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Antidepressant-Related Adverse Effects Impacting Treatment Compliance: Results of a Patient Survey

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ABSTRACT

Background: Despite the high prevalence of depression in the United States, few studies have identified which adverse effects (AEs) patients are willing or unwilling to tolerate when receiving antidepressants.

Objective: The aim of this study was to identify reasons for discontinuation and noncompliance with antidepressant medications, the impact of AEs on compliance and quality of life (assessed using impact of AEs on activities of daily living), and patients' suggestions for improving their medication, using a patient survey.

Methods: Patients aged 18 to 65 years with mild to severe depression were randomly selected by their physicians to be sent an invitation to complete the 42-question survey. Three hundred physicians nationwide assessed the severity of depression and symptoms of anxiety in each respondent, using their judgment. Patients were asked specific questions to assess reasons for discontinuation/noncompliance. Patients were also asked to rate AEs based on how difficult they were to "live with," and what 2 aspects of their antidepressant medication they would change if they could.

Results: In a separate, concurrent study, physicians classified 175 (50%) as mildly to moderately depressed and 84 (24%) as severely depressed. Ninety-one respondents (26%) were classified as having symptoms of anxiety. Two hundred seven patients (60%) indicated they had discontinued treatment with an antidepressant agent at some point in their lives, the most common reason for which was lack of efficacy (92 patients [44%]). Of the 344 patients currently being treated with an antidepressant, 75 (22%) reported noncompliance. The most common reasons for noncompliance were "have trouble remembering to take it" (19/44 patients [43%]), "gained a lot of weight" (11/41 [27%]), "unable to have an orgasm"

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(8/40 [20%]), and "lost interest in sex" (8/41 [20%]). The 4 AEs patients expressed as "extremely difficult to live with" were "weight gain" (104 patients [31%]), "unable to have erection" (83 [25%]), "difficulty reaching orgasm" (80 [24%]), and "tired during the day/no energy" (69 patients [21%]). The 3 most frequently cited improvements patients (n = 327) would make to their medications were better efficacy (176 patients [54%]) and eliminating AEs related to sexual desire and weight gain (112 [34%] and 105 [32%] patients, respectively).

Conclusions: The findings of this survey of patients with mild to severe depression suggest that compliance, and hence efficacy, can be promoted by (1) understanding what patients expect and desire from the antidepressants they are prescribed and (2) prescribing antidepressants associated with low rates of weight gain, sexual dysfunction, or tiredness. (*Curr Ther Res Clin Exp.* 2005;66:96–106) Copyright © 2005 Excerpta Medica, Inc.

Key words: noncompliance, antidepressants, tolerability, discontinuation.

INTRODUCTION

Depression is a common medical disorder, with one comorbidity report revealing a 10.3% 1-year risk and a 17.1% lifetime risk for major depression in people in the United States.[1] Despite that the total cost of depression is $44 billion per year and that suicide is the eighth leading cause of death in the United States, few studies have assessed compliance with antidepressant medications in patients with depression.[2,3] Only 1% to 2% of publications concerning the treatment of affective disorders have explored factors associated with medication discontinuation.[4] One study of reports concerning compliance with antidepressants for the years 1975 to 1996 showed that patients used only 65% of their recommended treatment.[5] In a study of antidepressant therapy in the primary care setting, 53% of patients discontinued their antidepressant treatment after they experienced clinical improvement, and of patients who discontinued treatment for any reason, 24% did not inform their physicians.[6]

A patient's reasons for noncompliance may be multifactorial and include misperceptions about the illness, concern about adverse effects (AEs), lack of efficacy, cost, and cultural issues.[7,8] A physician's ability and desire to address a patient's concerns and attitudes about antidepressants might enhance compliance and improve outcome.[9] Patient education and the management of AEs have also been found to be helpful.[10] A physician's initial choice of antidepressant medication can impact compliance, suggesting that this decision by physicians might play a vital role in a patient's willingness to take his or her antidepressant medication as prescribed.[11] Improved tolerability would be expected to lead to greater compliance and result in a more favorable treatment outcome.

Compared with the long-prescribed tricyclic antidepressants and monoamine oxidase inhibitors, newly developed medications offer comparable efficacy, fewer associated AEs, and a markedly reduced risk for serious AEs (eg, changes in blood pressure, severe adverse drug interactions).[7]

Based on a MEDLINE search (key terms: *patient compliance, patient satisfaction, adherence, antidepressant, depression,* and *depressive disorder*; years: 1966–2005), patient input is rarely sought when studying drug discontinuation. Bull et al[12] assessed why patients recently prescribed fluoxetine or paroxetine discontinued their medication and found that 43% of patients who discontinued treatment did so because of fatigue or drowsiness. However, the literature search revealed no studies of what aspects of their antidepressant patients would change if they could design their own.

The aim of this study was to identify reasons for discontinuation and noncompliance with antidepressant medications, the impact of AEs on compliance and quality of life (assessed using impact of AEs on activities of daily living [ADLs]), and patients' suggestions for improving their medication, using a patient survey.

MATERIALS AND METHODS

Study Investigators

The 42-question survey was administered by Market Measures Interactive (MMI), LP, Princeton, New Jersey, a marketing firm contracted by the study sponsor. A group of 300 physicians (103 general/family practitioners, 100 psychiatrists, and 97 internists) was recruited to participate in the study. MMI selected this group from its Medical Marketing Conference Panel, based on the physicians' antidepressant-prescribing practices, as follows: for psychiatrists, antidepressants typically prescribed to >75 patients per month; for internists and primary care physicians, antidepressants typically prescribed to >25 patients per month.

Survey Participants

Each physician on the panel was asked to select, from among their patients prescribed treatment for depression, 6 patients to complete the survey (2 patients each with mild to moderate depression, severe depression, and predominant depression with symptoms of anxiety). Patients were selected if they were aged 18 to 65 years, had mild to severe depression based on the physician's judgment, and had recently been prescribed an antidepressant medication. From this pool of 1011 patients, 750 were randomly selected, using a computer-generated list of random numbers, to receive a card inviting them to complete the survey and a letter explaining the details of the study. To achieve a balanced geographic representation, randomization was stratified by US region (Northeast, South, Midwest, and West).

The survey was considered by the sponsor exempt from the institutional review process, as specified in the US Food and Drug Administration's Code of Federal Regulations.[13] Participation in the survey was voluntary. Surveys were mailed only to patients who returned the invitation card. Compensation was provided to participating physicians and patients. To ensure confidentiality, patients were instructed not to include their names when completing and returning the survey.

Survey Components

Patients were asked to provide their age, sex, race/ethnicity, marital status, and household income. Patients were also instructed to self-assess the severity of their depression (mild, moderate, or severe).

Questions to Assess Reasons for Discontinuation/Noncompliance

To identify reasons for antidepressant discontinuation, patients were asked:

- Has a doctor ever prescribed a depression medicine for you that you completely stopped taking for one reason or another?
- If yes: How many medicines did you try that you completely stopped taking for one reason or another?
- Why did you completely stop taking your medicine?

Following the third question, a checklist of 20 reasons was provided (eg, "lack of efficacy," "side effects," "cost/lack of insurance," "resolution of symptoms," "did not need it anymore").

To identify reasons for noncompliance with patients' current antidepressant regimens, patients were asked:

- Do you always take your current antidepressant exactly as the doctor has recommended?
- If no, how often does each of the following reasons make you NOT take your antidepressant exactly as your physician has recommended?

The second question was followed by a list of 19 reasons for noncompliance (eg, specific AEs, cost, safety), with instructions to indicate the frequency with which each reason applied, using a 5-point Likert scale (1 = "is never a reason" to 5 = "is often a reason").

Questions to Identify Adverse Effects and Their Impact on Quality of Life

To assess the impact of AEs on patients' ADLs, the survey provided a list of 11 AEs, with the option to write in others. For each AE, patients were asked:

- Have you ever experienced this side effect as a result of the current antidepressant you take most often?
- If you have experienced this side effect, how difficult was the side effect to live with?
- If you have experienced this side effect as a result of your current depression medication, do you experience the side effect all of the time, sometimes, or did you experience it when you started the medication, but then it went away?

The second question was followed by a 5-point Likert scale (1 = "not at all difficult," 2 = "not very difficult," 3 = "somewhat difficult," 4 = "very difficult," or 5 = "extremely difficult").

Questions to Assess Patients' Opinions Concerning Improving Medication

To assess patients' views on improving their antidepressant medications, the survey provided a list of 7 potential improvements (eg, fewer specific AEs, "less expensive," "complete remission of depressive symptoms"), with the option to write in others, and asked:

- If depression medication could be improved, in just 2 ways, which of the following would you choose?

Data Analysis

Data were tallied and frequency counts were completed by MMI. Formal statistical analysis of the data was not performed.

RESULTS

Study Population

A total of 750 patients were selected to receive an invitation card. Of 664 surveys mailed to patients, 350 were returned (53% response rate). Two hundred twelve respondents (61%) were treated by psychiatrists, 110 (31%) by general/family practitioners, and 28 (8%) by internists. One hundred eighty-two patients (52%) reported they were prescribed ≥2 concurrent antidepressants at some time in their lives. Of the 350 respondents, 260 (74%) identified a specific antidepressant they had taken most recently or were currently prescribed. Patients who identified medications by name (n = 260) cited fluoxetine (84 patients [32%]), sertraline (52 [20%]), paroxetine (40 [15%]), bupropion sustained release (34 [13%]), citalopram (29 [11%]), and venlafaxine extended release (21 [8%]). In self-assessing their depression (n = 347), 241 patients (69%) categorized it as mild/moderate, and 106 (31%) defined it as severe. However, in a separate, concurrent study, physicians categorized 175 patients (50%) as mildly to moderately depressed, 84 (24%) as severely depressed, and 91 (26%) as having symptoms of anxiety.

Survey Components

Reasons for Discontinuation/Noncompliance

Two hundred seven respondents (60%) indicated they had completely discontinued at least 1 antidepressant medication at some point in their lives. The most frequently cited reason for discontinuation was lack of efficacy (92 patients [44%]). AEs accounted for the second most common reason for discontinuation (n = 204), with the most common AE being "didn't like the way the medicine made me feel" (75 patients [37%]), followed by "lost interest in sex" (46 [23%]), "tiredness" (36 [18%]), and "weight gain" (32 [16%]).

Of the 350 patients who returned the survey, 341 (97%) had been given at least 1 current prescription for an antidepressant medication. Of this subgroup, 75 (22%) indicated they had been noncompliant with their currently prescribed

antidepressant regimen. The 10 most common reasons for noncompliance indicated by patients are shown in **Figure 1** and included "have trouble remembering to take it" (19/44 patients [43%]), "gained a lot of weight" (11/41 [27%]), "couldn't have an orgasm" (8/40 [20%]), and "lost interest in sex" (8/41 [20%]).

Adverse Effects and Their Impact on Compliance and Quality of Life

The frequencies with which patients reported experiencing specific AEs are shown in **Figure 2**. Patients who responded to this question most frequently cited "tired during the day/no energy" (153/310 [49%]), "dry mouth" (151/313 [48%]), and "lost interest in sex" (142/304 [47%]).

The AEs most frequently rated as "extremely difficult to live with" are shown in **Figure 3**. Patients most frequently cited "weight gain" (38/124 patients [31%], "unable to have erection" (6/24 [25%]), "difficulty reaching orgasm" (29/122 [24%]), and "tired during the day/no energy" (31/145 [21%]).

In response to the question concerning whether AEs were experienced all of the time or sometimes or resolved, "weight gain" was assessed from the data as being the most common AE (70/118 [59%]), followed by "lost interest in sex" (60/134 [45%]), and "difficulty reaching orgasm" (55/128 [43%]).

Improving Medication

Among patients who indicated which aspects of their medications they would improve (n = 327), efficacy was cited most frequently (176 patients [54%]), followed by eliminating AEs related to sexual desire and weight gain (112 [34%] and 105 [32%] patients, respectively).

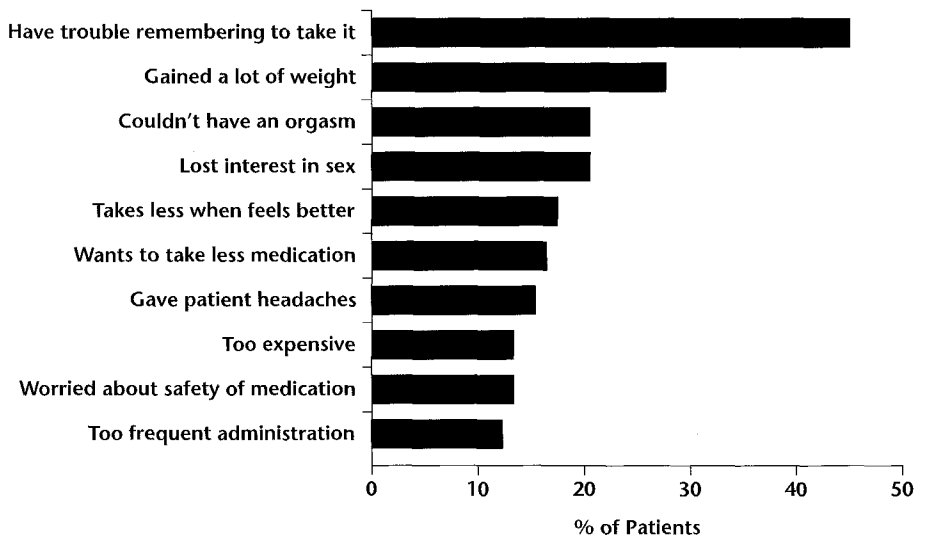

Figure 1. The 10 most common reasons for noncompliance reported by patients who received a prescription for at least 1 antidepressant medication.

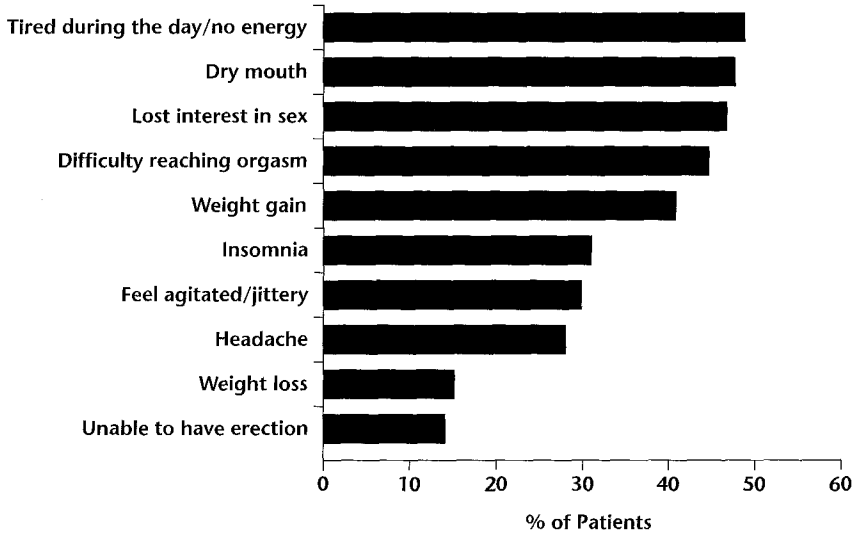

Figure 2. Frequency of adverse effects reported by patients who had received a prescription for at least 1 antidepressant medication.

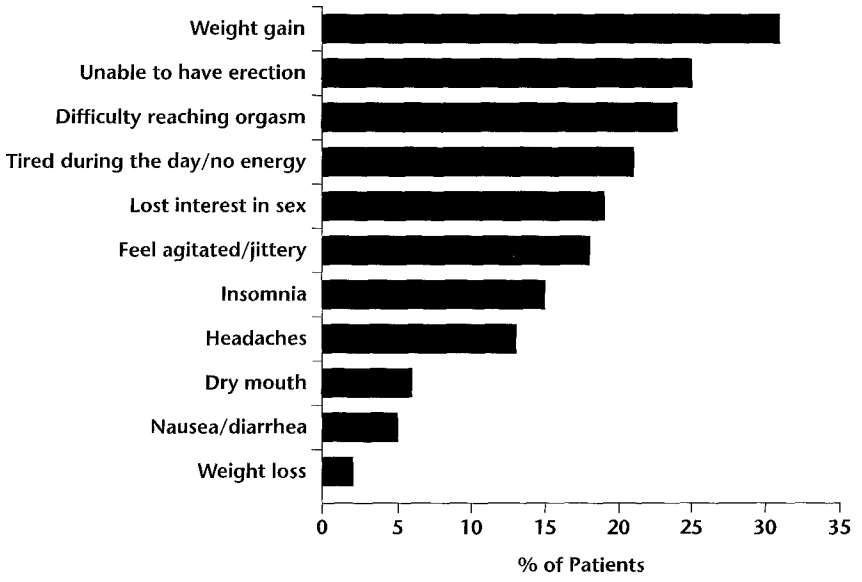

Figure 3. Frequency of adverse effects (AEs) reported by patients as "extremely difficult to live with."

DISCUSSION

Although individual patient opinions vary, these survey results provide a starting point for understanding the impact of AEs on patients' lives. Sixty percent of the respondents indicated a history of treatment discontinuation. In addition to "lack of efficacy," "lost interest in sex," "tired during the day/no energy," and "gained a lot of weight" were among the most common AEs that led to discontinuation. These AEs occur more often with certain classes of antidepressants, including, but not limited to, selective serotonin reuptake inhibitors. In addition to patients indicating discontinuation, an additional 22% of patients indicated noncompliance, with the chief reasons being "trouble remembering to take it," "gained a lot of weight," and sexual AEs. Finally, "weight gain" and sexual AEs were the AEs most difficult to "live with" according to patients.

These results suggest that there are ways for physicians to better serve patients and to potentially enhance treatment response and quality of life. Specifically, limiting the AEs that patients most want to avoid may increase patient satisfaction and promote compliance. The primary problems that patients described in this study can be classified into 2 categories—pharmacologic/pharmacokinetic properties and adverse effects (tolerability). Difficulty with pharmacologic/pharmacokinetic properties, such as lack of response to treatment, can be addressed through research and development of more effective antidepressants. Until then, prescribing medications that can be dosed once or twice daily would reduce the number of doses patients must remember to take, thereby enhancing compliance.[14] All antidepressants that have become available in the United States in the past 15 years meet this goal. So why, then, would patients still not derive the desired response to treatment? We believe most of these individuals are not dosed adequately or discontinue treatment as a consequence of intolerable AEs. It is not entirely clear which AEs patients find least acceptable. Interestingly, some of the most common AEs (ie, dry mouth, insomnia, nausea/diarrhea, and headache) were not the ones patients found most difficult to "live with." Our survey found that the 3 AEs patients most wanted to avoid were weight gain, sexual AEs, and tiredness. Typically, these AEs also were experienced much, if not all, of the time and did not decrease with time. These findings are consistent with those from prior studies.[15–17]

The results of our survey might assist physicians in selecting antidepressants for patients by providing data regarding which AEs might be most difficult for patients to accept. Patients might prefer medications that have a reduced risk for weight gain, sexual AEs, and tiredness. Avoiding these AEs might promote compliance and thus enhance efficacy in patients who otherwise may prematurely discontinue treatment. Patients who continue treatment have an increased likelihood of response.[18] This, at least in part, addresses the most common reason patients stopped taking their medication—the sense that they were not feeling any better.

Proper patient education might promote compliance. Unfortunately, education might not convince patients to take their medication, especially if

the AEs associated with it significantly compromise their quality of life. Although patient education is seemingly an obvious solution, it has not yet shown consistent results in improving compliance. Specifically, in a prospective study of compliance, Mundt et al[19] determined that approximately half of patients discontinued their antidepressant medication by week 12. This rate was not statistically significantly improved with patient education and is consistent with our retrospective survey data, which indicated that 60% of patients had discontinued their antidepressant use at some point.

Limitations of this study include lack of a placebo control, moderate sample size, and possible selection bias in the 53% of patients who returned their surveys. It is possible that patients with more severe illness are more willing to accept AEs, at least temporarily. Other limitations include unknown dosing regimens and names of antidepressants prescribed. Patients might have altered their dosing based on AEs and had a good outcome as a result.[20] This study was not designed to capture this group of patients. Inappropriate antidepressant dose or class would likely contribute to the types of AEs experienced, and impact efficacy. Nonetheless, the data presented provide initial insight into an area largely based on secondhand information obtained through individual patient reports to individual prescribers. A retrospective survey approach to determining compliance has also been reported by Bultman and Svarstad.[21] In their telephone survey, 82% of patients reported missing or discontinuing antidepressant dosing. These data corroborate our finding that lack of compliance is not a small problem.

Based on these findings, future studies to confirm this hypothesis might provide physicians with suggestions for making treatments more acceptable to patients. Additional research to develop better-tolerated antidepressants also is needed.

CONCLUSIONS

The findings of this survey of patients with mild to severe depression suggest that compliance, and hence efficacy, can be promoted by (1) understanding what patients expect and desire from the antidepressants they are prescribed and (2) prescribing antidepressants associated with low rates of weight gain, sexual dysfunction, or tiredness.

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