

RheumInfo.com – Medication Adherence for Rheumatologists

Consider these scenarios:

You assess a new patient with early rheumatoid arthritis. You prescribe oral methotrexate and hydroxychloroquine. Three months later the patient returns with absolutely no improvement. How do you know the lack of response isn't a reflection of poor adherence?

You are following a patient with RA on biologic monotherapy who flares 2-3 times per year. The flares are always controlled with a short course of prednisone and the patient does well for a few months before flaring again. How do you know those flares are not a reflection of poor adherence to therapy?

What is adherence?

Medication adherence is defined as the extent to which patients take medications as prescribed by their health care provider.¹ Adherence is usually higher in patients with acute conditions compared to those with chronic conditions. Persistence with medication is disappointingly low dropping most dramatically after the first 6 months of therapy.

How is adherence measured?

Adherence can be measured both directly and indirectly. Direct measurement of adherence involves direct observation of the patient receiving the medication or involves the measurement of the concentration of a drug or its metabolites after it is taken by the patient. In rheumatology the administration of IV medications is the best example of a direct measurement. Other examples of direct measurement would include measuring phenytoin levels in patients with epilepsy or measuring tacrolimus levels in transplant patients.

With oral DMARDs and sc biologics we are usually left with indirect measures of adherence. Examples include direct questioning of a patient, performing pill counts, or ascertaining clinical response. The problem with indirect measures is they often overestimate adherence.

What are the common patterns of non-adherence?

It is important to realize that adherence to medication is a dynamic feature and it is not stable over time. A patient may be perfectly adherent at the start of therapy but fatigue over time in terms of missing doses and not fulfilling prescriptions in a timely manner. With this in mind, there are three key components of adherence to consider:

1. Initiation: Does the patient actually fill the prescription and initiate therapy?
2. Execution: If they initiate therapy, do they take the medication as prescribed?
3. Persistence: Do they continue and persist with the medication over time?

For example, a perfectly adherent patient would initiate therapy as soon as it is prescribed, take the medication exactly as directed without delaying or missing doses, and persist with therapy over the long term. But what happens in real life? What does the data tell us?

About a third of patients are consistently adherent. Of those who are consistently adherent about half come close to perfect adherence and the other half take nearly all doses, but with some timing irregularity.² On the other hand, about a third of patients are consistently non-adherent. Of the patients who are non-adherent about half have a drug holiday monthly or more often, with frequent omissions of doses, and the other half take few or no doses while giving the impression of good adherence.² The

remaining 1/3 of patients fall into the middle of the pack. These patients range from missing an occasional single day's dose and have some timing inconsistency, to taking drug holidays three to four times a year with occasional omissions of doses.²

For your RA patients who are poorly controlled the real key is to determine where on the adherence spectrum they fall. This can be difficult. In this situation there are three things you probably need to consider:

1. What are the risk factors for non-adherence?
2. How can you determine non-adherence?
3. What strategies can you implement to promote adherence?

What are the risk factors for non-adherence?

For any practicing rheumatologist the risk factors for non-adherence are somewhat intuitive. It's important to recognize the association with medication adherence when these situations arise. Consider the following scenarios and ask yourself if you can relate given your clinical experience.

1. The **depressed or cognitively impaired patient** who isn't adherent because they forget or get confused about their medications.
2. A patient who lacks insight and really **doesn't understand the nature or severity of their illness** may be less likely to adhere to therapy. These are patients who may minimize their disease as a way to cope, "It's just my arthritis so it's ok if I forget my medicine."
3. A patient who **doesn't believe in conventional treatment** and would rather use a natural approach.
4. A patient with whom you struggle to develop a **trustworthy relationship** or perhaps they've had a severe side effect to a medication that has eroded trust in your relationship.
5. A patient who doesn't book follow-up appointments or **misses appointments**. The patient who falls off your radar and shows up 2 years later in a terrible state.
6. Patients who have **barriers to obtain medications** such as cost. The most obvious scenario is the patient without drug coverage who you're trying to advance along a therapeutic algorithm.
7. Patients who have **barriers to care**. Perhaps they have transportation issues such as a long commute to your office or they have to rely on others for transportation. Perhaps their work schedule makes it difficult for them to attend regular appointments.
8. Using **complex treatment regimens** can also result in poor adherence. Starting "triple therapy" on the initial visit is quite compelling from a scientific perspective, however, perhaps a structured staggered approach to initiating combination therapy may improve long-term adherence?

How can you determine non-adherence in patients who aren't responding?

It's important to always consider adherence to therapy when a patient isn't responding. Determining adherence with monitored IV medications like rituximab, abatacept, remicade, or tocilizumab is straightforward given the ability to directly observe therapy.

For oral and subcutaneous medications, the simplest and most practical suggestion for rheumatologists is to simply ask patients non-judgmentally how often they miss doses. Unfortunately, trying to assess adherence through simple questioning is not reliable or valid. Patients generally want to please their physician and will often say what they think their doctor wants to hear. However, it can be reassuring to the patient when the physician asks them, "*I know it must be difficult to take all your medications regularly. How often do you miss taking them?*" A patient who admits to poor adherence is generally being candid. It is also important to ask the patient if they are having any side effects to their medications, whether they know why they are taking the medications and are what the benefits of taking them since these questions can often expose poor adherence.

Validated instruments have been developed to measure non-adherence. These instruments tend to take more time to administer and score than a simple question and their utility in routine clinical interactions

may be limited. However, they may be more sensitive in identifying non-adherence. The Compliance-Questionnaire-Rheumatology (CQR) is a rheumatology specific instrument that was developed to measure patient compliance to medication regimens.^{4,5} This questionnaire was initially developed and validated in 32 patients through semi-standardized interviews. Unfortunately, equal weighting of items in this questionnaire did not perform well when compared to electronically measured medication compliance.⁵ When the 19-items were differentially weighted using discriminant analysis it performed much better in terms of sensitivity to detect <80% adherence. However, use of the CQR in the clinical setting requires a complex calculation. This really limits the utility of the CQR in clinical practice.

The two other commonly used adherence scales are the Morisky Adherence Questionnaire (MAQ)⁶ and the Medication Adherence Report Scale (MARS)⁷. Like the CQR both of these scales perform well compared to semi-standardized interviews but perform poorly compared to electronically measured medication compliance.⁸

Although a wide variety of subjective measures to assess adherence have been created there is no gold standard. Patient reported adherence is poorly correlated with electronic medication measures and pill counts.

As we've pointed out above, trying to assess patient adherence through simple questioning isn't reliable or valid. You can ask your patients if they're taking their medication. If they are truthful and tell you that they aren't then they are likely being honest. If they tell you they are taking all of their medication and rarely miss then you really don't know. It's important to remember that 1/3 of patients take most of their medicine, 1/3 perform fairly, and 1/3 are poorly adherent. The trick is trying to identify which group your patient falls into. Thinking practically, if the patient is doing really well with stable disease, no radiographic progression, and no flares then it probably isn't necessary to inquire about adherence. Adherence really becomes important for the patient who is chronically doing poorly or experiencing frequent flares. In these patients, are there any other clues you can use to tease out potential issues with adherence?

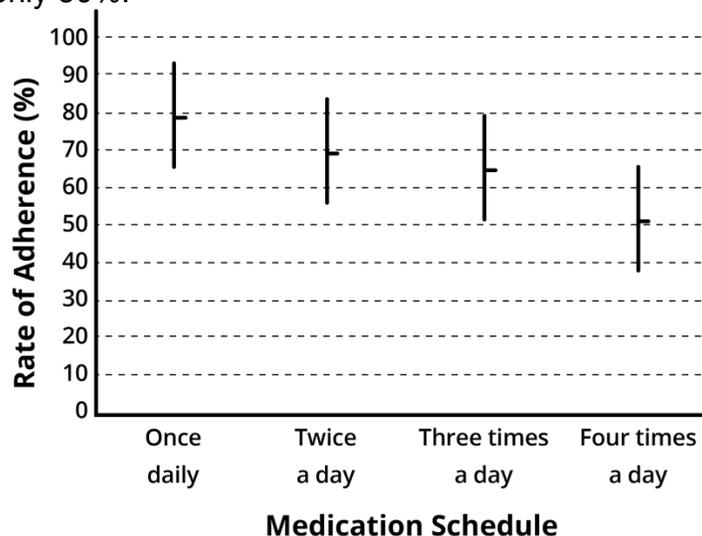
1. The timing and number of prescription refills may be a clue to non-adherence, although this information may not be easily available. Think about the patient who tells you they're taking all of their medication yet that 6 month prescription has somehow managed to last 12 months.
2. Ask the patient exactly how they take their medications. If they have trouble explaining then this may be a clue to poor adherence. One rheumatologist said, "I ask them what day they take their methotrexate. If they have to think about it or hesitate then I know they might not be taking it."
3. Think about the patient who has side effects to many prior medications or the one who calls with problems with current medications. I find when patients call telling me they want to stop a medicine, for whatever reason, then they've probably already stopped taking it.
4. The patient who frequently misses appointments or doesn't book regular follow-ups is likely to be less adherent.
5. Any patient without drug benefit coverage may also have issues with adherence.

What strategies can you implement to improve adherence?

As a rheumatologist, here are some strategies to help you maximize your patients' adherence:

1. Realize that adherence is partly predicted by a patient's belief about medication and disease. It's important for rheumatologists to learn to appropriately counsel patients about the risks and benefits of medications as it really makes a difference when patients weigh the risks and benefits of treatment. For example, when discussing methotrexate, it probably isn't productive to state, "this medication can cause liver toxicity" as this will likely scare a patient. An alternative approach might include, "this medication can irritate the liver but this is rare and I'll watch for this with regular blood tests".
2. Keep your medication regimens as simple as possible. If you have a once daily option then use it. A large systematic review of 76 trials found that adherence was inversely proportional to

frequency of dosing and patients taking medication on a qid schedule achieved average adherence rates of only 50%.³



Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther.* Aug 2001; 23(8): 1296-1310

3. If you're starting combination DMARD therapy, try to think about a staggered start if practical. Have the patient return 2-6 weeks after the initial visit to add the next medication and so on. This way you can assess for adherence with the original medication and counsel about the second.
4. Ask the patient if they have a private drug plan or how they will pay for their medication. Find out how much medications cost per year so patients will have an idea what they will be expected to pay.
5. Blister packs or dosette boxes are useful for patients who may have memory issues or mild cognitive impairment.
6. Beware with patients who miss appointments, show up infrequently and book appointments only when flaring, and those who regularly miss routine lab tests.

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