequences of this can be the hyperintensive questioning of doctors by patients about therapy and disease (in what has been described as the 'Internet printout syndrome'), and, worse still, the abandonment of therapy and falling prey to charlatans. We can advise our patients that only Internet information that follows the specific regulations of HonCode (<http://www.hon.ch>) or similar organizations, are dedicated to '...promoting and guiding the deployment of useful and reliable online medical and health information, and its appropriate and efficient use'.

An intriguing possibility, which can be rewarding both for patients and health providers, is patient education. In a systematic investigation,¹⁶ UC patients who were trained to start managing their flare-ups, benefited from more rapid treatment of relapses, less out-patient visits, less time spent in the clinic, lower travel costs and fewer missed appointments.

CONCLUSION

Our thoughts can be summarized in four simple points.

- 1 Adherence in IBD patients is frequently compromised.
- 2 Non-adherence is associated with more frequent flare-ups.
- 3 Non-adherence can be expected, detected and corrected.
- 4 One must understand that adherence is a very important part of IBD treatment.

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