Adherence to Treatment Regimens in Major Depression: Perspectives, Problems, and Progress

September 15, 2007 | Depression [1], Major Depressive Disorder [2], Addiction [3]
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Adherence, in a medical context, refers to the degree to which a patient follows the treatment plan that has been agreed on between the prescriber (usually, but not always, a physician) and the patient. Although the term "compliance" is often used by caregivers, it is a less desirable term than "adherence," because it implies an all-or-nothing obedience to the will of others. Adherence, like a religious belief, involves recognition that there may be aspects that are less acceptable than to others; accordingly, the patient may subscribe more to certain tenets than others. This is often (and more so than we believe) what patients do in practice. They skip doses because of adverse effects or to use recreational drugs. They may forget the treatment plan or come to disagree with it on the basis of something they have heard or read on the Internet.

There are different degrees of adherence, from complete to rare or nonexistent adherence. This article seeks to examine what underlies difficulties and challenges with treatment adherence of major depressive disorder and identifies approaches that the clinician can use to improve patient adherence to treatment. Perspectives on adherence

Adherence, from a dimensional perspective, can be defined as the percentage of time the patient takes his or her medicines as prescribed or how many times he performs the prescribed life-style interventions (eg, exercise). From a categorical perspective, nonadherence is often described in terms of the point below which a therapeutic benefit from an intervention is likely to be realized. Both definitions are dynamic and variable for each intervention and each patient.

Nonadherence may be willful or active: the individual consciously decides not to follow the prescribed treatment plan. One study found that 25% of patients told their doctors they were taking their medication when, in fact, the pharmacy database showed that they were not. Alternatively, nonadherence may be passive--patients forget or do not understand the instructions, or are unable to perform the activity correctly.

Assessment of adherence has been both direct and indirect. The most common example of a direct measure is the serum blood levels that are routinely used for management of lithium as well as many of the tricyclic antidepressants (TCAs). The downside to measuring blood levels is that they reflect the concentration of drug only at the time the blood is taken; there is no equivalent to the hemoglobin A1c assay for diabetes that is used to measure blood sugar concentrations over the preceding 3 months.

The most common indirect measures of adherence are the patient's self-report and the report of the family. It is generally accepted that the self-report method overestimates the degree of adherence. Some research studies have used pill-counting strategies or electronic caps on medicine containers to record the number of times the container is opened. Although this approach monitors medication-taking behavior, it cannot account for doses removed that are not actually taken. At a population level, claims records from public and private health insurance organizations can be used to estimate the number of prescriptions filled and refilled.

There are no sociological or personality characteristics that consistently predict difficulties with adherence; moreover, adherence varies over time and in response to different aspects of prescribed treatments. However, it is recognized that comorbid medical conditions and concomitant substance abuse are generally associated with compromised adherence. Use of the newer antidepressant classes of medications is generally associated with modest improvements in adherence, but it is receiving individually targeted mental health care services that consistently has been shown to be the strongest factor associated with increased adherence to antidepressant treatment. Older versus newer antidepressants
Before the advent of the SSRIs, TCAs were the primary choice of pharmacological treatment for major depression. It has long been recognized that adherence to TCAs is often poor, particularly in primary care practice. There are a host of reasons patients may have treatment-adherence difficulties with TCAs, including adverse effects and complicated dosing (eg, starting with a low dose and titrating to a therapeutic range).

It was assumed that the simplified dosing scheduling with SSRIs, as well as less problematic adverse effects, would result in improved adherence in patients with major depression. However, the results of recent studies have not been as resoundingly favorable as was anticipated. A number of meta-analyses of comparative treatment studies that examined dropout rates of patients taking SSRIs compared with those of patients taking older TCAs failed to find significant overall differences, although the rates were lower in the SSRI groups when adverse effects were identified as the reason for discontinuation. Direct comparisons of TCAs and SSRIs have only provided modest support for the belief that adherence is improved with SSRIs.

Thompson and colleagues randomized 152 patients in 10 primary care settings in the United Kingdom, in an open-label parallel-group study comparing fluoxetine and the TCA dothiepin at therapeutic dosages for 12 weeks. Similar numbers of patients dropped out of the study in both groups (37% vs 39%); the rate of withdrawal from the study because of an adverse event was 20% in the dothiepin group and 14% in the fluoxetine group, suggesting a modest advantage of fluoxetine. The level of adherence in the treated groups was nonsignificantly greater in the fluoxetine group (76%) than in the dothiepin group (64%) as measured by pill counts. The investigators concluded that there were, in fact, modest differences in the levels of adherence in the 2 groups; however, they pointed out that the study sample was insufficient to detect such a small effect size.

Adherence measures at the population level
The study of adherence to antidepressant treatment has evolved to examination of larger data sets from large health care organizations. The metric used to assess adherence is based on the criteria of the National Committee for Quality Assurance (NCQA) standardized performance measures that are voluntarily reported by health plans to the Health Plan Employer Data and Information Set (HEDIS). Adherence is simply defined as being in possession of the prescribed antidepressant as measured by pharmacy claims and attending mental health appointments identified by health claims (Table 1).

**TABLE 1**
NCQA HEDIS quality measures for treatment adherence
References: References


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