Pharmacoadherence: A new term for a significant problem

MARIE A. CHISHOLM-BURNS and CHRISTINA A. SPIVEY

Am J Health-Syst Pharm. 2008; 65:661-7

In 2003, the World Health Organization declared nonadherence to medical treatment a major public health concern, particularly among patients with chronic conditions. Research has found that adherence to long-term treatment regimens associated with chronic conditions is problematic, with nonadherence rates in the longer-term regimens ranging from 20% to 82%. Patient adherence to medical treatment regimens has been shown to be directly associated with health outcomes, with poor adherence or nonadherence contributing to increased morbidities and mortalities. Unfavorable outcomes associated with nonadherence also result in annual health care costs of approximately $100 billion. What exactly, though, are we referring to when we discuss the concept of adherence?

Adherence refers to the extent to which an individual’s behavior regarding a medical treatment regimen corresponds with the agreed-on recommendations of a health care professional. Distinct in meaning from the term “compliance” in the health care lexicon, “adherence” indicates collaboration between the patient and the health care professional, whereas “compliance” suggests obedience to the health care professional.

Several factors influence the assessment of adherence to medical treatment, including the type of treatment or behavior (e.g., medication, diet, exercise, appointments), the population studied (e.g., condition, disease), and the method used to measure adherence (e.g., observation, patient interview). Owing to the multiple influences involved in determining adherence, rates of adherence (or nonadherence) and meanings associated with those rates vary widely. Given the complex nature of adherence within a medical context, it may be useful to narrow down the concept to adherence subtypes. One such subtype is medication adherence, which we will coin as “pharmacoadherence.” Thus, the objectives of this article are to introduce and define a new term, pharmacoadherence, as a subtype of adherence. In addition, we wish to explore the measures available to assess pharmacoadherence and to provide an overview of the strategies and interventions that have been developed to improve pharmacoadherence.

Defining pharmacoadherence

The term pharmacoadherence denotes adherence solely associated with medication-taking behavior, narrowing the focus considerably to a patient’s practice of taking a prescribed medication, which includes the collaboration component necessary to distinguish adherence from compliance. We offer the following formal definition of pharmacoadherence: the extent to which a patient follows a given therapeutic medication regimen as agreed on in partnership with a health care professional.

Measures of pharmacoadherence

Pharmacoadherence can be measured directly, indirectly, and subjectively. Direct measures such as biochemical assays (e.g., serum concentrations) provide evidence that a medication has been administered. Indirect measures (e.g., pill counts, refill records), on the other hand, provide evidence merely suggesting that a medication has been taken. Both direct and indirect measures are considered objective. The third category, subjective measures (e.g., self-reports), provide testimony from the patient that medication has or has not been taken. Neither indirect nor subjective measures offer definitive proof that a medication has been consumed or taken. Both direct and indirect measures are considered objective. The third category, subjective measures (e.g., self-reports), provide testimony from the patient that medication has or has not been taken. Neither indirect nor subjective measures offer definitive proof that a medication has been administered, which is a limitation of each. The types of measures available within each of the three categories, as well as their advantages and disadvantages, are described in Table 1. The measure selection process to assess...
<table>
<thead>
<tr>
<th>Measure</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Direct measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct observation&lt;sup&gt;1,2,9-26&lt;/sup&gt;</td>
<td>Objective, highly specific, not invasive</td>
<td>feasibility issues, labor intensive (e.g., training observers), vulnerable to Hawthorne effect, not practical in clinic or outpatient setting</td>
</tr>
<tr>
<td>Serum drug concentrations&lt;sup&gt;25,27-32&lt;/sup&gt;</td>
<td>Objective, may be part of standard care, direct assessment of whether patient has taken medication</td>
<td>snapshot of behavior (not a day-to-day measure), affected by factors other than pharmacoadherence (e.g., metabolism, drug–drug or drug–food interactions, poor absorption), cost, invasive</td>
</tr>
<tr>
<td>Biological markers or tracers (e.g., bromide, phenobarbitone)&lt;sup&gt;26, 28, 29, 33, 34&lt;/sup&gt;</td>
<td>Objective, direct assessment of whether patient has taken medication</td>
<td>snapshot of behavior (not a day-to-day measure), affected by factors other than pharmacoadherence (e.g., metabolism, drug–drug or drug–food interactions, poor absorption), cost, invasive</td>
</tr>
<tr>
<td><strong>Indirect measures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electronic monitoring&lt;sup&gt;2,4,27-29,35-41&lt;/sup&gt;</td>
<td>Objective, indicates times and dates of bottle opening (and therefore provides real-time tracking and detects poor pharmacoadherence to dosing schedule), detects overestimation in other measures, detects pill dumping, not invasive</td>
<td>cost, not effective when pillboxes or liquid medications used, can malfunction and lose data, may interfere with personal pharmacoadherence strategies (e.g., pillboxes, daily decanting), device may be bulky and inconvenient to patient, may cause distress among patients (due to obviousness of pharmacoadherence surveillance), relies on assumption that medication removed from bottle has been consumed</td>
</tr>
<tr>
<td>Pill counts (includes medication weighing)&lt;sup&gt;2,4,27,28,33,42-46&lt;/sup&gt;</td>
<td>Objective, inexpensive, not invasive</td>
<td>time-consuming, computations involved may be complex, relies on assumption that medications not counted have been consumed, tends to overestimate pharmacoadherence&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Refill record&lt;sup&gt;2,5,27,28,33,43-47,50&lt;/sup&gt;</td>
<td>Objective, convenient, standardized data, identifies patients who fail to refill medication(s), not invasive, inexpensive</td>
<td>possible misinterpretation of use when changes are made to dosage, relies on assumption that filled prescriptions are consumed, assumes all sources of medication are captured, patterns of poor pharmacoadherence not detectable, only useful for long-term medications, increased complexity when using records from multiple pharmacies</td>
</tr>
</tbody>
</table>

Continued on next page
Table 1 (continued)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surrogate clinical parameters (e.g., blood pressure, blood glucose levels, low-density-lipoprotein cholesterol levels)(^{18,26,43})</td>
<td>May be assessed as part of standard care</td>
<td>Influenced by other variables (e.g., patient’s physical state, adequacy of medication), problems regarding reliability and validity</td>
<td>Considered poor substitute for more direct measures</td>
</tr>
<tr>
<td>Clinical outcomes (e.g., pain management)(^{26,43})</td>
<td>May be assessed as part of standard care</td>
<td>Influenced by variables other than medication adherence (e.g., physical therapy), problems regarding validity and reliability</td>
<td>Considered poor substitute for more direct measures</td>
</tr>
<tr>
<td>Subjective measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-reports (e.g., diaries, standardized questionnaires, interviews, visual analogue scales)(^{3,18,24,26-30,43,44,46,50,51})</td>
<td>Simple, quick, inexpensive, avoids sophisticated methodology and equipment, may provide information that explains variation in pharmacoadherence patterns and clinical response to medication therapy</td>
<td>Overestimates pharmacoadherence, low sensitivity; patients may provide socially acceptable responses; limited patient recall (impact of time); diaries may be burdensome, may not be returned, or may be returned incomplete; tends to be done around time of clinic visit when pharmacoadherence generally increases (introducing bias into results)</td>
<td>Independent predictor of clinical outcomes; correlated with electronic measures in some studies; patient reports of poor pharmacoadherence (as opposed to reports of good pharmacoadherence) are generally valid; generally considered unreliable</td>
</tr>
<tr>
<td>Clinician assessment(^{18,29,31,32})</td>
<td>Simple, quick, inexpensive, avoids sophisticated methodology and equipment</td>
<td>May be influenced by interactions with patients and by patient therapeutic outcomes</td>
<td>Clinician reports of poor pharmacoadherence (as opposed to reports of good pharmacoadherence) are generally valid; independent predictor of clinical outcomes; commonly fails to identify nonpharmacoadherent patients</td>
</tr>
<tr>
<td>Assessment by others (e.g., caregivers, significant others, research personnel)(^{17,31})</td>
<td>Simple, quick, inexpensive, avoids sophisticated methodology and equipment</td>
<td>Affected by amount of time spent with patient and level of involvement in patient’s care (e.g., accuracy of assessment may decrease if significant other has only limited involvement in patient’s treatment regimen)</td>
<td>Used and studied less frequently than other measures of pharmacoadherence</td>
</tr>
</tbody>
</table>

*Research suggests that unannounced home-based pill counts may be more accurate compared with scheduled and office-based pill counts.*

---

2. Measuring pharmacoadherence: An essential first step toward improving medication adherence
3. J Pharm Pract
4. Clinicians’ perceptions of medication adherence
5. J Gen Intern Med
6. Pharmacoepidemiology
7. J Clin Pharmacol
8. JAMA Intern Med
9. Am J Health-Syst Pharm
10. J Clin Epidemiol
12. J Gen Intern Med
13. JAMA Intern Med
14. Pharmacoepidemiology
15. J Clin Pharmacol
16. J Gen Intern Med
17. J Clin Epidemiol
18. J Clin Pharmacol
19. J Gen Intern Med
20. J Clin Epidemiol
22. J Gen Intern Med
23. J Clin Epidemiol
25. J Gen Intern Med
26. J Clin Epidemiol
27. J Clin Pharmacol
Pharmacoadherence generally depends on several factors, including setting (e.g., outpatient clinic), time, cost, and available resources.

**Strategies to improve pharmacoadherence**

Based on the literature, a model of four major factors that influence pharmacoadherence—motivation, knowledge, skills, and access—was developed.\(^2\)\(^,\)\(^5\)\(^3\)\(^5\) The core of the model, patient motivation, incorporates patient beliefs, values, attitudes, and willingness to follow the dosing regimen. This model suggests that the likelihood of patients’ pharmacoadherence is increased by factors that (1) improve their access to medication, (2) enhance their knowledge and skills concerning medication regimens and disease states, and (3) increase their motivation to adhere to medication regimens. A literature search of MEDLINE (PubMed) restricted by language only (English) was conducted to identify those intervention studies that address the factors associated with pharmacoadherence using combinations of the following search terms: “adherence,” “medication adherence,” and “intervention.” The literature search produced multiple studies, with pharmacoadherence interventions generally categorized as technical, educational, behavioral, affective, or multimodal.

Technical interventions address the medication regimen itself rather than external factors that influence a patient’s medication-taking behavior. Successful technical interventions have included simplifying the dosing regimen and schedule and the use of tools such as pillboxes.\(^2\)\(^,\)\(^5\)\(^3\)\(^5\) For example, it was found that single daily dose regimens were linked with significantly greater pharmacoadherence than that of multiple daily dose regimens.\(^5\)\(^4\)

Educational interventions focus on teaching and providing knowledge related to the patient’s medical condition and medication regimen. Some examples of this approach are notifying patients of medication-related adverse effects, distributing medication information in booklets or leaflets, and offering structured individual education sessions.\(^2\)\(^,\)\(^5\)\(^3\)\(^5\) For instance, an educational intervention consisting of an informative booklet, group and individual instruction sessions, and a self-management plan was found to improve pharmacoadherence.\(^5\)\(^6\)

Behavioral interventions attempt to modify a patient’s medication-taking behaviors through the use of cues, reminders, and reinforcements.\(^2\)\(^,\)\(^5\)\(^3\)\(^5\) For example, a telephone-linked reminder system was found to increase pharmacoadherence among elderly adults,\(^5\)\(^7\) and monetary reinforcers plus the use of personalized cues for remembering dose administration times were found to improve pharmacoadherence in HIV-infected patients.\(^5\)\(^8\)

Affective interventions attempt to improve pharmacoadherence by addressing a patient’s emotional needs and social support systems.\(^5\)\(^9\) Interventions in this category include family therapy and intensive individual counseling.\(^5\)\(^9\)\(^,\)\(^6\)\(^0\) For example, an intervention designed to promote HIV treatment adherence through the development of peer support relationships (i.e., each participant acts as both a peer advocate for adherence and a recipient of peer advocacy efforts) resulted in a 90% average pharmacoadherence rate for patients by the end of the study period.\(^5\)\(^1\)

Multimodal interventions use strategies from two or more of the four major categories—technical, educational, behavioral, affective—identified to address and improve pharmacoadherence. For example, an intervention consisting of individual counseling, detailed information about a medication regimen, an individually tailored medication schedule, telephone support, and regular clinic visits was found to have moderate effects on improving pharmacoadherence.\(^6\)\(^2\) The results of a meta-analysis indicate that combining interventions that include behavioral, educational, and affective components was most successful in improving pharmacoadherence,\(^6\)\(^3\) a finding that is generally consistent with systematic reviews of pharmacoadherence interventions.

Several systematic reviews of pharmacoadherence interventions conducted in recent years provide a cohesive overview of the effects of various intervention strategies. In 2002, McDonald and colleagues\(^6\)\(^4\) published a review of randomized controlled trials (RCTs) of pharmacoadherence interventions. An update of this review was conducted in 2005 by Haynes and colleagues.\(^6\)\(^5\) In both studies, <50% of interventions were associated with improvements in pharmacoadherence; however, the majority of interventions that were associated with improvements in pharmacoadherence also demonstrated improvements in clinical outcomes. The majority of effective interventions combined the use of technical, educational, behavioral, and affective intervention strategies. Virtually none of the RCTs examined had a follow-up of greater than two years, and thus the sustained impact of successful interventions is unknown.

A systematic review of RCTs of interventions to improve pharmacoadherence in chronic conditions found that a higher percentage of behavioral interventions demonstrated improvements in pharmacoadherence as compared with educational or combination interventions.\(^5\)\(^5\)\(^,\)\(^1\) Other studies, however, are consistent with the findings of McDonald et al.\(^6\)\(^4\) and Haynes et al.\(^6\)\(^5\) regarding the success of multimodal interventions as compared with other types of interventions. For example, a review of antipsychotic pharmacoadherence interventions found that the great-
est improvements were observed in eight studies that employed combinations of behavioral, educational, and affective strategies, while solely educational interventions produced the least improvement.59 Similarly, Vergouwen et al.66 found that 9 of 11 collaborative care interventions that incorporated behavioral, educational, and affective components significantly improved pharmacoadherence to antidepressant therapy. A review of interventions to improve pharmacoadherence among older adults found that multimodal interventions tailored to address age-related adherence barriers were most effective in promoting pharmacoadherence.67

The general findings of the systematic reviews discussed here suggest that the most effective pharmacoadherence interventions are those that include combination or multimodal techniques. The advantage of multimodal interventions is that they address multiple barriers to pharmacoadherence on multiple levels. However, there are also drawbacks or limitations to combination interventions. Their reproducibility is difficult to predict, and intervention outcomes may vary depending on the patient population.68 Often, studies do not evaluate multimodal interventions to determine the most effective or critical components and eliminate extraneous or superfluous techniques that distract from the primary strategies.55,68,69 In addition, the effect sizes of combination interventions vary with regard to changes in pharmacoadherence and clinical outcomes; variability in effect sizes related to clinical outcomes has also been noted for other categories of interventions.64,65,68,70 Kripalani and colleagues69 further suggest that clinical outcomes can-

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explain the medication regimen</td>
<td>Educational materials</td>
</tr>
<tr>
<td></td>
<td>In-depth discussions with patients, including asking patients open-ended questions to ensure patient understands what medication is for and how to take it</td>
</tr>
<tr>
<td>Tailor the medication regimen to the patient's lifestyle and daily routine</td>
<td>Develop dosing schedule around patient's primary daily activities such as work or school (e.g., a once-daily medication that could be taken before or after school or work)</td>
</tr>
<tr>
<td></td>
<td>Develop dosing schedule around a daily event such as breakfast (e.g., take medication before breakfast each morning)</td>
</tr>
<tr>
<td></td>
<td>Provide patient with container that allows convenient organization of daily medication</td>
</tr>
<tr>
<td></td>
<td>Provide patient with convenient medication containers that are easily transportable (if medications must be taken away from home)</td>
</tr>
<tr>
<td>Establish collaborative relationship with patient, and facilitate patient interaction with other pharmacy staff</td>
<td>Be available to address patient concerns regarding medication</td>
</tr>
<tr>
<td></td>
<td>Assist patient in developing strategies to maintain adherence</td>
</tr>
<tr>
<td></td>
<td>Provide patient with alternative pharmacist contact who can offer advice/answer questions on medication regimen if you are not available</td>
</tr>
<tr>
<td>Identify and address individual barriers to adherence</td>
<td>Ask patients what things lead to nonadherence to medication, and work with patient to develop strategies to address these challenges (e.g., setting an alarm to sound when it is time to take medication if a patient identifies forgetfulness as a barrier to adherence)</td>
</tr>
<tr>
<td>Refer special-needs patients to appropriate services</td>
<td>Identify patients with substance abuse and/or mental health issues and refer patients to support services</td>
</tr>
<tr>
<td>Promote self-efficacy</td>
<td>Provide positive reinforcement to pharmacoadherence successes; something as simple as offering words of encouragement can be extremely beneficial to the patient's confidence regarding his or her ability to follow a long-term medication regimen</td>
</tr>
<tr>
<td>Create and maintain an environment conducive to pharmacoadherence</td>
<td>Collaborate with other health care professionals (e.g., physician, home health nurse) involved in the patient's care to communicate the patient's level of pharmacoadherence and to strategize on promoting or improving pharmacoadherence</td>
</tr>
</tbody>
</table>

Table 2. Summary of American Psychological Association Recommendations To Promote Adherence to a Medication Regimen72
not be consistently linked to changes in pharmacoadherence. Finally, the cost and time involved in conducting multimodal interventions may limit their utility in clinical practice. Despite these limitations, combination or multimodal interventions have consistently demonstrated the most promise in addressing poor pharmacoadherence. Health care professionals and researchers would do well to focus on designing, implementing, assessing, and then finely tuning multimodal interventions to maximize pharmacoadherence and to promote adaptation and application of effective interventions to diverse patient populations.

The American Public Health Association proposed a four-step approach to promote adherence to medications that may also be useful for health care professionals. First, an assessment of factors influencing adherence should be conducted and barriers identified. Next, the health care professional should establish a therapeutic alliance with the patient to facilitate the development of a medication adherence plan. Third, multiple measures should be used to assess the patient’s level of medication adherence. Finally, multiple interventions should be conducted that target the barriers identified in the first step.

The American Psychological Association (APA) has also addressed the issue of adherence, noting that to be adherent to a medication regimen, patients must (1) have a basic comprehension of their regimen (e.g., how often and how much medication should be taken), (2) have confidence that they can follow the regimen, (3) remember to take their medication, (4) incorporate their medication regimen into daily routines, and (5) maintain adherence to their medication regimen in the face of changes in daily routine. To further assist health care professionals in promoting adherence, APA provided recommendations that include several elements of the adherence interventions identified as effective in the literature (Table 2).

**Summary**

We defined pharmacoadherence as the extent to which a patient follows a given therapeutic medication regimen as agreed on in partnership with a health care professional. Rates of pharmacoadherence among the general patient population are variable, with the World Health Organization estimating an average rate of 50%. Given the critical interplay between pharmacoadherent behaviors, health outcomes, and health care costs, it is important to have a clear understanding of what the term pharmacoadherence really means as well as reliable and valid assessment measures and effective interventions to target deficits in pharmacoadherence. Future research should continue to refine measures of assessment and intervention protocols to improve pharmacoadherence.

**References**

Pharmacoadherence


