

Patient Compliance in Depression

Based on a presentation by James Jefferson, MD

Presentation Summary

Results of a study of comorbidity reveal that Americans have a 10.3% 1-year risk and a 17.1% lifetime risk of experiencing a major depressive disorder. Identification and treatment of depression are vital to the outcome of the illness, whose course is characterized by 5 phases: response, remission, relapse, recovery, and recurrence.

Treatment must be seen as a 2-fold process involving continuation and maintenance of therapy to avoid relapses, which become more and more frequent after each depressive episode. Ensuring that patients comply with their medication regimens is a major challenge for physicians and requires patient understanding and cooperation.

The risk of experiencing depression is high. According to the National Comorbidity Study of the DSM-III-R, which included 8098 participants, the 12-month prevalence of major depressive disorder was 10.3%, and the lifetime prevalence was 17.1%.¹ If affective disorders are included, the percentages increase to 11.3% and 19.3%, respectively. Thus, identification and treatment of depression must be improved. There are, however, many factors that contribute to failure or success in diagnosis and therapy.

Treatment for Depression

Treatment for depression can be characterized by the “5 Rs:” response, remission, relapse, recovery, and recurrence (Figure 1).²

The treatment of depression begins with the acute phase in which treat-

ment is begun and a response (depressive symptoms diminish) is produced. After remission (full resolution of the episode) has occurred, treatment is continued for a number of months before discontinuation is considered. Recurrent depression often requires maintenance treatment to prevent future episodes.²

Clinicians must remember that response does not qualify as remission. However, in many clinical trials, a 50% reduction of depressive symptoms is considered to be a positive outcome.

Nevertheless, remission must be the goal in depression treatment, and only after several months of remission should the physician and patient consider reducing the medication dosage. During remission, continuing clinical evaluations of the patient is important because problems may develop if treatment is stopped too early.

Importance of Continuation Treatment

After remission has occurred, the continuation treatment phase is entered to reduce the likelihood of a

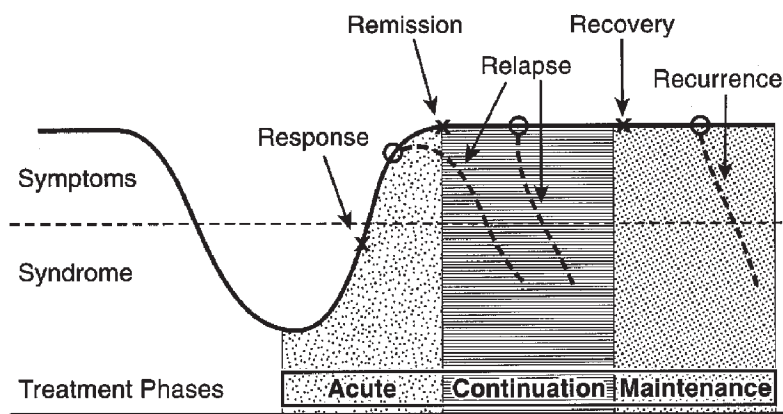
relapse. Ideally, treatment should be continued for 6 months or for a minimum of 4 months. Those time frames are suggested for the patient who has experienced only 1 episode of depression. A greater duration of treatment might be necessary for the patient with recurrent depression. There is, however, difficulty in continuing treatment during a time when the patient is depression free. One reason is he or she may now be less tolerant of the subtle side effects of the drugs being prescribed. This can lead to noncompliance, which can lead to recurrent episodes of depression.

When remission occurs and patients are tapered off their medication, about 50% of them experience no recurrent episodes. However, depression is often a recurrent illness, and as a result 50% of patients will experience another episode. For them, the treatment process may begin again and may result in the long-term use of medications to prevent subsequent recurrences.

Studies show that the risk of recurrence increases with each episode until that risk exceeds 90%.³ The patient whose first episode has been effectively treated has approximately a 50% chance of not having a recurrence. However, the recurrence rate increases to more than 70% after a second episode, to more than 80% after a third episode, and to more than 90% after a fourth episode.³ Therefore, therapy should often be viewed as a 2-fold process of continuation and maintenance.

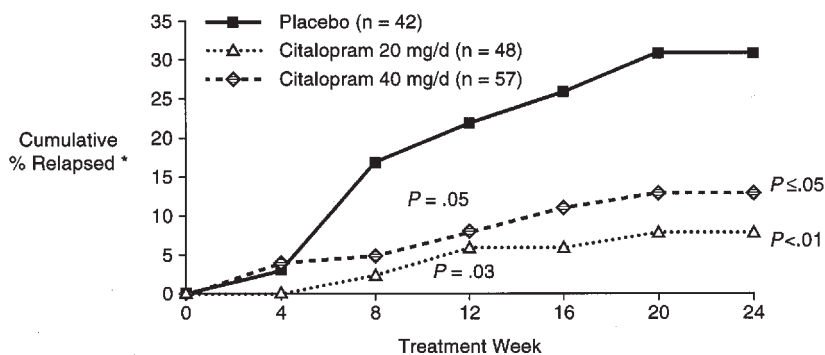
An imipramine maintenance study illustrates that long-term treatment is successful in preventing recur-

Figure 1. Outcomes of Depression Treatment—The “5 Rs”



Source: Reference 2.

Figure 2. Results of a Depression Relapse Study



*MADRS \geq 22.

Source: Reference 5.

rent depression. In that study, which included a 3-year follow-up, the use of imipramine alone or with interpersonal psychotherapy on a monthly basis was found to be more successful than nondrug treatment in preventing a recurrence.⁴ The study period was extended to 5 years in 20 patients, and of the 11 who remained on imipramine, 1 had a recurrence of depression. Of the 9 who were switched to placebo, 6 experienced a recurrence.

In another example of the importance of continuation and maintenance, a depression relapse study showed that whether citalopram was given as a dose of 20- or 40-mg per day over a 24-week period, it was substantially more effective than placebo at preventing recurrence (Figure 2).⁵

Although these studies illustrate that treatment is not always completely successful, they prove that continuation of drug therapy is more effective in preventing recurrence than discontinuing treatment completely.

Patient Compliance

There is debate over the use of the term "compliance", which has been said to suggest a power struggle. The term "adherence" in the same context is now used by some clinicians because it is interpreted as a more cooperative term. Whichever term is used, compliance (adherence) is a factor that is extremely difficult to assess. For example, how often does a patient have to miss or misuse a drug before he or she is considered non-compliant? That point has never been resolved, and study results vary enormously in that regard.

Can physicians predict compliance? Results of 6 studies reported by Greenberg⁶ indicate that 66% of physicians' predictions of patient compliance were correct. Thus, 1 of 3 physicians was unable to tell whether his or her patients were complying with prescribed treatment. Many of the ways in which a physician can

assess compliance include asking the patient, counting the pills, or measuring the patient's blood or urine drug levels. However, those approaches are often inaccurate or impractical.

Nevertheless, compliance and non-compliance are significant factors that contribute to the overall success and

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cost effectiveness of depression treatment. If depressed patients are non-compliant, they become more ill or may attempt suicide. Unfortunately, noncompliance is something that is seldom considered, often because the physician is concerned primarily with the neuropharmacologic effects of antidepressant drugs.

An example of the prevalence of overall noncompliance of treatment therapy is found in a study by Beers and associates,⁷ which examined the degree of compliance of geriatric patients in taking discharge medications 2 days after release from the hospital. The study revealed that half the patients did not take at least 1 of their prescribed drugs and that 73% misused the drugs. Overall, one third of the drugs prescribed were never used. "Overcompliance" was also found to be of concern; 64% of the patients studied took at least 1 drug that had not been ordered.⁷

Whether a patient is compliant with a medication regimen or not may be the direct result of the disorder itself. Medical and psychiatric comorbidities as well as the patient's personality, attitudes, and beliefs may also contribute. Common sense dictates that patients who are more ill

are more likely to do what is needed to get better. Thus, compliance is better in those with acute, symptomatic illnesses, such as diabetes and generalized anxiety disorder, but it is worse in patients with long-term asymptomatic illnesses such as hypertension or depression in remission. Patients' perception of the effectiveness or ineffectiveness of the prescribed drug also has a major effect on their decision about continuing with treatment.

Stigma is another important factor in medication noncompliance. It can manifest as outside pressure, which can lead to patients' denial that they suffer from an illness.

Noncompliance affects both treatment outcome and the physician-patient relationship. In one study of the reactions of physicians to patients' noncompliance, 59% of the physicians became defensive, 10% withdrew from the situation, and only 31% addressed the issue constructively.⁸

Side Effects of Medication and Compliance

Factors specific to the medication itself also provoke noncompliance. Side effects, early and late, are prime examples. If patients experience unpleasant side effects, they stop taking the medication. In particular, late-

onset side effects, such as weight gain or sexual dysfunction, are common adverse effects that often affect compliance. Some patients, especially those whose disease produces few symptoms, decide they prefer having the original disease to experiencing the side effects caused by the drugs needed for treatment.

Among the medications available to treat depression, selective serotonin reuptake inhibitors (SSRIs) are better tolerated than tricyclic antidepressants (TCAs). Data from clinical trials, however, do not demonstrate as great a difference in patient tolerance of SSRIs and TCAs as most clinicians find in their practice. For example, in 62 controlled trials,⁹ more than 6000 patients were evenly divided into 2 groups: those taking SSRIs and those taking TCAs. The data showed that 14.4% of patients taking SSRIs dropped out because of medication-related side effects, compared with a dropout rate of 18.8% in those taking TCAs. The total dropout rate was approximately 30% in each group.

In another study that compared dropouts from 7 placebo-controlled trials,¹⁰ side-effect dropout rates were 27% in those taking TCAs, 19% in those taking SSRIs, and 5% in patients taking placebo. The package inserts for the drugs cited indicate that SSRI dropout rates in clinical trials range from 15% to 20%. However, the rate occurring with placebo (ie, 6% to 8%) must be subtracted from those numbers to discover the true drug-induced dropout rates.

In a study conducted in Madison, Wisconsin, at the DeanCare Health Maintenance Organization the pharmacy database was reviewed to determine the percentage of patients who continued antidepressant therapy long enough to have been adequately treated (3 months was defined as adequate). Researchers found that of the approximately 400 patients studied, 60% continued their SSRI therapy, 47% continued their secondary TCAs, and 44% continued their tertiary TCAs.¹¹

Figure 3. Costs of Antidepressants

■ Citalopram	20 mg	\$60
	40 mg	\$63
■ Bupropion	20 mg	\$60
	30 mg	\$71
	40 mg	\$73
■ Fluoxetine	10 mg	\$72
	20 mg	\$73
■ Sertraline	50 mg	\$66
	100 mg	\$68

Source: Walgreens, Madison, WI 9/15/98.

With regard to the efficacy of SSRIs and TCAs, no significant differences have been found, although disagreement exists about their respective effectiveness in treating melancholic, inpatient, psychotic, and severe depression.

Improving Compliance

Today, a psychiatrist may see 30 to 40 patients each day, and primary care physicians may see even more. A 1980 study showed that a primary care physician spent an average of 15 to 20 minutes with each patient.¹² With the advent of managed care in recent years, the time spent with a patient is probably much less today. Having so little time with a patient can inhibit rapport necessary to ensure compliance with therapy.

Although no single intervention is sufficient to ensure long-term compliance, there are ways in which compliance might be improved. Factors specific to the clinician include being aware of noncompliance, communicating with patients regarding the reason for their failure to take the medication, educating patients as to the value of compliance, and having a receptive attitude to this sensitive topic.

There must be time allotted to educate patients about depression and the benefits of compliance with their prescribed medication therapies. Patients need to know that depression is an illness, that it is treatable, that antidepressant drugs work and are not addictive, that psychotherapy can play a role in recovery, and that information is available to help manage depression. Because most patients don't retain much of the information delivered during a face-to-face interview with the physician, providing written materials for patients is encouraged.

Another factor that may play a role in improved compliance is ease or simplicity of administration. For example, prescription labels should be clear and

easy to read, containers should be easy to open, and the dosing schedule should be convenient. Minimizing the number of medications and reducing the dosage schedule may also optimize medication compliance. Recently, a study of drug use in 12 nursing homes revealed that the average resident took 7.2 medications.¹³

The final element in the overall picture of prescribing behavior and patient compliance is cost, which is

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an issue for managed care organizations and for patients whether they have insurance or not. One aspect of cost is the expense of the medication. Figure 3 shows the retail cost for a month's supply of various antidepressants available at a Walgreen's in Wisconsin in 1998. Noncompliance is another factor that adds to the expense of depression management. The overall cost of medication noncompliance in the United States is estimated to exceed \$100 billion yearly.¹⁴

Summary

In a constructive therapeutic relationship, a practitioner can fulfill his or her responsibilities by listening to, supporting, and educating the depressed patient, and by involving others in the welfare of that patient. If such an approach is used, obstacles to compliance can be brought to the forefront and resolved in a positive manner.

... DISCUSSION HIGHLIGHTS ...

Dr. Goodman: Why is it clinicians feel obliged to continue to prescribe

certain antidepressants in more than once-a-day doses? The effect of antidepressants works over the course of days to weeks, so the half-life of a medication is not clinically relevant to its antidepressant effect.

Dr. Jefferson: Another way to ask that is: Do short half-life antidepressants work even once a day? They probably do, and studies have been done on the efficacy of trazodone, which has a half-life of about 6 hours, in which the effect of a single daily dose was compared with that of a divided dose, and the efficacy was the same. The problem with short half-life drugs is that when they come to market they have not been studied as single daily doses, so they cannot be marketed as a single daily dose. Whether all short half-life antidepressants are effective when dosed once daily remains to be determined.

Dosing and Efficacy Considerations

Dr. DeVane: I think dosing is partly an artifact of the way drugs are developed and promoted in this country. The manufacturers of the SSRIs [selective serotonin reuptake inhibitors] probably discovered they couldn't promote dosing schedules for drugs on which they don't have data. There are numerous studies that show the full dose of an antidepressant is best to prevent a relapse and that a partial dose is not as effective as a full dose, but it is still better than none.

You can see how that could be obscured in a clinical trial by decreasing a patient's dose to once a day. The dose might be partly effective, but that's not the goal of relapse prevention trials.

Dr. Jefferson: I am not aware of problems with antidepressants, but there is the problem with gabapentin, in

which you see a dose-dependent decrease of absorption. As the dose or the milligram amount gets higher, a lesser percentage of the dose is absorbed, which can be problematic. I don't think that has ever been looked at in depression.

There was a study done with lithium in terms of its effectiveness in maintaining remission. A single daily dose worked as well as a divided dose, but every-other-day dosing produced a substantial decline in remission rate. So there may be some concern for situations in which the dosing becomes less and less frequent.

Dr. DePaulo: Lithium develops a very fast peak level, and some side effects may be related to that. It is probably different than with the antidepressants in which levels don't vary as much.

With lithium, each patient probably has a different threshold for tolerating gastrointestinal side effects. We did a study in which we switched patients from a 1200-mg dose of lithium once a day to dosing 2 or 3 times a day. We used standard-release medications rather than the so-called slow-release ones. The patients did just as well, and they liked a single dosing schedule.

Patient Oversight and Compliance

Dr. Schreter: My practice is composed of 50% adults and 50% children. In the treatment of children and adolescents, dosing is even more of an issue because they don't want to take the medication. The question is: How much autonomy do you give the patients, and how much does that improve compliance? Does parental control improve or diminish compliance or does compliance become a power struggle?

Dr. DePaulo: The issue of attitudes and relationships is very important. We did a small compliance study and

found that no method is more adequate or better than another method. Instead of asking patients, "Did you take your medication?" we asked, "How many doses per week of your medication have you missed this month?" By framing the question in that manner, we give patients permission to acknowledge missed doses. The approach is the same for alcohol consumption. We don't ask, "Do you drink?" Instead, we ask, "About how much do you drink in an average day or week?" Then you can see the patient kind of hesitate, thinking, "Okay, if you're going to put it that way, let's talk about it." Otherwise, you often get a single-word answer.

Dr. Goodman: In the past, I asked the patient, "How are you feeling?" If the patient says "Fine," I replied, "Well, the medication must be working." Then, halfway through the session the patient says: "I didn't want to tell you, but I stopped taking the medication 2 months ago." So my clinical impression that the patient was getting better because of what I was prescribing goes completely out the window. That's when a physician might get a little frustrated because a physician's satisfaction develops out of the belief that the recommended treatment is helping the patient.

Dr. Jefferson: That's a good argument for educating the patient. You can point out that some patients who don't take their medications continue to do very well, but then let the patient know the statistics on the benefits of continuing the medication versus the results of going off.

Dr. Goodman: I ask my patients what they are taking to verify what I believe is being taken. That way, noncompliance becomes a chance to find out what a patient doesn't like about the medication and/or the illness.

Noncompliance and Aversion to Medication

Mr. Vodoor: Noncompliance also occurs because the administration of medication is a nuisance to a patient. Sometimes it has nothing to do with the illness or anything else. The patient just doesn't want to be bothered with taking the medication.

Dr. Goodman: I agree, except that I have patients who will take 8 supplements in the morning and 2 at night. They have difficulty taking 1 antidepressant once a day, but take 10 supplement pills a day. It's not the number of the pills; it's the meaning of the medicine to the patient. Supplements promote wellness; medication treats a disease. Everyone wants wellness; no one wants a disease.

Illness denial acts in this way: If I have a disease, I need to take medicine, but if I don't take the medicine I must not have the disease.

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