Compliance With Pharmacotherapy in Mood Disorders

by MONICA RAMIREZ BASCO, PhD; and A. JOHN RUSH, MD

Bipolar disorder (BPD) is a severe, chronic, and disabling mental illness that produces dramatic changes in thought, mood, and behavior. It afflicts nearly 1% of the adult population in the US, and results in suicide attempts in nearly 25% of these individuals. Episodes become more frequent over time, last longer, and leave individuals with briefer periods of normality.

Unipolar depression is more common, with a lifetime prevalence of up to 12% in men and 26% in women in the US. Recurrent episodes of depression over time is the rule for those afflicted, while 10% to 20% have a chronic and unremitting course. Symptoms of depression leave patients hopeless, fatigued, overwhelmed, and often unable to carry out their usual activities such as work or care of the home.

ASSESSMENT STRATEGIES

To adequately care for patients, the practicing clinician needs to be able to reliably assess the degree to which they adhere to treatment. Ideally, methods are needed for prediction of compliance problems before they occur so that appropriate preventive actions can be taken.

There are several ways to assess adherence to treatment. These methods include (1) patient interview, (2) patient self-report by questionnaire, (3) pill counts, (4) blood levels, (5) appointment attendance, (6) attrition, and (7) completion of homework assignments or directives from the clinician.

These methods vary in ease of administration and in accuracy. The easiest method, asking patients to report on their adherence levels, may also be the most inaccurate. When comparing patient self-report with medication plasma level, a more objective measure, several investigators have found considerable discrepancies. In comparing self-report of adherence to pill counts, Park and Lipman found that in 40% of cases, self-reports of adherence did not match the pill counts. However, these discrepancies tended to occur more frequently with minor than with major deviations.

While medication blood levels may be more accurate measures of adherence than self-report, the accuracy with which plasma
levels reflect dose ingested may vary with the type of medication,\textsuperscript{16} and within and between individuals.

**Lithium**

After control of acute episodes of depression and mania, maintenance (i.e., prophylactic) treatment is essential to control this illness, but often fails primarily due to premature discontinuation of or inconsistent adherence to medication regimens.\textsuperscript{17} In a meta-analysis of studies including lithium (Li) discontinuation, Suppes et al\textsuperscript{25} calculated that the risk of recurrence of bipolar episodes on discontinuation of Li is approximately 28 times higher per month without medication than with Li maintenance.

Based on appointment keeping, nonadherence to Li treatment ranges from 11\% to 12\%,\textsuperscript{13,18,23} but when plasma concentrations of Li are examined, either randomly or routinely, up to 46\% are "noncompliant."\textsuperscript{13,18,20,23,24} A meta-analysis of Li compliance studies using a Bayesian model to predict the likelihood that a patient treated with Li would be compliant with treatment is 60\% (SD 3.6\%).

**Anticonvulsants**

There have been no formal studies of compliance to anticonvulsants. However, using attrition rates as a crude measure of nonadherence, maintenance studies of carbamazepine (CBZ) show relatively similar dropout rates for patients randomized to either CBZ or Li. Placidi et al\textsuperscript{25} reported a 31\% dropout (13 of 42) for CBZ and 34\% dropout (14 of 41) for Li. Similarly, Luzat et al\textsuperscript{26} found a 33\% dropout (9 of 27) for CBZ and 22\% (6 of 27) for Li. In a review of the medical records of patients with bipolar disorder, Fawcett and Kravitz\textsuperscript{19} found that 50\% (17 of 34) of their patients on CBZ and 37\% (16 of 43) of their patients on Li were not taking their medications as prescribed.

**Antidepressant Medications**

Drug defaulting is also common in the treatment of major depression with tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). In clinical research trials, 38\% to 60\% of patients being treated with antidepressant medications stopped taking their medication prematurely.\textsuperscript{15,17,19} Higher rates of drug defaulting (68\%) have been found in general practice settings.\textsuperscript{20}

**Psychotherapy**

The same pattern of research clinic versus private practice dropout rates is reported in psychotherapy studies of depression. For example, Persons, Burns, and Perloff\textsuperscript{21} reported a 50\% dropout rate in private practice with cognitive therapy, while others\textsuperscript{22,33} found dropout rates ranging from 0\% (n = 12) to 31\% (n = 16) in research settings.

**Pharmacotherapy vs. Psychotherapy**

Patients with major depressive disorders dropping out of randomized controlled trials comparing short-term psychotherapy, pharmacotherapy, or the combination of both were examined as a crude measure of the relative levels of compliance to these forms of treatment. A meta-analysis using Baysian modeling\textsuperscript{34} was executed to determine the likelihood that the patients randomized to each cell would complete treatment events, and empirically patients would not drop out of treatment was 82\% ± 3.8\% for cognitive-behavioral therapies and 66\% ± 5.7\% (M. Basco, unpublished data) for other short-term psychotherapies. The probability of staying in a pharmacological treatment cell was 58\% ± 4.6\%, and for the combination of psychotherapy and pharmacotherapy, including both cognitive-behavioral and other psychotherapies, the probability of staying in treatment was approximately 72\% ± 5\%, lower than for psychotherapy alone.

**WHICH PATIENTS HAVE DIFFICULTY WITH ADHERENCE?**

Several studies have attempted to identify variables within the patient and/or the treatment modality that predict adherence. Sociodemographic variables such as age, gender, intelligence, education, marital status, and employment status have not consistently contributed to the prediction of treatment adherence across studies.\textsuperscript{13,18,20,27,32,35,39} Diagnostic variables, such as age of onset of the illness,\textsuperscript{27,37,39} number of previous episodes of illness,\textsuperscript{20,27,33,36,39} degree of inter-episode recovery,\textsuperscript{36,37} and polarity of the index episode of illness\textsuperscript{18,20,36,40} have been mixed. The most consistent diagnostic predictor of poor treatment adherence is current comorbid psychiatric illness, particularly substance abuse.

Last et al\textsuperscript{38} found an interaction between treatment type and patient depression diagnostic subtype in treatment dropout rates. Endogenously depressed patients were less likely to drop out of pharmacotherapy (amitriptyline) than were nonendogenous patients, while nonmelancholic patients were more likely than melancholics to complete psychotherapy. This suggests that "sicker" patients were more tolerant of the side effects of medication than were patients with less severe forms of depression. Conversely, those patients with less severe depressive symptoms were better able to tolerate the slow recovery time in psychotherapy than were patients with more severe forms of depression.

(continued on page 276)
The treatment process, including the patient-clinician relationship and medication side effects, can affect treatment adherence. In several studies, when patients with mood disorders were asked to list their reasons for prematurely discontinuing treatment, they indicated that medication side effects was a factor in their decision. A third treatment-related obstacle to adherence reported by patients is the general idea of having to take medication. For example, Jamison et al. asked patients with bipolar illness to rank order common reasons for discontinuing their medication against medical advice. The top ranked response was the idea of taking medication followed by missing the highs, feeling depressed, being bothered by the idea of having a chronic illness, feeling well and seeing no need for medication, and the hassle of taking medication. Patients with MDD in the Simons et al. psychotherapy study reported practical issues such as time and transportation as reasons for discontinuing treatment.

Enhancement of Treatment Adherence

In general, psychosocial interventions, when used as an adjunct to pharmacotherapy, tend to improve treatment adherence and, thereby, reduce the rate or recurrence of illness. The elements common to most psychosocial interventions are didactics about the illness, teaching patients how to cope with interpersonal and psychosocial difficulties, and providing emotional support. For example, Davenport et al. found that bipolar patients assigned to the couples psychotherapy group (N = 12) had fewer instances of rehospitalization, fewer marital failures, and better social functioning and family interaction than those in a Li group (N = 11) or community-based aftercare (N = 4). Both long- and short-term group therapy, when combined with pharmacotherapy, have also been found to be helpful in reducing the frequency and length of hospitalization in bipolar patients.

Cochran found that patients with bipolar disorder assigned to a 6-week individual cognitive therapy intervention were significantly less likely than the standard care group to (a) be rated as having major adherence problems, (b) terminate Li against medical advice, (c) have nonadherence-precipitated episodes, and (d) be hospitalized. Schwarcz and Silbergeld conducted an announced morning Li levels on 26 outpatients in a Li clinic 2 hours after their morning dose. Eleven patients (42%) were found to be nonadherent to their daily Li regimen by these "spot checks" as indicated by lower plasma Li levels than were expected. All patients were counseled regarding their apparent nonadherence and 6 of the 11 patients subsequently became more adherent.

Patient Education to Improve Treatment Adherence

Several studies have examined the effect on adherence of simply providing education to patients and their family members about the illness and its treatment. For example, VanGent and Zwart found that 6 months after providing five educational sessions, the partners of bipolar patients demonstrated more knowledge of the illness, Li, and of social strategies for coping with the patient's symptoms. The patient's level of adherence remained comparable to baseline levels, as measured by plasma Li level, avoiding the deterioration in adherence levels over time often found in Li-treated patients.

Altamura and Mauri found increased treatment adherence in patients receiving education compared to standard care control groups as measured by pill count or blood level to dose ratio. Seltzer, Roncari, and Garfinkel provided nine lectures for inpatients about their diagnosis, course of treatment, medication, side effects, relapse, and importance of support. Patients with schizophrenia (N = 44), bipolar disorder (N = 16), and major depressive disorder (N = 7) were placed in either diagnostic specific educational groups or a no education control group. At the 3-month follow-up, the educational groups demonstrated greater treatment adherence (by pill counts or medication blood levels) and were less fearful of side effects and drug dependency than the control group.

Myers and Calvert randomly assigned outpatients with major depression (N = 120) to three groups: (1) written and verbal information about medication side effects; (2) information on the beneficial effects of treatment; or (3) no education. Assessment of adherence (pill counts and interviews) and presence of side effects was conducted at 3 and 6 weeks of treatment. The two information groups reported significantly fewer side effects and had better treatment adherence than the control group at the 6-week follow-up.

Summary and Conclusions

Compliance is a common problem in the management of mood disorders, with whatever treatment is being considered. Thus, the psychopharmacologist and psychotherapist should anticipate that many patients will encounter such difficulties. Because it is difficult to predict levels of compliance based on patient characteristics, preventive measures should always be taken. Essential elements include patient education, careful attention to and management of side effects, and special focus on the therapeutic alliance to create an envi...
room in which compliance is openly discussed in a nonpunitive fashion.

We have found it useful to (1) define the goals of treatment with the patient, to ensure that the patient agrees with the plan and views it as both realistic and feasible; (2) anticipate compliance problems by asking patients when they are most and least likely to stick with treatment (e.g., time of day or week, symptom status, mood, time of year, etc.), and (3) develop plans to combat compliance problems. In essence, regular discussions of compliance issues and difficulties should be as inherent to clinical management as discussion of side effects and symptoms. Further studies are needed to better define compliance "packages" and the patients for which they are most suitable.

REFERENCES


INFORMATION FOR CONTRIBUTORS

Psychiatric Annals is a peer-reviewed journal that focuses on a single topic in psychiatry each month, with a circulation of 34,000. Each issue is coordinated by a Guest Editor, who has expertise in that particular area of psychiatry. The Guest Editor is responsible for outlining the content of the issue and inviting authors to write on the various aspects of the topic. The Guest Editor then reviews the articles he or she has solicited. When the issue is completed, the Guest Editor submits the papers, which then undergo double-blind peer review.

Submitted manuscripts are processed by the Managing Editor, who handles revisions, final drafts, and all correspondence with authors. All articles are copyrighted by SLACK Incorporated, the publisher. An honorarium is paid to the Guest Editor and may be distributed among contributing authors at the Guest Editor's discretion.

We welcome letters of inquiry from prospective Guest Editors. Topics should be of interest to all practicing psychiatrists and should reflect current research. Please indicate the topic of your special interest and include a list of proposed articles and authors. Please enclose your curriculum vitae. Send to: Managing Editor, Psychiatric Annals, 6900 Grove Road, Thorofare, NJ 08086-9447.