Underrecognition of Clinically Significant Side Effects in Depressed Outpatients

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Objective: The presence of medication side effects is one of the most frequent reasons depressed patients discontinue medication, and premature discontinuation of medication is associated with poorer outcome in the treatment of depression. Despite the clinical importance of detecting side effects, few studies have examined the adequacy of their detection and documentation by clinicians. We are not aware of any studies comparing psychiatrists' clinical assessments to a standardized side effects checklist in depressed patients receiving ongoing treatment in clinical practice. The goal of the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project was to test the hypothesis that fewer side effects would be recorded by psychiatrists in their patients' charts compared to the number reported by patients on a side effects checklist.

Method: Three hundred depressed outpatients (diagnosed according to *DSM-IV* criteria) in ongoing treatment completed a self-administered version of the Toronto Side Effects Scale (TSES). The patients rated the frequency of each of the 31 side effects and the degree of trouble caused by them. A research assistant reviewed patients' charts to extract side effects information recorded by the treating psychiatrist. The study was conducted from June 2008 to July 2008.

Results: The mean number of side effects reported by the patients on the TSES was 20 times higher than the number recorded by the psychiatrists ($P < .01$). When the self-reported side effects were limited to frequently occurring or very bothersome side effects, the rate was still 2 to 3 times higher ($P < .01$).

Conclusions: Psychiatrists may not be aware of most side effects experienced by psychiatric outpatients receiving ongoing pharmacologic treatment for depression.

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The presence of medication side effects is one of the most frequent reasons depressed patients discontinue medication.[1–8] In one of the first studies to demonstrate the importance of side effects in discontinuing antidepressant medication, Lin et al[9] interviewed 155 primary care patients 1 and 4 months after initiating treatment. The patients reported that the most common reason for early and late termination was the presence of side effects. Demyttenaere et al[5] followed patients initiated on an antidepressant by their primary care physician monthly for 6 months. By the sixth month, slightly more than half of the 221 patients had discontinued treatment, with symptom improvement and the presence of adverse events as the most common and second most common reasons for stopping medication. In another prospective follow-up study, Goethe et al[2] interviewed 406 depressed patients prescribed a selective serotonin reuptake inhibitor (SSRI) 3 months after beginning treatment and found that the most common reason given by patients for stopping their medication was the presence of a side effect. Bull and colleagues[3] found that within the first 3 months of initiating antidepressant medication, the presence of side effects was the most common reason for treatment discontinuation, whereas 4 to 6 months after treatment initiation, clinical response, or lack of response, was the most common reason for discontinuation, and the presence of side effects was the second most common reason for stopping medication. Thus, while the presence of medication side effects may have its greatest impact on treatment discontinuation early in the course of treatment, it continues to play a significant role after the first couple of months of treatment.

Premature discontinuation of medication is associated with poorer outcome in the treatment of depression.[10] Despite the importance that side effects have on premature medication discontinuation, there is some evidence that clinicians may not do a thorough job of eliciting information regarding their presence. Two studies[11,12] found that physicians did not routinely inquire about antidepressant-induced side effects. Anecdotal discussions with primary care providers and psychiatrists suggest that, when inquiring about side effects, the usual method of inquiry is based on global open-ended questions without reference to the presence of specific side effects. This approach, which is

For Clinical Use

- Among outpatients receiving ongoing pharmacologic treatment for depression, almost all report experiencing at least 1 side effect.
- Almost two-thirds of patients report experiencing a side effect often or every day.
- About half of patients report experiencing a side effect that is very or extremely troubling.
- Clinicians must be vigilant in monitoring, recording, and managing side effects during the acute, continuation, and maintenance phases of treatment for depression.

consistent with the method typically used in controlled, industry-funded treatment studies of the efficacy of medication, may result in the underrecognition or underreporting of side effects.

Some studies have empirically examined the adequacy of open-ended questions in the detection of side effects in controlled clinical trials. In a study of subjects receiving placebo during a controlled treatment study of benign prostatic hypertrophy, Bent et al[13] found that the use of a checklist resulted in approximately a 20-fold increase in the number of side effects reported compared to an open-ended global question. Wallander et al,[14] in a clinical trial of felodipine as an adjunctive antihypertensive, found that up to 10 times as many symptoms and adverse events were reported on symptom checklists than with an open-ended question. Wallin and Sjövall[15] reported similar results in a clinical trial of bacampicillin for gonorrhea. In a study of depressed patients focusing on the recognition of sexual dysfunction, Montejo-González et al[16] found that the frequency of sexual dysfunction due to SSRIs was much higher when direct inquiry of its presence was made compared to nonspecific inquiry of the presence of any side effects. In a study of depressed patients treated with imipramine, phenelzine, electroconvulsive therapy, or placebo, Greenblatt[17] found that 10 times as many side effects were elicited in patients assessed with a checklist than in patients assessed with an open-ended question. Hu and colleagues[11] ascertained the frequency of 17 side effects in depressed patients 3 to 4 months after beginning treatment with an SSRI. The prescribing physicians were asked to complete a questionnaire and estimate the frequency of side effects in their patients. The physicians significantly underestimated the frequency of 9 of the 17 side effects. However, this study was not a direct examination of how well clinicians detected side effects in the patients they were treating.

We are not aware of any studies comparing psychiatrists' clinical evaluations of side effects to a standardized side effects checklist in depressed patients. The goal of the present report from the Rhode Island Methods to Improve Diagnostic Assessment and Services (MIDAS) project was to test the hypothesis that in depressed outpatients in ongoing treatment, fewer side effects would be recorded by psychiatrists in their patients' charts compared to the number reported by patients on a side effects checklist.

METHOD

Participants were a consecutive series of 300 psychiatric outpatients who were being treated for a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) major depressive episode in the Rhode Island Hospital Department of Psychiatry outpatient practice. This private practice group predominantly treats individuals with medical insurance on a fee-for-service basis, and it is distinct from the hospital's outpatient residency training clinic that predominantly serves lower-income, uninsured, and medical-assistance patients. The sample included 89 men (29.7%) and 211 women (70.3%) who ranged in age from 18 to 84 years (mean = 44.9, SD = 13.3 years). The educational level achieved by the subjects was that 4.4% (n = 13) did not graduate high school, 54.7% (n = 162) graduated high school or achieved equivalency, and 40.9% (n = 121) graduated college. Data on educational level were missing for 4 subjects. The mean number of medications taken by the patients was 2.1 (SD = 0.9). The majority of patients were taking 2 or more psychiatric medications (67.3%, n = 202). More than one-quarter of the patients were taking 3 or more medications (29.7%, n = 89), and a small number were taking 4 or more medications (6.3%, n = 19). The most frequently prescribed medications were SSRIs (57.3%, n = 172), benzodiazepines (30.3%, n = 91), selective norepinephrine-serotonin reuptake inhibitors (24.0%, n = 72), and bupropion (19.3%, n = 58). The majority of the patients had been in treatment for more than 12 months (65.3%, n = 196).

Six psychiatrists recruited the patients into a "quality of care" study. All 6 psychiatrists were full-time and board certified, with at least 3 years' experience postresidency (mean = 8.2 years; range, 3–15 years). Five of the 6 psychiatrists (all except M.Z.) were blind to the hypothesis of the study. The psychiatrists were kept blind to the information being collected because they might have altered their assessment or documentation of medication side effects. At the end of the appointment, the psychiatrists handed their patients an envelope and told the patients that our group was doing a quality-of-care study that involved the completion of a brief questionnaire. Patients were asked if they would be willing to take 5 minutes to complete the questionnaire in the waiting room after their appointment and hand

the envelope with the completed form to the secretary. Few patients asked about the content of the questionnaire, but, if asked, the psychiatrists responded that they did not know the exact details of the study so as to not bias the results. To further maintain the blind, written informed consent was not obtained by the treating psychiatrist recruiting the patients into the study. However, an introductory letter inside the envelope described the nature of the study and indicated that completion of the side effects questionnaire would denote consent. The Rhode Island Hospital Institutional Review Committee approved the research protocol. Because the participating psychiatrists could be considered as study subjects, the physicians (except M.Z.) were deidentified by the research assistant immediately after extracting information from the patients' charts. We analyzed the data with and without the findings from the unblinded psychiatrist, and because the results were the same, we present the data for the entire sample.

The envelope given to the patients included an introductory letter explaining the purpose of the study and 2 one-page questionnaires. The first questionnaire asked patients for some basic demographic information (age, sex, education) and to list their current psychiatric medications and indicate how long they had been taking the medication. The second questionnaire was the Toronto Side Effects Scale (TSES).[18] The TSES was originally developed as a clinician-administered checklist of 31 side effects commonly reported by patients taking antidepressant medications. We adapted the scale for self-administration. The instructions on the scale were "This questionnaire lists common side effects caused by psychiatric medications. Please read through each side effect and indicate how frequently the side effect occurred during the past week and, if it occurred, how much trouble it caused you during the past week." Side effect frequency was rated on a 5-point scale (1 = never; 2 = sometimes; 3 = about half the time; 4 = often; 5 = every day). Similarly, the severity of the trouble caused by the side effect was rated on a 5-point scale (1 = no trouble; 5 = extreme trouble).

In order to maintain the blind, the study was conducted over a 6-week period of time. This minimized the number of patients who had more than 1 appointment during the study period and who might inadvertently mention the study to their treating psychiatrist at a subsequent visit. The psychiatrists indicated that the blind was not broken during course of the study.

A research assistant reviewed patients' progress notes for the days of the appointments to extract side effects information recorded by the treating psychiatrists. A standardized progress note form is used by all psychiatrists in the outpatient division of the Rhode Island Hospital Department of Psychiatry, and this form has a labeled section to record information about side effects. Every progress note reviewed by the research assistant had written information regarding side effects. The form had 3 blank lines available for the psychiatrist to record side effects information or a box to check indicating that no side effects were present. The information abstracted from the clinical chart was recorded on a side effects checklist that was repeatedly modified and updated throughout the course of the study in order to incorporate all of the side effects noted by the psychiatrist. Immediately after reviewing the patients' charts and extracting the relevant information, the research assistant deidentified the information so that it could not be linked to either the patients or treating psychiatrists.

Paired *t* tests were used to compare the mean number of side effects according to the psychiatrists' assessment and the TSES. Categorical variables were compared by the McNemar test for correlated proportions.

RESULTS

The 300 patients reported 2,301 side effects on the TSES (mean = 7.7, SD = 6.1). Side effect frequency ratings were missing for 68 (3.0%) of 2,301 side effects, and severity ratings were missing for 587 (25.5%) of 2,301 side effects. We compared the demographic characteristics of patients with and without missing ratings and found no difference in sex or age. Patients with missing ratings were significantly less likely to have graduated from college (32.0% vs 65.0%, $\chi^2 = 6.9$, $P < .05$).

For the 2,233 side effects with frequency ratings, slightly more than one-quarter (27.5%, n = 615) were reported as occurring often or every day. For the 1,714 side effects with severity ratings, more than half (58.3%, n = 999) were rated 1 or 2 on the 5-point severity scale, suggesting that the side effect did not cause more than minimal discomfort to the individual, and approximately one-fifth were rated 4 or 5 (20.4%, n = 349), suggesting that the patients considered the side effect very or extremely troubling. The vast majority of patients reported at least 1 side effect on the TSES (90.3%, 271/300). Nearly two-thirds of the patients reported experiencing a side effect often or every day (63.7%, 191/300), and slightly more than one-half reported experiencing a side effect that was very or extremely troubling (52.2%, 121/232).

The psychiatrists recorded 167 side effects in their notes. The mean ± SD number of side effects reported by the patients on the TSES was significantly higher than the number recorded by psychiatrists (7.4 ± 5.9 vs 0.6 ± 1.2, $t = 20.5$, $P < .01$). The percentage of patients with at least 1 side effect was significantly higher on the TSES than on the psychiatrists' evaluation (90.3% vs 26.0%; McNemar test, $P < .01$).

An important question is whether the difference between self-report and psychiatrists' assessment of side effects is related to the frequency or severity of the side effects. Perhaps psychiatrists do not document infrequent or clinically unimportant side effects. However, the difference between self-report and psychiatrist-recorded side effect frequencies was significant even when self-reported side effects on the TSES were limited to those rated as occurring often or every

Table 1. Frequency of Side Effects Based on Patient Self-Report and Psychiatrist Clinical Interview in 300 Depressed Outpatients

	Self-Reported Frequency Based on Toronto Side Effects Scale, %				
Side Effect	A, All Side Effects	B, Frequently Occurring Side Effects[a]	C, Very Bothersome Side Effects[b]	D, Side Effects Frequency Based on Psychiatrist Evaluation, %	2-Group Comparisons Between Self-Report and Psychiatrist Interview[c]
Nervousness	44.1	10.0	3.8	0.7	A, B, C > D
Agitation	41.4	6.7	4.8	0.7	A, B, C > D
Tremor	18.8	3.7	1.4	2.0	A > D
Twitching	20.7	2.7	2.1	0.3	A, B > D
Abdominal pain	13.8	1.3	1.4	0.7	A > D
Upset stomach	22.9	3.0	2.1	2.0	A > D
Nausea	17.5	2.4	2.1	2.7	A > D
Diarrhea	16.7	2.3	1.1	0.3	A, B > D
Constipation	22.4	8.7	5.3	1.3	A, B, C > D
Decreased appetite	21.5	4.4	1.4	0.3	A, B > D
Increased appetite	27.2	5.7	4.0	1.3	A, B, C > D
Weakness or fatigue	41.1	11.7	8.6	5.0	A, B, C > D
Dizziness	21.7	3.7	0.4	1.3	A > D
Dizzy when getting up	25.5	5.0	1.4	1.0	A, B > D
Daytime drowsiness	43.5	11.7	4.8	6.3	A, B > D
Increased sleep	27.4	9.0	2.5	0.0	A, B, C > D
Decreased sleep	26.8	7.0	5.0	1.3	A, B, C > D
Sweating	34.1	12.0	6.9	2.3	A, B, C > D
Flushing	17.7	3.7	1.8	0.0	A, B, C > D
Edema	11.7	3.7	2.1	0.0	A, B, C > D
Headache	29.6	3.4	2.6	0.3	A, B > D
Blurred vision	14.0	2.7	1.4	0.7	A > D
Dry mouth	42.6	15.4	8.9	3.3	A, B, C > D
No orgasm	28.8	13.2	11.7	4.0	A, B, C > D
Increased libido	10.8	1.7	0.7	0.7	A > D
Decreased libido	36.3	19.7	15.4	6.0	A, B, C > D
Premature ejaculation[d]	11.4	3.4	3.4	2.2	A > D
Delayed ejaculation[d]	30.3	10.1	7.2	12.4	A > D
Erectile dysfunction[d]	32.2	14.9	17.4	10.1	A > D
Weight gain[e]	31.3	18.4	12.1	3.7	A, B, C > D
Weight loss[e]	12.2	5.7	1.4	0.0	A, B > D

[a]Frequently occurring side effects were rated 4 or 5 on the Toronto Side Effects Scale.
[b]Very bothersome side effects were rated 4 or 5 on the Toronto Side Effects Scale.
[c]Significant 2-group differences, $P < .05$.
[d]Percentages based on male sex.
[e]Weight gain and weight loss were not rated on the frequency scale. Rather, on the Toronto Side Effects Scale, the amount of weight gain or loss is rated instead of frequency. For the weight gain and weight loss items, a scale value of 4 or 5 indicates a minimum weight change of 6 pounds.

day or rated very or extremely troubling. The mean ± SD number of frequently occurring side effects reported on the TSES was more than 3 times higher than the total number of side effects recorded by psychiatrists (2.1 ± 2.7 vs 0.6 ± 1.2, $t = 9.7$, $P < .01$), and the number of patients with at least 1 frequently occurring side effect reported on the TSES was significantly higher than the rate based on the psychiatrists' evaluation (63.7% vs 26.0%; McNemar test, $P < .01$). Likewise, the mean ± SD number of troubling side effects reported on the TSES was significantly higher than the total number of side effects recorded by the psychiatrists (1.6 ± 2.3 vs 0.7 ± 1.3, $t = 5.5$, $P < .01$), and the number of patients with at least 1 very or extremely bothersome side effect reported on the TSES was significantly higher than the number of patients noted by the psychiatrists as having a side effect (52.2% vs 29.3%; McNemar test, $P < .01$).

We examined whether having recently begun a new medication impacted side effect ratings. We hypothesized that the clinicians would be more likely to identify side effects in patients who had recently begun a medication than in patients who had not started a new medication. While it was true that clinicians were significantly more likely to record at least 1 side effect in the 62 patients who began a medication within the past 3 months compared to the remainder of the patients (38.7% vs 22.7%, $\chi^2 = 6.6$, $P < .01$), there was still a significantly higher frequency of patients with at least 1 side effect reported on the TSES (95.2% vs 38.7%; McNemar test, $P < .01$). Likewise, in the patients who began a medication within the past 3 months, the difference between self-report and clinician assessments remained significant for any frequent side effect (69.4% vs 38.7%; McNemar test, $P < .001$) and any bothersome side effect (66.7% vs 45.8%; McNemar test, $P < .05$). For the patients who had not begun a new medication within the past 3 months, a significantly higher percentage of patients with at least 1 side effect was reported on the TSES based on the analyses of any side effect (89.1% vs 22.7%; McNemar test, $P < .01$), frequent side effect (62.2% vs 22.7%; McNemar test, $P < .01$), and bothersome side effect (48.4% vs 25.0%; McNemar test, $P < .01$).

Looking at the frequencies of specific side effects, the data in Table 1 show that each of the 31 items on the TSES was reported by more than 10% of the patients, whereas

only erectile dysfunction and ejaculatory delay were identified with this frequency by the psychiatrists. The frequency of all 31 side effects was significantly higher on the TSES (all Ps < .001 except premature ejaculation, $P < .01$). When the TSES side effect rate was limited to frequently occurring side effects, the rate was significantly higher than the psychiatrist rate for 21 of the 31 items, and when the TSES side effect rate was limited to very troubling side effects, 14 of the 31 differences were significant.

DISCUSSION

The findings of the present study indicate that clinicians do not record in their progress notes most side effects reported on a side effects questionnaire by psychiatric outpatients receiving ongoing pharmacologic treatment for depression. The total number of side effects reported on the questionnaire was more than 20 times higher than that recorded in psychiatrists' charts. When the self-reported side effects were limited to frequently occurring or very bothersome side effects, the rate was still 2 to 3 times higher. The recency of having begun a new medication had an impact on the number of side effects recorded by the psychiatrists, but the self-reported side effect frequency was still significantly higher in the patients who began a medication in the prior 3 months as well as the patients with no recent medication changes.

Alternative explanations for the findings should be considered. Was the higher self-reported rate of side effects due to a documentation problem rather than an assessment problem? Perhaps the psychiatrists did not systematically record side effects that were ongoing and had been previously recorded, but recorded only side effects of new onset. Post hoc conversations with the clinicians indicated that all side effects reported by patients on the day of the appointment were recorded in the progress note, whether or not they had been previously reported by the patients; thus, underdocumentation was not responsible for the discrepancy.

Did the patients, when asked by the psychiatrists about the presence of side effects, underreport their occurrence? All of the psychiatrists used the same general approach toward eliciting side effects information—a global, open-ended question. This approach toward the ascertainment of side effects is similar to the one used in most industry-sponsored clinical trials. The only specific side effect that was regularly inquired about was sexual dysfunction because of concerns that some patients might be too embarrassed to spontaneously report its presence. Perhaps, as a result of such direct inquiry, sexual dysfunction was the most frequently recorded side effect by psychiatrists. We hypothesize that patients stopped reporting to the psychiatrists, in response to an open-ended question, side effects that they had grown accustomed to, but they reported these side effects on the self-report scale when specific inquiry was made of their presence. Studies comparing the use of a global, open-ended question to a checklist to determine the frequency of side effects have consistently found a much higher frequency of side effects using the checklist.[13–15,17,19] Each of these studies was conducted as part of acute-phase clinical trials, thus acclimation to long-standing side effects was unlikely to result in patient underreporting. Thus, while acclimation may account for some patient underreporting in the present study, we believe that the method of ascertainment also impacts the number of side effects reported by patients. Unfortunately, we did not follow up with patients to determine if they were experiencing side effects that they did not report to their physician.

Did patients report side effects on the TSES that were considered by the psychiatrists to be symptoms of depression rather than side effects? Several of the items on the TSES, such as sleep disturbance, appetite disturbance, fatigue, and nervousness, are also common symptoms in depressed patients. While we cannot rule out the possibility that confusion between side effects and symptoms contributed to the large difference in total side effect rates between the self-report scale and psychiatrists, it does not fully explain the findings because the differences between self-report and the psychiatrists cut across all 31 side effects on the TSES, many of which are unlikely to be symptoms of depression.

Did patients report side effects on the TSES that were considered by the psychiatrists to be side effects of nonpsychotropic medications or symptoms of medical illnesses? We did not systematically collect information on nonpsychiatric medications or medical illnesses and cannot rule out this possibility as a contributor to the discrepancy between the 2 methods of assessing side effects.

Medication compliance and adherence has been the topic of increasing discussion and research.[1,2,8,20–25] The treatment of depression has been conceptualized as consisting of 3 phases: acute, continuation, and maintenance. The initial, acute phase refers to the first 8 to 12 weeks of treatment, and the goal is to achieve a reduction in symptoms and psychosocial impairment. During the continuation phase, which is generally considered to occur during the first 6 months to a year after the initial treatment response, the goal is to maintain these gains. In the maintenance phase, which occurs after a sustained period of improvement, the goal is to further maintain the gains. Many patients treated with antidepressants receive them for maintenance treatment, and the American Psychiatric Association's treatment guidelines for depression indicate that it is important to monitor side effects throughout all phases of treatment.[26] The presence of side effects is only one factor, albeit one of the most important, responsible for medication discontinuation. Discussion about potential side effects prior to the initial prescription may reduce noncompliance.[3] We would hypothesize that ongoing dialogue about side effects will reduce premature medication discontinuation in depressed patients and that this would reduce relapse rates. In the

present study, the psychiatrists were not aware of most of the side effects experienced by their patients. Consistent with recent suggestions that measurement-based care using self-report questionnaires be incorporated into routine clinical practice in order to better recognize residual symptoms in depressed patients who have responded to treatment,[27,28] we believe that the use of self-administered side effects checklists will improve side effects detection. However, an important question is whether such improved detection results in greater or lesser adherence to medication. Improved side effect detection could potentially reduce medication noncompliance and, thus, relapse rates because patients' concerns and questions can be addressed in treatment. On the other hand, it can be argued that systematic use of a side effects checklist will heighten patients' awareness and concerns about the adverse effects of treatment and result in greater levels of medication discontinuation. Quite possibly, recommendations regarding the use of a side effects checklist might depend on patient characteristics. For example, it might be prudent not to use such checklists in patients who are prone to experiencing somatic symptoms and report a history of medication sensitivity. We are not aware of studies of the clinical impact of systematic inquiry about side effects or studies identifying characteristics of patients who might or might not benefit from the use of side effect scales.

Most studies of medication discontinuation have focused on the acute phase of treatment. It is likely that the issues involved in discontinuation due to side effects are different in the acute and continuation and maintenance phases of treatment. Patients may be willing to tolerate some side effects, such as sexual dysfunction, early in the course of treatment, but they are less willing to tolerate these side effects that reduce their quality of life during ongoing treatment. It therefore is important for clinicians to continually be vigilant for the presence of side effects during the continuation and maintenance phases of treatment.

Although accurately determining the presence of side effects may be enhanced by direct inquiry using standardized interview schedules,[29] such measures are unlikely to be incorporated into routine clinical practice because they take too much time. The use of a self-administered questionnaire to identify side effects is a potentially feasible approach to improve side effect recognition. Some studies have demonstrated the reliability and validity of self-report checklists for detecting side effects of first-generation antipsychotic medications in patients with schizophrenia.[29,30] We would expect comparable, if not better, levels of agreement between self-report and interviewer-administered standardized side effect schedules in depressed patients.

One implication of the study is that side effect frequencies reported in industry-sponsored studies, based on a global approach toward assessment, underestimate the prevalence of side effects. The clinical importance of this underestimation is that clinicians might not be accurately informing their patients about the likelihood of side effects, and a lack of adequate preparation might result in medication discontinuation.[3]

A limitation of the present study is that it was conducted in a single outpatient practice in which the majority of the patients were white and female and had health insurance. Replication of the results in other clinical samples with different demographic characteristics is warranted. The side effects questionnaire used in the study was originally developed as a clinician-administered checklist. We adapted the scale for self-administration, and it, therefore, has unknown reliability and validity. However, other studies of self-administered side effects checklists found good levels of agreement with a clinician-administered version of the scale.[29,30] Most of the patients in the study were in the continuation and maintenance phases of treatment. Studies of side effect frequencies, adherence, and discontinuation of treatment are typically conducted during the acute phase of antidepressant treatment. However, we found that the difference between self-reports and clinician reports was significant in patients who had begun a medication within the past 3 months as well as in patients who did not have a recent medication change. Nonetheless, replication of the present results in patients receiving acute-phase treatment is warranted. The majority of the patients were taking more than 1 medication. Thus, the findings of the study are not specific to antidepressant medications but, instead, refer to the pharmacologic management of depressed patients who are treated in routine clinical practice.

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REFERENCES

1. Burra TA, Chen E, McIntyre RS, et al. Predictors of self-reported antidepressant adherence. *Behav Med*. 2007;32(4):127–134.
2. Goethe JW, Woolley SB, Cardoni AA, et al. Selective serotonin reuptake inhibitor discontinuation: side effects and other factors that influence medication adherence. *J Clin Psychopharmacol*. 2007;27(5):451–458.
3. Bull SA, Hu XH, Hunkeler EM, et al. Discontinuation of use and switching of antidepressants: influence of patient-physician communication. *JAMA*. 2002;288(11):1403–1409.
4. Bolling MY, Kohlenberg RJ. Reasons for quitting serotonin reuptake inhibitor therapy: paradoxical psychological side effects and patient satisfaction. *Psychother Psychosom*. 2004;73(6):380–385.
5. Demyttenaere K, Enzlin P, Dewe W, et al. Compliance with antidepressants in a primary care setting, 1: beyond lack of efficacy and adverse events. *J Clin Psychiatry*. 2001;62(suppl 22):30–33.
6. Maddox JC, Levi M, Thompson C. The compliance with antidepressants in general practice. *J Psychopharmacol*. 1994;8(1):48–53.
7. Rosenberg KP, Bleiberg KL, Koscis J, et al. A survey of sexual side effects among severely mentally ill patients taking psychotropic medications:

impact on compliance. *J Sex Marital Ther*. 2003;29(4):289–296.
8. Masand PS. Tolerability and adherence issues in antidepressant therapy. *Clin Ther*. 2003;25(8):2289–2304.
9. Lin EH, Von Korff M, Katon W, et al. The role of the primary care physician in patients' adherence to antidepressant therapy. *Med Care*. 1995;33(1):67–74.
10. Melartin TK, Rytsala HJ, Leskela US, et al. Continuity is the main challenge in treating major depressive disorder in psychiatric care. *J Clin Psychiatry*. 2005;66(2):220–227.
11. Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry*. 2004;65(7):959–965.
12. Sleath B, Rubin R, Huston S. Hispanic ethnicity, physician-patient communication, and antidepressant adherence. *Compr Psychiatry*. 2003;44(3):198–204.
13. Bent S, Padula A, Avins AL. Brief communication: better ways to question patients about adverse medical events: a randomized, controlled trial. *Ann Intern Med*. 2006;144(4):257–261.
14. Wallander MA, Dimenas E, Svardsudd K, et al. Evaluation of three methods of symptom reporting in a clinical trial of felodipine. *Eur J Clin Pharmacol*. 1991;41(3):187–196.
15. Wallin J, Sjövall J. Detection of adverse drug reactions in a clinical trial using two types of questioning. *Clin Ther*. 1981;3(6):450–452.
16. Montejo-González A, Liorca G, Izquierdo J, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther*. 1997;23(3):176–194.
17. Greenblatt M. Controls in clinical research. *Clin Pharmacol Ther*. 1964; 5:864–870.
18. Vanderkooy JD, Kennedy S, Bagby R. Antidepressant side effects in depression patients treated in a naturalistic setting: a study of bupropion, moclobemide, paroxetine, sertraline, and venlafaxine. *Can J Psychiatry*. 2002;47(2):174–180.
19. Downing RW, Rickels K, Meyers F. Side reactions in neurotics, pt 1: a comparison of two methods of assessment. *J Clin Pharmacol J New Drugs*. 1970;10(5):289–297.
20. Brook OH, van Hout HP, Stalman WA, et al. Nontricyclic antidepressants: predictors of nonadherence. *J Clin Psychopharmacol*. 2006;26(6):643–647.
21. Delgado PL. Approaches to the enhancement of patient adherence to antidepressant medication treatment. *J Clin Psychiatry*. 2000; 61(suppl 2):6–9.
22. Demyttenaere K. Compliance during treatment with antidepressants. *J Affect Disord*. 1997;43(1):27–39.
23. Hunot VM, Horne R, Leese MN, et al. A cohort study of adherence to antidepressants in primary care: the influence of antidepressant concerns and treatment preferences. *Prim Care Companion J Clin Psychiatry*. 2007; 9(2):91–99.
24. Keller MB, Hirschfeld RM, Demyttenaere K, et al. Optimizing outcomes in depression: focus on antidepressant compliance. *Int Clin Psychopharmacol*. 2002;17(6):265–271.
25. Mitchell AJ. Depressed patients and treatment adherence. *Lancet*. 2006; 367(9528):2041–2043.
26. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder [revision]. *Am J Psychiatry.* 2000;157(suppl 4):1–45.
27. Trivedi MH, Daly EJ. Measurement-based care for refractory depression: a clinical decision support model for clinical research and practice. *Drug Alcohol Depend*. 2007;88(suppl 2):S61–S71.
28. Zimmerman M, McGlinchey JB, Chelminski I. An inadequate standard of care: lack of measurement of outcome when treating depression in clinical practice. *Prim Psychiatry*. 2008;15:67–75.
29. Lindstrom E, Lewander T, Malm U, et al. Patient-rated versus clinician-rated side effects of drug treatment in schizophrenia: clinical validation of a self-rating version of the UKU Side Effect Rating Scale (UKU-SERS-Pat). *Nord J Psychiatry*. 2001;55(suppl 44):5–69.
30. Day JC, Wood G, Dewey M, et al. A self-rating scale for measuring neuroleptic side-effects: validation in a group of schizophrenic patients. *Br J Psychiatry*. 1995;166(5):650–653.

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