

## Medication Adherence

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Failure on the part of a patient to take all doses of medication exactly as prescribed is one of the most common therapeutic misadventures. Nonadherence is typically defined as taking less than 80% of prescribed doses of a medication, although it may also include taking too many doses. In actual clinical practice, by this definition, rates of nonadherence average about 50%—much higher than in the randomized clinical trials required for approval of the same drugs.<sup>1–4</sup> This adherence gap represents an important potential therapeutic opportunity, as the clinical consequences of varying degrees of nonadherence are often poorly understood but frequently detrimental to the patient.<sup>5–10</sup>

To understand medication adherence prescribers must be aware of the many factors influencing it, an awareness that goes well beyond the prescriber's gestalt of the patient's ability to remember to take a medicine. A conscientious prescriber evaluates the patients' beliefs about the efficacy, affordability, and adverse effects of the medications they are prescribing; the presence of medical comorbidities including psychiatric and substance use disorders that can affect drug taking; structural factors such as out-of-pocket drug costs, accessibility to health service resources, and the social and cultural context in which a patient's treatment occurs.<sup>11–15</sup> All are important approaches to determining a patient's risk for nonadherence, although none is completely predictive.

The ability to objectively measure adherence is often limited. Drug concentration monitoring (also known as therapeutic drug monitoring; TDM) is a direct and objective measurement of adherence but is available for only a small number of drugs and often reflects drug-taking behavior over a short preceding term. For drugs whose plasma half-life is short, the value of TDM as a measure of adherence is extremely limited.<sup>16</sup> Adherence can be assessed indirectly through objective measures of disease activity, such as blood pressure, hemoglobin A1C, or HIV plasma virus RNA concentration (viral load). Such measures are sensitive but not specific indicators of adherence, as they can be affected by a number of factors in addition to drug-taking

behavior.<sup>5,17</sup> Patient self-reporting remains the most convenient and frequently used mode of adherence assessment. Although patients often overestimate their own adherence, self-assessment is often as effective as more sophisticated methods.<sup>17–20</sup> Pill counts are a feasible and effective adjunct to self-reporting but can be perceived as obtrusive by the patient and may promote dose dumping.<sup>17</sup> Tracking pharmacy refill records is an effective and unobtrusive alternative that tends to have both positive and negative predictive value for assessing adherence but requires ready access to all pharmacies the patient might be using.<sup>21</sup> These methods assume the patient is actually consuming the medication and is not sharing it with others.

Once nonadherence is identified, what can be done about it? The initial and most critical step is a thorough investigation into the underlying factors contributing to each patient's unique nonadherent behavior pattern. Careful communication between the patient and the prescriber about the medication's purpose, administration instructions, and common side effects is an important second step.<sup>22,23</sup> Additional strategies shown to improve adherence include reducing dosing frequencies and pill burden through long-acting and combination formulations, recruiting allied health professionals to provide support, education, and counseling interventions, and enhancing patient communication and engagement through technologies such as text messaging,

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electronic health record patient portals, and mobile phone applications.<sup>24-27</sup> Finally, keeping patients in care is arguably the most important adherence intervention; even patients who only achieve 50% adherence in care will have better outcomes than those lost to follow-up who are receiving no medications.<sup>28</sup>

The following clinical vignettes illustrate the diverse ways that medication nonadherence may manifest itself and the prescriber's critical role in evaluating and promoting medication adherence to achieve important therapeutic goals.

**Case 1: Mr. S.** is a 28-year-old man who works as an investment banker at a prestigious firm in a major metropolitan area. He has a history of HIV infection that was diagnosed 5 years ago on a routine screening test at a time when he was regularly drinking alcohol and using intravenous heroin with friends on the weekends.

He has maintained an undetectable HIV plasma viral load since he started on treatment with a one-pill once-a-day fixed-dose antiretroviral regimen and has been successful in abstaining from opioids since he started seeing a psychotherapist every month.

As his physician reviews Mr. S.'s chart, she notices that it has been a few months since he last saw his therapist and that he has missed or canceled his last 2 appointments with her, too.

In the office, Mr. S. seems withdrawn and distracted. He responds to questions with polite but brief answers, seemingly in a hurry to be somewhere else. He has no complaints to report. His physical exam is unremarkable. While typing his orders into the computer, his physician asks him: "Any problems with your medication?" "No," he replies. "Anything else you want to talk about today?" After a pause, again he replies: "No."

The next day, laboratory results from the visit show Mr. S.'s previously undetectable HIV viral load is now 50,380 copies/mL (lower limit of quantification is 40 copies/mL).

His physician calls Mr. S. and arranges for him to return to the clinic to discuss his laboratory findings as soon as possible.

Late that next afternoon, Mr. S. returns to the clinic. After careful questioning, his physician learns about a high-profile new project he has been assigned to manage at work. This is his first time in management, and the experience has been extremely stressful. His anxiety keeps him up all night, and he has started drinking 4 or 5 glasses of whiskey every evening to calm his nerves and get to sleep. He is having problems concentrating on things, and he has started to question "what the point of it all is." He admits that over the past few months he has not been taking his medication most days, but

on some days he will feel guilty and take a "double or triple dose" to try and make up for the missed ones.

His physician arranges for Mr. S. to see his psychotherapist, and they work together to build new strategies for him to manage his anxiety. HIV genotype testing shows that Mr. S.'s infection now has resistance to 1 of the drugs in his fixed-dose antiretroviral therapy, and he must start a new regimen that substitutes a drug from a different therapeutic class. Mr. S. enrolls in the clinic's medication support team, where a nurse and a pharmacist start working with him weekly to promote adherence to his antiretroviral therapy. Over the course of the next few months and with the support of his multidisciplinary treatment team, Mr. S. is able to stop drinking alcohol and again start taking his medication every day. His poor sleep, anxiety, and depressed mood all begin to improve, and he is again able to achieve and maintain an undetectable viral load.

**Case 1 commentary:** Mr. S.'s story teaches us how critical it is for prescribers to remain vigilant for those subtle behaviors that may suggest nonadherence. No 2 episodes of nonadherence are identical, but with close examination, we can appreciate the anatomy of Mr. S.'s particular presentation: new stress at work led to an exacerbation of an undiagnosed anxiety disorder; uncontrolled anxiety drove self-medication with alcohol; alcohol use in turn provoked a substance-induced depressive episode; finally, the resulting low mood and lack of motivation impacted his ability to adhere to his antiretroviral therapy. This episode might not have been discovered so quickly if not for the abnormality in the HIV viral load, a marker of disease activity that in this case correlated with medication nonadherence, prompting timely evaluation and the initiation of a comprehensive and effective treatment plan. Still, Mr. S.'s nonadherence could have been discovered sooner. Missed appointments are correlated with nonadherence, and the sudden change in Mr. S.'s appointment show-rate likely represented the earliest sign of his newly nonadherent behavior.<sup>28</sup> Mr. S.'s nonadherence was not without consequence: his future antiretroviral medication options will be permanently limited by the drug resistance mutations he acquired during this period.

**Case 2: T.S.** is an 11-year-old girl with moderate persistent asthma that was diagnosed 3 years ago. Since her diagnosis, her symptoms have been well controlled on an oral leukotriene receptor antagonist, a low-dose inhaled corticosteroid, and an as-needed albuterol inhaler.

However, over the past 3 months T.S. has been to the emergency department 4 times for asthma exacerbations that required oral steroid therapy.

At an outpatient visit following her most recent emergency room encounter, T.S.'s primary care physician asks her if she has been taking her medications as they are prescribed. Her mother, who always accompanies T.S. to her appointments, is quick to respond in the affirmative, while T.S. keeps silent. T.S.'s inhaled corticosteroid dose is increased, and she is scheduled to return again in 2 months.

At the next visit T.S.'s mom reports that they've had to make 2 visits to an urgent care center for asthma exacerbations and that T.S. is still using her albuterol inhaler almost every day.

Perplexed by the worsening symptoms despite the increased dose of inhaled steroid, her physician asks about any new exposures in T.S.'s home environment, but her mother reports none. T.S.'s inhaled corticosteroid dose is increased again, to the maximal dose, and she is scheduled to return in 1 month. After the visit, T.S.'s physician contacts the pharmacy and discovers that T.S. hasn't filled her inhaler prescriptions for more than 3 months.

T.S.'s physician asks her to come back in to clinic later that week and to bring her inhalers with her. This time, her physician focuses her questions on T.S., who reports that about 6 months ago she assumed responsibility for managing her own medications. When asked to demonstrate how she uses her corticosteroid inhaler, T.S. puts it about 6 inches in front of her mouth, puffs it once into the air, and takes a shallow breath. She reports that she uses the inhaler "all the time, every day, sometimes twice" but admits that she may sometimes forget to take doses—the inhaler is prescribed 2 puffs twice per day.

T.S.'s physician reviews proper inhaler techniques with her, and, together with her mother, they come up with a plan to help her remember to use her inhaler. T.S. decides she will set an alarm on her phone to remind her to take the medication before and after school. Her mother plans to keep a dosing chart for T.S. on the refrigerator, where she can check a box each time she uses her inhaler, and she will earn points toward a reward with each week of full adherence.

Two months later, T.S. returns to her primary care physician's office proud to report that she has not had any further asthma exacerbations and that she rarely needs to use her albuterol inhaler. Over the next few months her primary care physician is able to wean T.S.'s dose of inhaled corticosteroid back down.

**Case 2 commentary:** T.S.'s story is common among adolescents with medical problems who struggle with many transitions that affect their health care. There were several factors that contributed to nonadherence in this case: the switch from the parent to the patient assuming responsibility for medication administration

led to lapses in adherence that were not identified initially; the patient was incorrectly using her inhaler and didn't understand timing and dosages; and finally there were lapses in memory and routine leading to additional missed medication doses.

As providers, we often assume that the individual who provides history is responsible for medication administration, but in pediatric, geriatric, and special needs' populations, it is important to explicitly define who holds this responsibility.<sup>29,30</sup> In this case false assumptions from the primary caregiver initially led to missed identification of medication nonadherence. Warning signs of nonadherence include increasingly frequent or severe exacerbations of chronic disease or disease refractory to increased medication doses, especially in a patient whose disease process was previously well controlled.<sup>31</sup> Incorrect medication administration is a form of nonadherence and, as in this case, the teach-back method and in-office simulation of medication administration can help to improve adherence.<sup>32,33</sup> Pairing medication administration with daily routines, or using alarms and pill boxes, can help overcome the forgetfulness that challenges patients of all ages.<sup>34</sup> Developmentally appropriate reward systems and positive reinforcement can be of additional use in enhancing medication adherence in pediatric patients.<sup>5</sup>

**Case 3: Mrs. K.** is an 83-year-old woman with a history of senile cataracts, hypertension, and dyslipidemia. She lives with her husband on their farm in a small rural town one hour from the family medicine clinic where she sees her primary care physician.

She only started seeing a physician regularly about 10 months ago, after she was briefly hospitalized for a transient ischemic attack. Although she has been diligent in attending her appointments, Mrs. K.'s blood pressure has been very difficult to control despite increasing doses of antihypertensive medications. Over the past few months Mrs. K. has also complained of chronic watery diarrhea and a progressive lightheaded sensation.

This morning in clinic Mrs. K.'s blood pressure is 188/75 mm Hg with a heart rate of 52 beats per minute while sitting and 152/72 with a heart rate of 54 while standing. Her physician decides to review her medications with her.

"Mrs. K., on our last visit I asked you to double your lisinopril dose from 20 to 40 mg per day. Did you make that change?"

"That's the blue one, right? Yes, I started taking 2 per day like you asked me. I took them this morning before breakfast."

"Yes, and you're still taking the cholesterol medicine, the aspirin, and the beta blocker they started in the hospital for your ministroke, right?"

“Yes, the triangle one, the aspirin . . . I take everything that I am prescribed, doctor.”

“Your hypertension is still not controlled. I’m worried we’re going to have to start a third blood pressure drug.”

“Oh, doctor, since our last visit, I have been having this burning pain in my shoulders and thighs. The diarrhea is still happening, too, I have to rush to the bathroom 6 or more times a day. And I am still so lightheaded, doctor, it is even worse than before. Every time I stand up.”

Mrs. K.’s physician stops and then asks her: “Mrs. K., do you think you could bring all of your medicines in to show me how you take them?”

“Of course, doctor.”

Three days later, Mrs. K. returns to the clinic with a plastic bag full of pill bottles. There is a bottle of lisinopril 5 mg, a bottle of atorvastatin 80 mg, and 3 different bottles of metoprolol in both short and long-acting formulations, with doses between 12.5 and 50 mg, some prescribed 10 months prior by a doctor from the nearby hospital. She also produces bottles of docusate and senna, also prescribed by the other doctor. The bottles with the most recent fill date are from the mail order pharmacy that is currently listed in Mrs. K.’s chart as her preferred pharmacy. Some of the older bottles, however, are from a rural pharmacy near Mrs. K.’s home, and the oldest bottles are from the outpatient pharmacy at the nearby hospital where she had been admitted 10 months ago.

Her physician asks: “Show me how you take all of these”.

“Okay, well every morning I just take 1 of each. I take 1 of the pink ones (she holds up a metoprolol tablet), 1 of these white ovals (she holds up another formulation of metoprolol), and 1 of these white circles (the third metoprolol formulation). I also take my blood pressure medicine, the lis-lisipitor, 2 of these each morning like you told me to (she holds up the atorvastatin [trade name Lipitor<sup>®</sup>] bottle). I also take 1 of these (she holds up the lisinopril bottle), and my aspirin.”

“And what about these?”

“Oh yes I have been taking these as well since I left the hospital” (she gestures to the docusate and senna bottles). “They told me I needed to take all of these every day to keep myself from having a stroke.”

“Do you have any trouble reading these labels, Mrs. K.?”

She looks towards the floor. Softly, she admits, “Yes, I do. I ask my husband for help, but he didn’t get very far in school either. We have our color system, though, I think it keeps me from mixing them up.”

The cause of Mrs. K.’s multiple symptoms begins to clarify. Her physician reconciles her medications and

sends her to the clinic’s nurse for help with organizing them into a weekly pill box. A home health nurse starts visiting Mrs. K. each week over the next month to teach both her and her husband how to organize her medications independently. Her physician also discontinues the laxatives, which were never on his version of her medication list.

On her return visit, Mrs. K.’s blood pressure is 138/72 mm Hg, with a heart rate of 76 beats per minute. Her lightheadedness, diarrhea, and myalgias have all resolved. For the first time in almost a year, she feels good.

**Case 3 commentary:** Sometimes we make assumptions that hurt our patients. In this case Mrs. K.’s reticence to disclose her limited literacy and her physician’s initial overestimation of it led to months of progressively dangerous medication misadministration. Thankfully, the excessive beta-blockade did not lead to a syncopal event or a resultant complication such as a hip fracture, and the toxic doses of atorvastatin did not precipitate rhabdomyolysis or resultant renal failure. Literacy is an important predictor of several key health behaviors, and assessment of this attribute plays a critical role in detecting nonadherence.<sup>35</sup>

Two other factors in this case were Mrs. K.’s hoarding of duplicate medications from multiple pharmacies and prescribers and her confusion between generic names, trade names, and sound-alike medication names. These behaviors caused her to duplicate her metoprolol dosing and to increase her “lisipitor” (atorvastatin, trade name Lipitor<sup>®</sup>) instead of her lisinopril dose. Therapeutic duplication, hoarding, multiple prescribers, and confusion between generic and trade names have all been associated with nonadherence and poor health outcomes.<sup>36</sup>

Finally, Mrs. K.’s case illustrates the critical importance of careful medication reconciliation during transitions of care. Medications that are initiated for an inpatient complication, such as treatment or prevention of constipation, are sometimes continued on discharge without strong justification. Failure of either the discharging inpatient physician or the receiving outpatient physician to complete accurate medication reconciliation can lead to medication errors and adverse events.<sup>37,38</sup> Fortunately, Mrs. K.’s laxative-induced diarrhea did not cause significant hypovolemia or any life-threatening electrolyte abnormalities.

## Conclusion

Nonadherent behavior has a multitude of biologic, social, and economic influences, clinical manifestations, and potential complications. With the concepts reviewed in these vignettes and summarized in the table

**Table 1.** Summary of the Predictors for, Measures of, and Interventions to Improve Adherence

| Predictors of Adherence <sup>a</sup>   | Measures of Adherence <sup>b</sup>       | Interventions to Promote Adherence <sup>c</sup>  |
|--|--|--|
| <i>Patient factors</i>   | <i>Direct measures</i>                   | Ask about barriers to adherence  |
| Age  | Directly observed therapy                | Educate about the medication's purpose, administration instructions, and common side effects                       |
| Literacy   | Therapeutic drug monitoring              | Simplify the medication regimen as much as possible  |
| Beliefs about the medication   |  | Recruit allied health professionals (nursing, pharmacy, therapy) for additional support, education, and counseling |
| Comorbid cognitive impairment, psychiatric disease, or substance use disorders | <i>Indirect measures</i>                 | Enhance communication and engagement through technology  |
| Missed appointments  | Patient self-report                      | Encourage a medication-taking system such as a pill box  |
| Drug hoarding  | Measurements of disease control          | Recruit patient's family, friends, and community services for help   |
|  | Pill counts                              | Consider transdermal or depot (extended release) medications when adherence seems unlikely                         |
|  | Pharmacy refill record tracking          |  |
| <i>Prescriber factors</i>  | Patient diary                            |  |
| Therapeutic duplication  | Electronic medication monitoring systems |  |
| Polypharmacy   |  |  |
| Complex dosing schedules   |  |  |
| Look- or sound-alike drugs   |  |  |
| Inadequate knowledge about the disease or treatment guidelines                 |  |  |
| <i>Shared factors</i>  |  |  |
| Impaired patient-prescriber communication                                      |  |  |
| Lack of trust  |  |  |
| <i>System factors</i>  |  |  |
| Healthcare accessibility   |  |  |
| Drug costs   |  |  |
| Multiple prescribers   |  |  |

<sup>a</sup>Based on References 5, 36, 39, 40.

<sup>b</sup>Based on References 5, 17, 21.

<sup>c</sup>Based on References 5, 22–27.

the reader is armed with the tools necessary to detect and ameliorate nonadherent behavior in his or her practice.

## Disclosures

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