

Antidepressant Noncompliance as a Factor in the Discontinuation Syndrome

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Compliance is generally defined as the extent to which a patient adheres to a treatment regimen and, specifically, takes medication as prescribed. While little research is available about the number of patients who consistently skip antidepressant doses, the literature indicates that about 30% of patients discontinue treatment suddenly within the first month. Both missed doses and abrupt stoppage of treatment place a patient at risk for experiencing discontinuation symptoms. A variety of reasons ranging from forgetfulness to lack of knowledge about the importance of taking every dose may lead to nonadherence to an antidepressant regimen. By spending time on patient education, providing reasons why patients should take every antidepressant dose, discussing alternative treatments, and conveying empathy, support for, and understanding of the patient, physicians may be able to minimize noncompliance and consequently decrease the likelihood that a patient may experience discontinuation symptoms. Discontinuation of an antidepressant can cause a patient to be irritable, experience severe dizziness, or act emotionally absent, which may have a sustained adverse impact both on job performance and on family and social relationships.

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Compliance is generally defined as the extent to which a patient adheres to a treatment regimen and, more specifically, takes medication as prescribed. Non-compliance may consist of a variety of behaviors from consistently skipping antidepressant doses to abruptly stopping medication without informing the physician; these behaviors may lead to discontinuation symptoms.

Patients are at risk for experiencing discontinuation symptoms when they stop taking antidepressants without the guidance of their physicians. A group of investigators in Seattle who examined patterns of antidepressant use found that up to 75% of patients being treated for depression by primary care physicians discontinued medication within 30 days.¹ An analysis of data on the duration of antidepressant therapy for a group of health maintenance organization enrollees, performed by the same research group,² showed that 66% of patients failed to fill four or more antidepressant prescriptions within 6 months. Similarly, Priest et al.,³ reporting on the results of a survey in the United Kingdom on lay people's attitudes toward the treatment of depression, noted that most patients who begin antidepressant therapy abandon it prematurely.

REASONS FOR BEING NONCOMPLIANT

A patient's compliance with antidepressant medications may be affected by various circumstances including differences among patients, physicians' attitudes, and clinical environments (e.g., acute, continuation, or maintenance treatment; first or second episode of illness vs. treatment-resistant depression). Fawcett⁴ listed several reasons for poor medication compliance (which are listed in Table 1) including illness content (e.g., guilt-ridden depressed patients may be reluctant to take medication); physicians who fail to provide adequate reassurance and hope for benefit; a lack of continuity of care, which includes close follow-up during the early stages of treatment; a complicated treatment regimen; the cost of medical care; chronic illness, especially if the depression has remitted and the antidepressant is prophylactic; and comorbid symptoms such as panic attacks, severe anxiety, and alcohol and drug abuse. In addition, some patients occasionally respond to suggestions that appear in the lay press or come from friends to take a "drug holiday" to avoid the sexual side effects of antidepressants.

Efficacy of the agent is a major factor in patient non-compliance, in three different ways. First, some patients are noncompliant because of lack of efficacy of the drug. Individuals who are displeased with their response to antidepressants may stop taking the medication and experience discontinuation symptoms as a consequence. In a study of the relationship of compliance to successful long-

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Table 1. Reasons for Patient Noncompliance, According to Physicians' Experience*

- Reluctant to take medication due to guilt
- Physician fails to provide reassurance and hope
- Lack of continuity of care, including follow-up
- Complex treatment regimen
- High cost of medical care
- Chronic illness
- Comorbid symptoms such as panic attacks, severe anxiety, and alcohol and drug abuse
- Displeased with treatment response (efficacy)

*Adapted from reference 4.

Table 2. Reasons Patients Say They Are Noncompliant

- Unaware of the importance of consistently taking the medicine
- Perceive lack of a friendly relationship with the physician
- Too much waiting room time
- Need to take medicine 3 or 4 times daily
- Side effects

term treatment, Frank et al.,⁵ who assessed compliance by regularly measuring blood drug levels, found that only 2 of 28 patients who remained well for 3 years were periodically noncompliant as opposed to 6 of 12 patients who experienced a recurrence of depression. Second, some patients discontinue a drug due to a perceived lack of efficacy before it even has a chance to begin working because they think antidepressants work in the same way as analgesics; patients expect to feel better immediately. Third, still other patients are noncompliant even if the agent has been efficacious; patients who have responded well to antidepressants sometimes interrupt treatment abruptly after 3 or 4 months to test whether the medication is still necessary. Since they have usually been warned by their physician that relapse is likely if they do not continue treatment for 4 to 9 months, they often fail to tell their physician about the stoppage.

Patients themselves list a variety of reasons for being noncompliant with treatment (Table 2). Most often they say that they miss doses of medicine because the physician failed to inform them about the importance of taking every dose. They also say their compliance depends on whether they like their physician, how long they spend in the waiting room, how many doses of medicine they are required to take per day, and how uncomfortable the side effects of the drug are. Patients who like their physician are less likely to skip doses than those who do not view their relationship with their doctor as friendly. People who believe they have to wait overly long to see the physician are less compliant than those who are satisfied with their waiting room time. Forgetfulness is particularly common for medication that has to be taken more often than twice a day, but even patients who are taking an antidepressant only once or twice a day sometimes leave home for a few days without their medicine and do not want to bother their physician by calling and asking that a

prescription be telephoned to their new location. Finally, patients sometimes say they are noncompliant because of severe side effects of the medication. Side effects usually appear at the beginning of treatment, which may account for the large proportion of patients who discontinue antidepressants abruptly within the first month. In one study,⁶ 62% of patients who stopped taking antidepressants during the first month of treatment attributed the discontinuation to severe side effects.

IMPORTANCE OF COMPLIANCE

Guidelines from the U.S. Agency for Health Care Policy and Research⁷ recommend that upon remission of depressive symptoms, antidepressant treatment should be continued for 4 to 9 months to minimize the chance of relapse. Maintenance treatment for 1 to several years may also be appropriate for patients who have had three previous episodes of depression or who have had two episodes but also have a first-degree relative with bipolar disorder or recurrent major depression; a history of severe, sudden, or life-threatening depression; or onset before the age of 20 years. If a patient is noncompliant, the likelihood of discontinuation symptoms including sleep problems, agitation, anxiety, and flu-like symptoms, as well as the strong possibility for relapse of their depression, argues strongly against drug holidays or any sudden, temporary discontinuation.

Because of these risks, physicians should be aware of the reasons that patients stop antidepressant treatment and plan several strategies to reduce the likelihood of noncompliance. Patients should be educated about the possibility of experiencing discontinuation symptoms after missing as few as two doses of agents that have shorter half-lives, such as venlafaxine or paroxetine. Physicians themselves need to be more aware of the likelihood of discontinuation symptoms, which are sometimes misdiagnosed as physical illness or mistaken for a recurrence of the primary psychiatric illness. As a result, patients may undergo expensive unnecessary tests or be restarted on treatment for depression. When patients who are being treated with antidepressants report these symptoms, the first question for the physician to ask is, "Have you missed or forgotten to take any doses?"

Recurrence can be differentiated from discontinuation symptoms by the time frame. Discontinuation events tend to occur within 24 or 72 hours of stopping all SRIs (paroxetine, sertraline, fluvoxamine, and venlafaxine) except fluoxetine, while recurrence is unlikely before 2 to 3 weeks after the antidepressant is stopped. Discontinuation symptoms generally remit after 7 to 14 days; they are time-limited and transient. Thus, the likelihood that a patient is experiencing recurrence of illness rather than discontinuation symptoms increases with the length of time from the end of treatment with all SRIs except fluoxetine.

The extended half-life of fluoxetine often provides protection against discontinuation symptoms.

STRATEGIES TO IMPROVE COMPLIANCE

Several clinical strategies can be employed to increase patients' adherence to antidepressant regimens (Table 3). First, physicians should plan time during office visits to teach patients about the nature of depression, how antidepressants work, and the importance of completing the course of treatment. Some of this education can be provided by office staff and by the use of written materials and videotapes. Multiple methods of presentation are extremely important for severely depressed patients whose ability to concentrate is often diminished. Second, patients need to be given reasons why it is important to take every dose of medication, including the possibility of experiencing discontinuation symptoms when several doses are missed or the medication is abruptly stopped. Third, it is important to discuss alternative treatments with patients to reduce the likelihood they will abandon treatment independently because of perceived lack of efficacy. Finally, the physician should effectively communicate empathy, support for, and understanding of the patient since many patients say they are noncompliant because they lack a friendly relationship with their physician. These strategies to prevent noncompliance are described below.

Patient Education

Since patients frequently report that they skip doses or temporarily interrupt treatment because they didn't understand that it was important to take every dose of medication, physicians should spend time teaching patients about the nature of depression, how antidepressants work, and the importance of completing the course of treatment. The explanation of the illness should provide a rationale for the use of medication and include an inquiry into the patients' hesitations and fears about taking antidepressants. Patients and family members need to be reassured about potential medication side effects. The expected time until onset of action and the duration of treatment should also be explained. Depressed patients and their significant others should be informed that response to antidepressants may take up to 2 to 4 weeks and that the risk of recurrence is high if treatment is not continued for at least 4 to 9 months. The amount of time spent on patient education is a crucial factor in obtaining compliance to antidepressant treatment.

Studies have shown that medication compliance is increased when health care providers spend additional time with patients, when patients attend educational meetings, and when patients receive written instructions about their regimen.^{8,9} For example, 217 depressed patients who enrolled in a 12-month study were randomly assigned to ei-

Table 3. Clinical Strategies to Reduce Noncompliance

- Educate patients about the nature of depression, how antidepressants work, and the importance of completing the course of treatment
- Provide reasons why patients should take every dose of the antidepressant (i.e., receive beneficial effects in time, prevent discontinuation symptoms)
- Discuss alternative treatments
- Convey empathy, support for, and understanding of the patient

Table 4. Specific Educational Messages To Improve Compliance*

- It will take 2 to 4 weeks before you notice beneficial effects
- You should continue taking the medication even after you begin to feel better
- Check with your physician before you stop taking the antidepressant
- Take the medication as directed
- Call your physician with questions

*Adapted from reference 6.

ther usual care or intervention groups.⁸ The patients in the intervention group met with a physician more frequently than the patients in the usual care group, received booklets on the biology of depression and how antidepressants worked, and saw videotapes that reinforced the information in the pamphlets. These patients were significantly more likely to adhere to a medication regimen for 90 days. In patients with major depression, the intervention group was more likely than the controls to continue taking an antidepressant for 90 days or more (75.5% vs. 50.0%; $p < .01$). Similarly, 79.7% of the patients with minor depression in the intervention group as opposed to 40.4% of the controls adhered to the regimen for 90 days or more ($p < .001$). In an extension of this study,⁹ which involved 153 patients, counseling to improve adherence to treatment was provided to those in the intervention group. At 4-month follow-up, intervention patients with major depression were significantly more likely to adhere to antidepressant treatment than the controls (89% vs. 62%; $p < .02$). Intervention patients with minor depression were significantly more likely than controls to report adherence to antidepressant treatment at both 4-month (74% vs. 44%; $p = .01$) and 7-month (65% vs. 41%; $p = .04$) follow-up.

In a study designed to identify specific educational messages that will improve patient adherence to antidepressant therapy, Lin et al.⁶ found that patients were more likely to be compliant if they were asked about prior use of antidepressants. Compliance also improved in patients who received the following four specific educational messages (Table 4): (1) It will take 2 to 4 weeks before you notice beneficial effects. (2) You should continue taking the medication even after you begin to feel better. (3) Check with your physician before you stop taking the antidepressant. (4) Take the medication as directed. These patients were more likely to continue treatment if they

Table 5. Strategies To Promote Effective Communication

- Be enthusiastic
- Avoid giving orders
- Individualize your approach by listening to the patient
- Recognize patients who may be at risk for being noncompliant (e.g., guilt-ridden depressed patients, patients who lack social supports)
- Provide information in a variety of formats (e.g., pamphlets, videotapes, workshops, one-on-one)
- Differentiate between the needs of patients who are acutely ill and those who need chronic treatment
- Make sure the information is appropriate for the patient
- Encourage the patient to ask questions
- Find out if the patient understands the instructions, is able to follow them, and intends to follow them.

were instructed to call the physician's when they had questions. The telephone is a useful tool for avoiding unnecessary follow-up visits.

Some patient education can be completed by nonphysicians. The ongoing Pittsburgh Study of Maintenance Therapies,¹⁰ in which about 85% of patients meet stringent compliance criteria for 3 years, uses a treatment team consisting of a nonphysician primary clinician (a psychologist, social worker, or nurse-clinician) and a physician consultant. During the acute and continuation phases of treatment, patients are seen by both the physician and the nonphysician at each visit. During the maintenance phase, the physician generally sees the patient only once every 6 months. In addition, after the acute phase of treatment is over and improvement has been noted, the patient and family members are invited to special psychoeducational workshops.

Provide Reasons for Taking Every Dose

When patients are provided with a series of reasons why it is important to adhere faithfully to a treatment regimen, they will be less likely to forget doses or suddenly stop taking the antidepressant. These reasons include: (1) the beneficial effects of antidepressants that will come within a few weeks; (2) the fact that a reemergence of symptoms, which may appear when treatment is prematurely interrupted, increases the likelihood that treatment-resistance will develop over time; and (3) that discontinuation symptoms may occur, particularly if treatment is interrupted suddenly or several doses are missed. Thus, the more information patients have about potential discontinuation events, the more compliant they will be. The symptoms of discontinuation should be described, and patients should particularly be warned about skipping doses of paroxetine and venlafaxine, which have shorter half-lives. Because the general public generally thinks about medication in terms of an analgesic, which acts almost immediately, patients must be routinely told about the delay in onset of action for antidepressants, in order to reduce the chances that they abandon treatment prematurely and experience discontinuation phenomena.

Besides short-lived but distressing discontinuation symptoms, interruptions in treatment have other risks. Chronicity may result when the underlying disorder is recurrently exacerbated by temporary discontinuation of treatment. Quality of life issues may have long-term consequences. For example, the effects of irritability and emotional absence can have a sustained adverse impact on family relationships and job performance. Patients sometimes miss work days because of discontinuation symptoms.

Discuss Alternative Treatments

A treatment plan should be described to patients either at the outset of treatment or as soon as improvement is noted. A plan provides patients with a clear picture of their illness and the available options for treating it. Dysthymic patients, in particular, need the reinforcement of a treatment plan. Because behavioral symptoms are often difficult to assess, specific symptoms should be targeted. The treatment plan should also include the expected duration of both an effective and an ineffective medication trial, the length of time to try a specific antidepressant dose, and the total intended duration of treatment including the continuation and maintenance phases. The plan should be concrete and presented in a way that is easily understood by the patient, which means tailoring the amount and complexity of information to the individual. It should be emphasized to the patient that antidepressants need to be tapered slowly to avoid possible discontinuation symptoms. Presenting a treatment plan is a particularly helpful approach for encouraging patients to accept the need for long-term treatment since, when patients are beginning to feel better, they sometimes stop taking medication and experience discontinuation symptoms that may be mistaken for a relapse.

Effective Communication

Compliance is increased when physicians convey empathy, support for, and understanding of the patient. One of the aims of the long-term Pittsburgh Study is to build an alliance between the health care providers including the office staff and the patient.¹⁰ One strategy used by the researchers in this study was to characterize treatment of depression as an experiment that the patient and clinician undertake together. The ability of physicians, including primary care physicians, to establish rapport, assess patient attitudes and beliefs, and negotiate physician-patient differences in beliefs and expectations influences adherence to treatment, as does a hopeful attitude toward eventual recovery from depression.

Table 5 lists a variety of strategies to promote effective communication between the health care provider and the patient. They include expressing enthusiasm, establishing a therapeutic alliance, using a variety of channels of communication, providing the correct amount of information at a level that is appropriate for the individual patient, solicit-

ing questions from the patient, and making sure the patient is able and intends to take the medication as directed.

CONCLUSION

About 30% of patients discontinue treatment within the first month, and many more consistently skip doses. When medication is stopped suddenly or as few as two doses of an SRI with a shorter half-life, such as paroxetine, sertraline, or venlafaxine, are missed, there is a possibility that the patient will experience discontinuation symptoms. Physicians can help improve patient adherence to treatment—and concurrently reduce the risk of distressing discontinuation symptoms—by spending time educating patients about the nature of depression and its treatment, by providing a rationale for taking every medication dose, by making sure the patient understands that alternative treatments are available, and by establishing a therapeutic alliance with the patient. When physicians minimize noncompliance, patients are less likely to experience discontinuation symptoms that can affect their mental and physical health and that may have a sustained adverse impact on job performance and on family and social relationships.

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Discussion

Dr. Kaplan: In clinical practice, the behavioral symptoms of abrupt antidepressant discontinuation are often mistaken for relapse. A patient stops taking an antidepressant, becomes agitated or irritable, and these symptoms are misconstrued as a relapse of depressive symptoms.

Dr. Haddad: The discontinuation symptoms may be perpetuating poor compliance if they are unrecognized. Patients who experience symptoms after forgetting a few doses may think the drug is addictive and then refuse to take it. Clinicians who mistake discontinuation symptoms for signs of relapse may reinstate unnecessary long-term treatment.

Dr. Zajecka: I have seen patients who stop taking paroxetine for 48 hours and then experience sleep problems, agitation, anxiety, and flu-like symptoms. When patients report that they are anxious or not sleeping, particularly after they have initially responded to an antidepressant, the first question I ask is, "Have you missed or forgotten a dose?"

Dr. Kaplan: Patients sometimes stop taking their antidepressant without telling me. These are people who have had a beneficial clinical response and then, around Month 3 or 4, wonder, "What will happen if I stop? I think I am over this depression. I really don't need this medication any more." Because I initially educated them about the importance of continuing to take the antidepressant even after they begin to feel better, they don't inform me.

Other patients experience symptoms when they go away for 3 or 4 days without their antidepressant and miss several doses. Some take "drug holidays." I've had several patients experience discontinuation symptoms after they

have tried drug holidays because they read about them in the popular press. The concept of drug holidays started in the psychiatric literature and filtered down to the lay press.

Dr. Zajecka: If a physician suggests that a patient take drug holidays to have sex, it might lead the patient to think, "If I could skip the antidepressant this weekend for sex, I could skip it next weekend for another reason." Giving patients a drug holiday conveys the wrong message, particularly when we look at the potential discontinuation symptoms these patients can have.

Dr. Young: Some patients stop taking antidepressants because the beneficial effects are delayed. When patients think of medicine, they think of antibiotics. When patients take antidepressants, the adverse effects come immediately and the beneficial effects come later. The patient may have difficulty resolving the issues in his or her mind.

Dr. Rosenbaum: I have found the telephone to be an enormously helpful tool for ensuring compliance. Patients who believe they can reach me by phone are less likely to quit taking their antidepressant.

Dr. Kaplan: Patients need to be told about the negative consequences of sudden discontinuation. We can reduce this problem of noncompliance by being good physicians and spending time with our patients. I find myself, particularly with patients who are taking paroxetine or venlafaxine, doing something I didn't do in the past. I say, "Make sure you do not stop this medication abruptly and you do not skip several doses because here is what could happen." When I educate my patients about the possibility of a discontinuation phenomenon, they become more compliant and are less likely to skip doses.