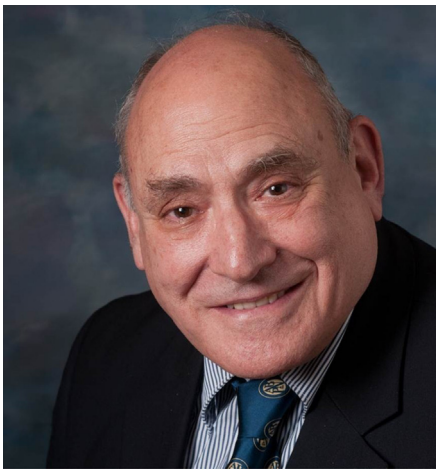
Editor-in-Chief's Note

Adherence Measurements in Clinical Trials and Care



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Probably all practicing clinicians have encountered nonadherent patients. We used to say these patients were noncompliant, but this latter descriptor has largely been discarded because it has paternalistic connotations to some. It has also been suggested that calling patients noncompliant impugns their character. In a thoughtful commentary on this distinction, Emily Wolfe[1] noted that compliance is paternalistic, passive, and episodic, whereas adherence is collaborative, active, and continuous. Nevertheless, across countries and cross-sectional populations, my belief is that this semantic distinction is unimportant, because I cannot imagine that clinicians use either of these terms when speaking with patients. I have asked whether a patient has skipped or missed any doses. I have followed by asking why this has happened. Sometimes doses are forgotten, other times medications have been left at home, and still other times patients say they thought they were taking too much or were having side effects. I really doubt that any clinician-reader has said: "Have you been nonadherent since I last saw you?" Or, "one reason you are feeling worse is because you were nonadherent."

The most frequent problems with nonadherence are seen in patients with chronic illness (eg, hypertension, diabetes). One report suggests that 133 million patients in the United States have chronic conditions and that an estimated 50% who take medications do not take them as directed by their clinicians.[2] Other sobering estimates are that close to 2 billion instances of nonadherence occur yearly; that somewhere between 30% and 65% of all hospitalizations are attributable to nonadherence; that elderly patients, patients with low incomes, and patients labeled as minorities are particularly susceptible to nonadherence.[2] Furthermore, it is estimated that nonadherence costs ~$290 billion (USD) annually, largely because of avoidable usage of emergency departments, clinician office visits, and hospitalizations.[3] Of note, this figure considers only medication adherence; it does not consider the economic burden of nonadherence to prescribed diet and exercise regimens, such as those discussed in this month's Specialty Update on Exercise in Neurological Disorders.[4–8]

Nonadherence can complicate other conditions that are both chronic and episodic. It is generally better to treat these conditions by using preventive strategies. Examples include migraine headaches and certain seizure disorders. Given the debilitating effects of migraine headaches, some may feel surprised that migraineurs do not always take their preventive treatments. In a study of 8688 patients who met full criteria for chronic migraine, 71% to 74% of patients were nonadherent, depending on the criteria used to define nonadherence; at 12 months, the nonadherence rate ranged from 80% to 83%. This smaller cohort was chosen from a pool of 75,870 patients found in a large medical claims database.[9] Here is another example. In a cross-sectional study of 450 patients with documented seizure disorders who were randomly selected from a larger pool of patients, nonadherence with antiepileptic agents was reported to be ~38%.[10] Factors considered to contribute to nonadherence included taking medication for >6 months, having to pay for medications, lack of information about their medications, inadequate support systems, stigma, and bothersome side effects. Among the methods used to assess adherence are pill counts and spot checks for blood or urine levels; each of these has its limitations. Finally, patients who are depressed have compromised adherence not just for their antidepressant medications but also for medications they may be taking for concurrent conditions.[11]

In addition to the reasons for nonadherence noted above, a key contributing factor is dosing regimen. Claxton et al[12] found 76 reports in which adherence was tracked by using electronic monitoring. They defined adherence in two nonoverlapping ways: i) taking the prescribed amount of pills per day = "dose-taking," and ii) consuming pills at a specified time = "dose-timing." Dose-taking was correct in 71% of patients. What is most important from their analyses is that adherence worsened as a function of the number of times per day a drug was to be taken. Once-a-day dosing was associated with 79% adherence; results with schedules of twice a day, three times a day, and four times a day were 69%, 65%, and 51%, respectively. Only 14 of these 76 studies reported on dose-timing. The mean dose-timing adherence rate was 59%. To anyone who has taken medications long term, these findings are not at all surprising. A limitation to all electronic monitoring studies is that, although one can learn when and how often dispensing bottles are opened, there is no way of knowing whether the patient has actually swallowed the pill(s). Furthermore, although the size of these devices has diminished with each iteration, costs remain prohibitive.

A champion of electronic monitoring was the late Dr. John Urquhart. Many consider him to be the father of this field of research. John was a friend of many years, and I had the opportunity to learn from him each year when he lectured on adherence in the postgraduate course on drug development that we, at the Center of the Study of Development at Tufts University, offer. John died at the age of 81, just a month after he taught for us in 2016. John developed the Medication Event Monitoring Systems (MEMS). On the basis of studies using this device, he described six patterns of adherence. For example, there are patients who only skip drugs on weekends; only 17% of patients fit the properly adherent pattern. Interested readers may find this review of electronic monitoring devices useful.[13]

I first learned about nonadherence during a medical school infectious diseases rotation; optimal responses were likely to occur only when all doses of an antimicrobial agent were taken for a specified duration. Later, in the 1980s, I learned about the importance of directly observed therapy (DOT) as an essential element in the treatment of tuberculosis (TB). Currently, the Centers for Disease Control and Prevention considers DOT to be the best and only way to ensure treatment adherence in patients with tuberculosis (TB).[14] When DOT is implemented, the patient with TB meets on a specified schedule with a trained health care worker who hands the medication to the patient and watches while the medication is swallowed. There will always be some patients who will pretend to swallow their medications; they are purposely sequestering their medication under their tongues or in their cheek pockets. I have never seen data on how often this occurs for patients with TB; however, I did observe patients addicted to opioids do this with their methadone. The use of liquid formulations or having patients open their mouths may be the only way to ensure adherence with DOT; unfortunately, this can undermine the building of trusting relationships.

In subsequent years, my interest in nonadherence was reinforced by several research experiences. We examined plasma level of alprazolam in 237 patients with panic disorder who were in the Cross-National Collaborative Panic Disorder Study.[15,16] This was a placebo-controlled randomized trial; patients who were randomly assigned to treatment were included only if they had not recently been on a benzodiazepine agent. However, in both screening and baseline plasma samples, 21% of the patients were found to have detectible levels of diazepam and desmethyldiazepam. This rate was found in both the alprazolam and placebo cohorts. Three weeks into the protocol, 6.7% of the alprazolam group still had levels comparable with their baseline values; this was true for 15.5% of the patients on placebo. At eight weeks, the values were 4.1% and 9.2%, respectively. A post hoc analysis that excluded the nonadherent patients did not alter the results; alprazolam was still clinically and statistically superior to placebo.

We also participated in the National Institutes of Health Hypericum Depression Trial. *Hypericum perforatum* is commonly known as St. John's wort. When this agent is ingested, hyperforin readily appears in the plasma. We obtained and studied usable plasma samples from 292 of the 340 patients with major depression who were treated in this randomized, placebo-controlled trial.[17] Sertraline served as an active control in this 3-arm study. Hyperforin was detected in 17% of patients in the placebo arm; none was found in the sertraline arm. Importantly, no hyperforin was detected in17% of the patients assigned to the *H perforatum* arm.